

BIOCHEMICAL TARGETS OF PLANT BIOACTIVE COMPOUNDS

A pharmacological reference guide to
sites of action and biological effects

GIDEON POLYA



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Boca Raton London New York Washington, D.C.

Library of Congress Cataloging-in-Publication Data

Polya, Gideon Maxwell.

Biochemical targets of plant bioactive compounds : a pharmacological reference guide to sites of action and biological effects / Gideon Polya.

p. cm.

Includes bibliographical references and index.

ISBN 0-415-30829-1

1. Materia medica, Vegetable—Handbooks, manuals, etc. 2. Botanical chemistry—Handbooks, manuals, etc. 3. Plant products—Handbooks, manuals, etc. 4. Pharmacology—Handbooks, manuals, etc. 5. Plants—Metabolism—Handbooks, manuals, etc. I. Title.

RS164 .P766 2003

615'.32—dc21

2002155281

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International Standard Book Number 0-415-30829-1

Library of Congress Card Number 2002155281

Printed in the United States of America 2 3 4 5 6 7 8 9 0

Printed on acid-free paper

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Preface

Plants defend themselves from other organisms by elaborating bioactive chemical defences. This is the essential basis of the use of herbal medicines that still represents a major therapeutic resort for much of humanity. However, at the outset, it must be stated that any plant that is not part of our evolved dietary cultures is potentially dangerous. Commercial herbal medicinal preparations approved by expert regulatory authorities have a significant place in mainstream conventional medicine and in complementary medicine. The first and last message of this book on the biochemical targets of bioactive plant constituents is that use of herbal preparations for medicinal purposes should only occur subject to expert medical advice. In the language of popular culture, **DO NOT TRY THIS AT HOME!**

This book arose from 40 years as a student, researcher and academic teacher in biochemistry, a discipline fundamentally informed by both chemistry and physiology. This book is aimed at a very wide readership from biomedical researchers and practitioners to a wide range of scientifically literate lay persons. Lay readers (notably high school and university students and graduates) would range from everyone following public media reports and discussions on health, environmental and other scientific matters to potential readers of popular generalist scientific journals such as *Scientific American* or *New Scientist*. The scientific readership would include researchers, professionals, practitioners, teachers and industry specialists in a wide range of disciplines including the life sciences, ecology, nursing, naturopathy, psychology, veterinary science, paramedical disciplines, medicine, complementary medicine, chemistry, biochemistry, molecular biology, toxicology and pharmacology.

This book condenses a huge body of information in a succinct and user-friendly way. Ready access to a goldmine of key chemical structure/plant source/biochemical target/physiological effect data from a huge scientific literature is via a Plant Common names index, a Plant genus index and a Compound index. Such information is obviously useful for biomedical and other science specialists. The introductory chemical and biochemical summaries will be very useful to students in these and allied disciplines. However, at a universal, everyday level, one can also use the book to readily find out about the nature and targets of bioactive substances in what you are eating at a dinner party. Further, plants and their constituents play an important part in human culture and the bed-time or aeroplane reader will find a wealth of interesting snippets on the historical, literary, artistic and general cultural impact of plant bioactive substances.

Many people have variously helped and encouraged me in this project, most notably my wife, Zareena, my children Daniel, Michael and Susannah, my mother and siblings, recent

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research collaborators, colleagues who have given computing and scientific advice and further colleagues and other professionals who have read specific chapters. I must gratefully acknowledge the profound influence of my late father, Dr John Polya. Any deficiencies of this book are simply due to me and have occurred despite such helpful interactions.

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August 2002

1 Plant defensive compounds and their molecular targets

1.1 Introduction

Higher plants are sessile and are consumed by motile organisms, namely other eukaryotes and prokaryotes. Plants defend themselves by physical barriers including cell walls at the cellular level, by the waxy cuticle of leaves and by bark and thorns at the macroscopic level. Plants also defend themselves from fungal and bacterial pathogens and animal herbivores by elaborating a variety of bioactive secondary metabolites and defensive proteins. There may be as many as 100,000 different kinds of plant defensive compounds of which about 30,000 have been isolated and structurally characterized. Biochemical targets have been determined *in vitro* or *in vivo* for some thousands of the defensive compounds isolated to date.

The word “target” is being used rather broadly and loosely here to encompass the molecular sites of interaction demonstrated for such compounds. However, the demonstrated binding of a plant compound to a protein *in vitro* or *in vivo* does not necessarily mean that this particular interaction is actually the critical site of action of the defensive compound. Further, a particular defensive compound may have multiple molecular sites of action and may well have synergistic effects with other such compounds. This book is concerned with the biochemical targets of plant defensive compounds.

This treatise has been designed to address a very wide audience ranging from scientifically literate lay people to researchers in many disciplines and health professionals. Plant products have had a huge impact on the way in which different human societies have developed, especially over the last twelve thousand years since the advent of agriculture. Thus, the evolution of specific day-length and temperature requirements for plant development meant adaptation of specific plants to particular latitudes. Accordingly, exploitation of “useful” plants (and of domesticatable animals feeding upon them) would have spread rapidly on an East–West axis. This contributed to the technological and military dominance of cultures of the Eurasian axis in the colonial era (as opposed to those of the North–South long axis continents of Africa and the Americas) (Diamond, 1997).

Particular plant products have had a massive impact on human populations and cultures in recent centuries as evidenced by the slave trade to the Americas (for the purposes of coffee, sugar and cotton production), colonial conquest in the East (opium, indigo, tea, cotton and preservative spices), African subjugation (slavery, cocoa, rubber and timber) and temperate colonization (grain, cotton, timber and herbivore production). Notwithstanding the European “Enlightenment”, these economic expansions and social reorganizations (both domestic and colonial) were accompanied by horrendous abuses connected with war and famine (problems that are continuing today in the “New World Order”).

Plants provide a bulk supply of carbohydrate (typically as seed or tuber starch) to support the global human population that now totals 6 billion as compared to an estimated 1 million

2 1. *Plant defensive compounds and their molecular targets*

hunter-gatherers before the advent of agriculture-based civilization twelve thousand years ago. However, plants also provide humanity with a variety of bioactive constituents used for their taste, preservative, psychotropic or medicinal properties. Notwithstanding synthetic sweeteners, non-plant preservatives and an explosion of psychotropic drugs and other pharmaceuticals, plants are still major sources of such ameliorative and protective agents. While the “Western” pharmaceutical global market reached a value of US\$354 billion in 2000, the total global herbal medicine market is currently about US\$30 billion. Herbal medicine remains a major core recourse for the impoverished majority of the world’s population.

Herbal medicinal traditions can be traced back to our primate forebears. Thus, parasite-infected chimpanzees make recourse to particular plants, which they evidently associate with symptomatic relief. Human cultures in general have accumulated medicinal protocols based on use of plants, major traditions including Chinese medicine and Indian Ayurvedic herbal medicine. As detailed in this book, in some instances, specific bioactive substances from medicinal plants (or derivatives of such compounds) have found application in conventional medicine. Thus, the cardiotoxic cardiac glycoside sodium pump (Na^+ , K^+ -ATPase) inhibitors derived from the initial use for cardiac insufficiency of digitalis (dried leaves of the foxglove, *Digitalis purpureum*).

Determining the molecular sites of action of bioactive medicinal plant constituents is clearly important for establishing the chemical and physiological basis for herbal medicinal efficacy, for quality control of commercial herbal preparations and for the discovery of “lead compounds” for synthetic (or semi-synthetic) pharmaceutical development. Of course, it must be recognized that medicinal plant efficacy may derive from complex synergistic effects or even from quasi-placebo effects connected with the taste, mild effects and appearance of the preparation. While recognizing these possible “holistic” complications, in order to find out how such preparations work, it is clearly important to initially isolate, structurally characterize and define the biochemical targets of plant bioactive substances.

1.2 **Organization and scope of the book**

The book has been devised and organized so that it can be used by a wide range of people as (a) a textbook, (b) a user-friendly reference and (c) as a comprehensive summary of the biochemical pharmacology of plant compounds. This book focuses specifically on purified plant compounds (secondary metabolites and proteins) and the molecular entities (principally proteins) with which they interact in the target microbial pathogens and animal herbivores. In contrast, there are many essentially ethnobotanical books that variously deal with medicinal and psychotropic plants, detailing the nature, distribution, physiological effects, chemical components (where known) and cultural significance of such plants. In addition, there are many books that deal with purified and characterized plant defensive components from a chemical structure perspective. The Merck Index (Budavari, 2001) and the Phytochemical Dictionary (Harborne and Baxter, 1993) are notable examples of such chemical compendia that were particularly useful in the writing of this book and indeed are very useful adjuncts to the present work (especially for the chemical structures of plant compounds).

This first chapter deals with the structural diversity of plant defensive compounds. Chapter 2 provides a succinct but comprehensive summary of the essentials of biochemistry (the chemistry of living things). This biochemical review provides a detailed background for understanding the nature and function of the targets of plant defensive metabolites and proteins. The remainder of the book summarizes (mainly in table form) a wealth of information

about the molecular targets which are mainly proteins (such as receptors and enzymes) but also include polynucleotides (RNA and DNA), phospholipids and reactive oxygen species (ROS).

It will be apparent from a preliminary scan of this book that most of the biochemical targets are directly or indirectly concerned with cellular signalling, that is, the machinery enabling cells to perceive and respond to extracellular signals. Obvious major differences aside (e.g. the occurrence of chloroplasts in plants), the fundamental biochemical processes of metabolism and replication in plants and the organisms that consume plants are very similar. Accordingly, plants must be protected from compounds they produce that poison metabolism and replication. Such protection is achieved, for example, by defensive compounds being deposited extracellularly, being temporarily inactivated by chemical modification (e.g. glycosylation) and being highly specific for the non-plant targets. However, a major “strategy” that has evidently evolved in the defence of sessile plants against their mobile enemies has been to impair signalling processes, that is, it is energetically more efficient for plants to discourage rather than kill plant-consuming organisms.

1.3 Description of the tables

Most of the book is comprised of tables dedicated to specific targets or groups of targets of plant defensive compounds. Target-related tables are grouped into specific chapters that are prefaced by succinct summaries of the biochemistry of the targets. The tables in general have three columns that are dedicated respectively to (a) compound name, synonym and general chemical class, (b) plant sources of the compound together with common plant names of well-known plants, plant family and the plant part involved and (c) the biochemical target being considered, a measure of the affinity of the compound for the target, other biochemical targets and *in vivo* cellular and physiological effects of the compound. The information provided for any compound entry has been pared to a minimum and extensive use is necessarily made of abbreviations that are defined within the text and at the end of the book.

It should be noted that the literature covered for this book was enormous and varied. Accordingly, plant parts, numerous plant sources and compound affinities are not given in all entries. Measures of the affinity of a compound for its target are given in various ways. IC_{50} value (concentration for 50% inhibition of an enzyme, 50% displacement of a known ligand from the target molecule or 50% inhibition of an *in vivo* process) is routinely presented in round brackets in micromolar units (μM ; micromoles per litre; 10^{-6} moles per litre). Compound-target dissociation constant (K_{d}) or inhibitor-target dissociation constant (inhibitor constant, K_{i}) (another measure of tightness of association) is presented in square brackets in micromolar units. For simplicity, the IC_{50} , K_{d} or K_{i} values (when provided) are given as a simple number with the unit (μM) being assumed because most of these values are indeed in the range of 1–100 μM . However, in cases when these values are much less than 1 μM , the value is given with the appropriate unit explicitly specified, for example, nM (nanomolar; nanomoles per litre; 10^{-9} moles per litre) and pM (picomolar; picomoles per litre; 10^{-12} moles per litre). Of course, the quantitation of such affinities depends upon the conditions of measurement and the source of the biochemical target entity. However, it was felt that provision of such values in many cases would give a useful “ball park” figure for comparative purposes and for indicating concentrations required for *in vitro* or *in vivo* effects. Thus (1 pM) would indicate that the compound binds very tightly to the target or causes *in vitro* or *in vivo* effects at extremely low concentrations. Conversely, (100) (i.e. 100 μM) would indicate a low affinity of the compound for the target and a relatively high concentration being required for *in vitro* or *in vivo* effects.

4 1. Plant defensive compounds and their molecular targets

A selection of major plant sources has been provided in the tables but space limitations precluded an exhaustive listing of plant sources. Thus, the triterpene bioactive betulinic acid has so far been found in some 460 plant species and the flavonol kaempferol has been isolated from over 150 plant species. Conversely, some 600 bioactive secondary metabolites have been isolated from plants of the *Piper* genus alone. Most of the information on the plant bioactives and their sources have been derived from Web searching (e.g. using Alta Vista, Google and the PubMed system of the National Library of Medicine of the National Institutes of Health, USA), Biological Abstracts, review journals, a huge body of primary research papers and key compendia such as the Phytochemical Dictionary (Harborne and Baxter, 1993), the Merck Index (Budavari, 2001) and the Bioactive Natural Products series (Atta-ur-Rahman, 2001). Of especial use in surveying and checking bioactive compounds, plant sources and compound biological effects were the Merck Index (Budavari, 2001), the Phytochemical Dictionary (Harborne and Baxter, 1993) and a key Web-accessible compendium, namely Dr Duke's Phytochemical and Ethnobotanical Databases (the US Department of Agriculture (USDA) Agricultural Research Service, Beltsville, Maryland, USA).

Scientific and common names are provided for the compounds described. Obviously in some cases, the chemical structure can be rigorously defined in words understandable to readers with a modest chemistry background (e.g. the amino acid neurotransmitter GABA = γ -aminobutyric acid = gamma-aminobutyric acid = 4-aminobutyric acid = $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COOH}$). In other cases, a similar rigorous specification is based on the structure of a parent nucleus that is substituted (e.g. the flavonol phenolic quercetin = 3,5,7,3',4'-pentahydroxyflavone) and indeed the structures of a variety of such "parent compounds" (e.g. flavone) are described later in this chapter and in the Appendix. For the lay reader, typical covalent chemical bonding can be summarized "Lego"-style by saying that hydrogen (H), oxygen (O), nitrogen (N), carbon (C) and phosphorus (P), respectively, have 1, 2, 3, 4 and 5 "friends" (i.e. single bond or equivalent single/double/triple bond combination connections). Reduced sulfur (S) is bivalent in hydrogen sulfide ($\text{H}-\text{S}-\text{H}$) but is hexavalent in the highly oxidized sulfate ion $[\text{O}-\text{S}(=\text{O})_2-\text{O}]^{2-}$.

In many cases the compound structure is very complex but the name(s) and general chemical class description (provided for all compounds) provide a reasonable structural definition given the space limitations. However, the information provided will generally enable rapid sourcing of the chemical structure via the Web, the Merck Index (Budavari, 2001), the Phytochemical Dictionary (Harborne and Baxter, 1993), Chemical Abstracts and other chemical compendia and chemical and biochemical textbooks listed in the Bibliography. In this chapter and Chapter 2, the structures of a large number of bioactive compounds are given precisely in the text where this is readily possible. However, more complex structures are efficiently dealt with in a way to be described later that succinctly conveys the essential "skeletal" structure of a compound without confusing the reader with lengthy descriptions of additional structural details.

It must be appreciated that compounds with a carbon (C) atom having four different substituents (A, B, C and D) can exist as stereoisomers (mirror image configurations) that can only be interconverted by breaking and re-forming bonds (this interconversion being called racemization). You can readily establish this for yourself using matches tetrahedrally disposed on a piece of fruit representing the C atom (or by inspecting your "mirror image" left and right hands). Such isomerism can be of major importance for biological activity. Thus the α -amino acids that are constituents of proteins (poly-amino acids, polypeptides) can, in general, exist as mirror-image stereoisomers referred to as the so-called L- and

D-configurational isomers – however, only L-amino acids are found in proteins. The reader must be aware that such stereoisomerism is indicated in some key examples but not in all cases for reasons of space and didactic effectiveness.

In tables dealing specifically with proteins, a convention has been followed that the genus name of the protein source is generally given prior to naming the protein because particular types of defensive proteins (e.g. lectins, lipid transfer proteins and Bowman–Birk protease inhibitors) have been isolated from a variety of plants. Further, a brief description of the protein involving selected bits of information is provided in parentheses, for example, how many amino acids constitute the polypeptide (x aa); the molecular mass (x kDa = x kilodaltons, where 12 Da = the mass of a carbon-12 atom); the number of cysteine residues in the protein (x Cys); the number of disulfide bonds formed between cysteine residues ($x/2$ S–S); whether the protein is a glycoprotein and is glycosylated, that is, has sugar residues attached.

Because some compounds have been found to interact with a variety of targets, it was necessary to make a large number of abbreviations that are comprehensively listed at the end of the book. Thus, for example, an “Acetylcholine receptor of the nicotinic kind” is abbreviated as “nACh-R”. The abbreviations for the particular targets that are the subject of specific tables are also defined within those tables.

For some particular targets (such as particular hormone receptors that have only recently been detected, purified or expressed), very few interacting plant compounds have as yet been identified and accordingly the tabulation process has been simple. However, in many cases a large number of compounds belonging to different chemical classes have been found to interact with particular targets. These compounds have been grouped into various categories, namely alkaloids, phenolics, terpenes, other compounds and non-plant reference compounds (the latter category being introduced to link the plant compounds with notable non-plant compounds of pharmacological and medical interest). Within such groupings the compounds are listed alphabetically and indeed throughout the tables compounds, compound synonyms, plant families and physiological properties of compounds are all consistently listed in alphabetical order for convenience.

Non-plant reference compounds are provided (listed within square brackets) for many targets (notably in the tables concerned with compounds binding to hormone or neurotransmitter receptors). Some of these non-plant compounds derive from fungi and indeed in some cases from pathogenic fungi growing on plants. Others are well-known bioactive compounds derived from other organisms or synthetic compounds of pharmacological and/or clinical importance. In some cases the affinities of plant substances for particular targets have been determined from the ability of the plant compound to displace a radioactively labelled non-plant ligand from the target protein or the plant compound and the non-plant compound compete or antagonize each other in bioassays. The *in vivo* physiological effects of the various bioactive compounds are very briefly described in square brackets at the end of each entry.

Finally, it was recognized that plants and their constituents have an intimate place in human cultures for a variety of reasons connected with food, hunting, medicine, war, religious practice, poisoning and psychotropic properties. Accordingly, in entries scattered throughout the tables, brief mention is made of historical, medicinal and toxicological properties of well-known plants and their products. In particular, the tables have been leavened by reference to notable interactions of famous people (including scientists) with particular plants or plant defensive compounds.

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1.4 Using the tables

Because of the comprehensiveness of this book and the need to update entries in the future, the tables have been organized rationally in relation to groups of biochemical targets. In short, if you know the name of the compound or the plant genus from which it has been isolated, then you can rapidly turn to table-specific entries (as opposed to page-specific entries). If you know the common name of the plant, you can find the “genus” part of the binomial scientific name of the plant by consulting the Common Plant Name Index at the end of the book. Knowing the genus name of the plant species, you can look up the Plant Genus Index and find the relevant entries successively specifying genus name, table number, specific target section (a capital letter) and subsection (a lower case letter – a for alkaloid, p for phenolic, t for terpene and o for other; n specifies a non-plant compound). In tables dealing specifically with plant proteins, the name of the protein is preceded by the genus name. One can also look up the separate Compound Index listing all chemical compounds referred to in the tables and also obtain table references as described above.

By way of example, you can quickly find from the Plant Genus Index what has been found in *Coffea arabica* (family Rubiaceae) (coffee), the entry being:

Coffea 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 9.2p, 10.2a, 10.2t, 10.4a, 10.4o, 10.4p, 10.4t, 13.8ZOp, 14.1Ap, 14.2p, 14.5p

It is “common knowledge” that coffee contains caffeine (a methylxanthine compound) and inspection of the Compound Index yields the following entry:

Caffeine 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 10.2a

These entries succinctly describe coffee constituents that have been isolated, structurally characterized and shown to interact with particular biochemical targets.

1.5 The structural diversity of plant defensive compounds

As previously indicated, some 30,000 plant defensive compounds (either secondary metabolites or proteins) have so far been purified and characterized. This huge diversity has been reviewed in major monographs and monograph series listed in the Bibliography at the end of the book. A huge literature was examined in preparing this book, this amounting to tens of thousands of individual primary scientific papers and reviews describing the isolation, structural characterization, pharmacological effects and biochemical targets of thousands of plant-derived and other chemical compounds. Because of limitations of space it was simply not possible to reference each entry (such documentation would have required thousands of pages in itself). For the primary literature, for each entry the reader is referred to Web search vehicles (notably Google and PubMed) and the abstracting compendia, monographs and monograph series listed in the Bibliography.

Because of the need for user-friendly tables, the chemical complexity of plant-derived natural products has been simplified in this book into four categories, namely the alkaloids (a), phenolics (p), terpenes (t) and “other compounds” (o). These categories have been used flexibly so that the “alkaloids” category includes nitrogen-containing, heterocyclic pseudo alkaloids and the “phenolics” category includes some compounds that are phenolic derivatives. The chemical complexity of these various groups of compounds is briefly reviewed below. The chemical complexity increases through covalent modification of many of these compounds through processes such as glycosylation, hydroxylation, methylation and epoxide and *N*-oxide formation. Further, new bioactive entities may be generated after ingestion of plant material through hydrolysis of peptide, ester and glycoside linkages.

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As indicated previously, space simply does not permit comprehensive presentation of the chemical structures of the thousands of plant defensive compounds dealt with in this book, although the structures of particular representative compounds or their related “parent” compounds are shown in the Appendix. Indeed there are clear advantages in attempting to “distil” molecular complexity down to readily comprehended groupings of covalently linked moieties that can be described by succinct text. Thus, this approach enables common structural patterns of pharmacological interest to become more evident and reduces molecular complexity to a kind of functional “Lego” that can be appreciated by chemist and non-chemist readers alike. The conventions for the simplified skeletal structural presentations used in this chapter are summarized below.

Carbon chain length of alkyl groups or the total number of carbons in a molecule is represented as C_n , for example, ethane (C_2 ; CH_3-CH_3). When a C has four different substituents, as for example the α -C of α -amino acids, parentheses are used to define the substituents. Thus, the general structure of an α -amino acid is $^-OOC-CH(R)-NH_3^+$ and the structure of the α -amino acid alanine ($R=CH_3$) is $^-OOC-CH(CH_3)-NH_3^+$.

In describing ring structures, the total number of C atoms is given as C_n and the other atoms (typically O, S and N) are also indicated. Thus, tetrahydropyrrole (a fully reduced or saturated five-membered ring with four Cs and one N) is C_4N . In order to keep the descriptions as simple as possible the number of double bonds will not be specified but some attempt is made to address this by specifying particular structures (e.g. phenyl or benzene (Phe); isoquinoline (IQ); methylene dioxy ($-O-CH_2-O-$) (MD); and epoxy ($-O-$), pyrrole, pyridine, furan and pyran as themselves) and by blanket statements about groups of compounds (e.g. the sterols are polycyclics largely involving unsaturated, alicyclic ring structures).

Dihydro-, tetrahydro- and hexahydro- simplify to DH, TH and HH, respectively, as in dihydrofuran (DHfuran), tetrahydrofuran (THfuran; C_4O , a cyclic ether), tetrahydropyran (THpyran; C_5O , a cyclic ether) and hexahydropyridine (HHpyridine) (C_5N). Note that hexahydropyridine is completely reduced, that is, fully saturated. Cyclic esters (lactones) have a $-C-CO-O-C-$ moiety and are specified as C_nOL . Cyclic hemiacetals have a $-C-O-CH(OH)-C-$ grouping and are specified as C_nOH . Again, to keep structural representations simple, aliphatic side chains will be represented explicitly if they are small (e.g. ethyl, $-CH_2-CH_3$) or simply represented as C_n if large and complex.

In some cases, a group cross-links across a ring and hence creates two further rings; however, clarity dictates that in this case the cross-link is indicated simply in square brackets. Thus, a compound with a ring cross-linked with a N-methyl group would be denoted $X[-CH_3-N<]$, the epoxy analogue as $X[-O-]$ (or $X[\text{epoxy}]$) and the dimethylene cross-link analogue as $X[-CH_2-CH_2-]$.

In polycyclic structures, rings joined by C-C bonds are simply indicated thus: C_n-C_n or $C_n-C_n-C_n$. Thus the stilbene “skeleton” (Section 2, Appendix) could be “loosely” presented as $Phe-C_2-Phe$ or, precisely, as $Phe-CH=CH-Phe$. Where rings are fused and share two Cs, the fusion is indicated thus: $C_n|C_n$, for example, fully reduced naphthalene is precisely $C_6|C_6$. When three Cs are shared in a polycyclic fusion, the symbol $||$ is employed. When only one C is shared, the notation is $C_n\cdot C_n$. When more than two rings are fused, the structure could be “linear” or “angular” and it is assumed (unless stated otherwise) that the angular “foetal” orientation is the default situation. Thus, anthracene is $Phe|Phe|Phe$ (linear), phenanthrene is $Phe|Phe|Phe$ (angular) and the fully reduced entities are $C_6|C_6|C_6$ (linear) and $C_6|C_6|C_6$ (angular), respectively (see Appendix, Section 4).

Further complexity arises when, for example, three rings are all fused with each other (as opposed to the linear and angular arrangements indicated above) and share a common C.

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A simple example is the tricyclic aromatic phenalene, this arrangement being indicated by an asterisk: Phe*|Phe*|Phe* (or C6*|C6*|C6* in the case of the fully hydrogenated entity). In very few and very complicated structures multiple “shared Cs” are indicated by * and *’ superscripts (or, in the most complicated example to be encountered here, by 3*, 3*’ and 4* superscripts to indicate two Cs each shared by three rings and another C shared by four rings).

Unsaturated heterocyclic ring compounds to be encountered include thiophene (C4S), pyrrole (C4N), furan (C4O), pyran (C5O), pyrylium (C5O⁺) and pyridine (C5N). When alkaloid rings are fused and share a N, a similar system is used of a vertical line to indicate sharing of two C atoms, * to indicate a C shared with three rings and N# to indicate sharing of a N (thus a pyrrolizidine ring involving two fused five-membered rings sharing a C and a N is represented as C4N#|C4N#). Just as we describe 2-hydroxy, 3-hydroxy and 4-hydroxy benzoic acid as *ortho* (*o*-), *meta* (*m*-) and *para* (*p*-)benzoic acid, we can conveniently apply the same nomenclature to rings containing more than one N. Thus the unsaturated six-membered ring compounds 2-azapyridine, pyrimidine and pyrazine are denoted here as *o*C4N2, *m*C4N2 and *p*C4N2, respectively. The frequently encountered five-membered ring compound imidazole can be simplistically denoted as C3N2, the Ns being separated by a C. The important heterocyclic “parent” compound purine found in RNA and DNA is pyrimidine|imidazole (or *m*C4N2|C3N2).

The “rules” outlined above conveniently provide simple, succinct representations of complex polycyclic compounds and avoid the problem of the reader being “unable to see the wood for the trees”. The structures of key “parent” ring compounds to be encountered in this book are presented in the Appendix together with the structures of some representative alkaloids, phenolics, terpenes and other compounds. Before sketching the complexity of plant bioactive compounds and their modes of action, it should be noted that many such compounds act as “agonists” by mimicking the action of particular hormones or neurotransmitters at specific receptors whereas others may act as “antagonists” by simply competing for binding to the receptor and thus blocking the normal receptor-mediated response.

1.6 Plant alkaloids

The alkaloids are basic compounds in which an N atom is typically part of a heterocyclic ring but in some cases is merely a substituent of an alicyclic or aromatic ring system (as for example with colchicine, some peptide alkaloids and some Amaryllidaceae alkaloids). Various N-based heterocyclics such as the purine and pyrimidine bases of DNA and RNA (see Chapter 2) and the methylxanthine purine derivatives variously found in tea and coffee (caffeine, theobromine and theophylline) are sometimes referred to as pseudoalkaloids and for consistency will be included as alkaloids in this classification. Indeed all plant heterocyclics with a ring N will be conveniently lumped in with the alkaloids in the tables for didactic simplicity and consistency.

Alkaloids are widespread in plants and include some very well-known poisons (notably coniine and strychnine), hallucinogens (morphine, cocaine and muscimol) and other potentially lethal compounds that are nevertheless used in medical practice (e.g. atropine, codeine, colchicine and morphine). As indicated by the preliminary snap-shot above, alkaloids typically have names ending in -ine and which are often related to the plant source or properties. Thus, morphine was named after Morpheus (the God of sleep) and coniine derives from *Conium maculatum* (hemlock), the plant used in the judicial murder of Socrates (399 BC). Various chemical tests for alkaloids are used as preliminary indicators of alkaloid presence in crude plant extracts. Finally, it should be noted that alkaloids can also exist as *N*-oxides of the alkaloid base.

i. Monoterpene alkaloids are formed from iridoid monoterpene lactone glycoside precursors (with ten carbon chain (C₁₀) deglycosylated aglycones) such as loganin (C5|C5O, C5|pyran) and seco-loganin (C5O, DHpyran) by condensation with ammonia (NH₃). Indeed such reactions may occur during isolation in the presence of ammonium hydroxide (NH₄OH). Monoterpenes in turn derive biosynthetically from two isoprene (C₅) (2 × C₅ = C₁₀) precursors. Examples include the bicyclic monoterpenes tecomine (a hypoglycaemic antidiabetic) from *Tecoma stans* (Bignoniaceae) and the anti-inflammatory compounds gentianamine, gentianadine and gentianine (pyridine|C5L) (from *Gentiana* species (Gentianaceae)). The tricyclic *N*-(*p*-hydroxyphenethyl)actinidine (*p*-OH-Phe-CH₂-CH₂-N-pyridine|C5) from *Valerian officinalis* (valerian) (Valerianaceae) is an acetylcholinesterase (AChE) inhibitor.

ii. Sesquiterpene alkaloids deriving from the sesquiterpene farnesol (3 × C₅ isoprene units = C₁₅) include α-nupharidine (furan-C5N#|C5N#) and thiobinupharidine (furan-C5N#|C5N#·C4S·C5N#|C5N#-furan) from *Nuphar* species (Nymphaeaceae) rhizomes used for sedative and narcotic extracts.

iii. Diterpene alkaloids derive from diterpene (4 × C₅ isoprene units = C₂₀) precursors and include some very toxic compounds, for example, heart-slowing, blood pressure-lowering, voltage-gated Na⁺ channel activators from *Aconitum* (wolfsbane) species (Ranunculaceae) (aconitine, aconifine, delphinine, falaconitine, hypaconitine, indaconitine, jesaconitine, lappaconitine, lycoctonine, mesaconitine and pseudoaconitine) and neuromuscular blockers with curare-like effects from *Delphinium* species (Ranunculaceae) (condelphine, elatine and methyalaconitine), the representative compound of this group being aconitine ([-CH₂-N(CH₂CH₃)-CH<]C6|C7|C5|C6-O-CO-Phe]). Further diterpene alkaloids include the cardiotoxic, digitalis-like Na⁺, K⁺-ATPase inhibitors from *Erythrophleum guineense* (Fabaceae) (cassaine, cassaidine and erythrophleguine) (C6|C6|C6-alkylamine); and ryanodine (methylene-[pyrrole-CO-O-C5*|C4O*,'|C5*,'|C6*']) from *Ryonia speciosa* (Flacourtiaceae) (a ligand that modulates the endoplasmic reticulum “ryanodine receptor” Ca²⁺ channel that is variously opened in excited skeletal muscle, cardiac and neuronal cells).

iv. Steroid alkaloids derive from triterpene (6 × C₅ isoprene units = C₃₀) precursors. These generally toxic compounds include some AChE inhibitors from *Lycopersicon* (tomato) and *Solanum* (potato) species (Solanaceae) such as demissidine (C6|C6|C6|C5|C4N#|C5N#) and tomatidine (C6|C6|C6|C5|C4O·C5N) and their glycosylated derivatives (demissine and tomatine, respectively). A number of steroid alkaloids are teratogenic (cause embryological defects) including some from *Veratrum* species (Liliaceae) namely 3-*O*-acetyljervine, *N*-butyl-3-*O*-acetyl-12β, 13α-dihydrojervine, cyclopamine, cycloposine, *O*-diacetyljervine, 12β,13α-dihydrojervine, jervine (C6|C6|C5|C6·C4O|C5N), *N*-formyljervine, *N*-methyljervine and protoverine (C6|C6|C5|C6|C5N#|C5N#). Related teratogens from *Solanum* tubers include the glycosides α-chaconine, α-solanine and solasonine and their aglycones (deglycosylated entities) α-chaconidine (C6|C6|C6|C5|C4N#|C5N#), solanidine (C6|C6|C6|C5|C4N#|C5N#) and solasodine (C6|C6|C6|C5|C4O·C5N), respectively.

v. Peptide alkaloids or cyclopeptides have macrocyclic 13–15-membered rings involving several peptide (-CO-NH-) links. Cyclopeptides have been isolated from various sources, notably *Ceanothus* and *Zizyphus* species (Rhamnaceae) (e.g. Zizyphine A). These 0.6 kDa cyclopeptides are synthesized by a non-ribosomal mechanism in contrast to the much larger 2–3 kDa protease inhibitory cyclotides that are cyclic peptides synthesized as proproteins on

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ribosomes (see Chapter 13) (and as such are considered under “other” plant defensive compounds in Section 1.9).

vi. Betalain alkaloids are non-toxic, water soluble, purple or yellow coloured plant pigments deriving from the amino acid derivative 3,4-dihydroxyphenylalanine (dopa, 3-hydroxytyrosine). Dopa rearranges to yield betalamic acid (a tetrahydropyridine, C₅N) and can form a further derivative cyclodopa (a dihydroindole, Phe|C₄N). Betalamic acid condensation with cyclodopa yields purple betacyanins that can be further modified by glycosylation. Betalamic acid condensation with aliphatic amino acids yields yellow betaxanthins. *Beta vulgaris* (beetroot) (Chenopodiaceae) contains betalamic acid, purple betacyanins (namely betanidin, DHpyridine=CH-CH=(N)-indole) and glycosylated betanidin derivatives (betanin and betanin sulfate) and yellow betaxanthins (vulgaxanthins I and II, DHpyridines). A relatively common inability to degrade these compounds gives rise to the coloured urine of “beeturia”. The gorgeous purple of *Bougainvillea* species (Nyctaginaceae) bracts derives from betalains such as the glycosylated betanidin bougainvillein-r-1.

vii. Indole alkaloids include a variety of polycyclic compounds involving the bicyclic basic compound indole (2,3-benzopyrrole, Phe|pyrrole, Phe|C₄N) and hence related to the amino acid tryptophan (Trp, 2-amino-3-indolylpropionic acid). Tryptophan decarboxylates to tryptamine (3-(2-aminoethyl)indole) which is thence converted to a variety of neuroactive compounds acting as agonists for serotonin receptors (5HT-Rs) including: bufotenine (*N,N*-dimethyl-5-hydroxytryptamine) (hallucinogenic); *N,N*-dimethyltryptamine (hallucinogenic); 5-hydroxytryptamine (5HT) (the excitatory neurotransmitter serotonin); 5-methoxy-*N,N*-dimethyltryptamine and gramine (3-(dimethylaminomethyl)indole) (agents causing *Phalaris* staggers in sheep); and the hallucinogens psilocin (3-dimethylaminoethyl-6-hydroxyindole) and psilocybin (6-phosphopsilocin) (from the *Psilocybe* “magic mushroom” species).

Further “simple” indoles include the faecal-smelling 3-methylindole and indole; and the cell wall-expanding plant hormone indole 3-acetic acid (IAA, auxin) and its precursors indole-3-acetonitrile and indole-3-carboxaldehyde. Tricyclic indoles include: harman (a DNA intercalator) (Phe|pyrrole|pyridine), the related hallucinogens harmine and harmaline (3,4-dihydroharmine) and chanoclavine (Phe*|pyrrole*|C₆*); the narcotic mesembrine (saturated indole-Phe); and the Fabaceae tricyclic AChE inhibitors eseramine (Phe|DHpyrrole|THpyrrole), eserine (physostigmine) (Phe|DHpyrrole|THpyrrole) and eseridine (Phe|DHpyrrole|C₄NO). Indican (3-(β-glucoside)indole) from *Indigofera* species (Fabaceae) and *Polygonum tinctorum* (Polygonaceae) oxidizes to yield the dark blue dye indigo. Similarly isotan B (a 3-hydroxyindole sugar ester) from *Isatis tinctoria* (Brassicaceae) (the woad used for body painting by the ancient Britons) is oxidized to yield indigo. A sulfur-containing *N*-methoxyindole derivative methoxybrassinin is a phytoalexin produced by *Brassica* species (Brassicaceae) in response to fungal infection.

A variety of more complex indole compounds derive from condensation of an indole precursor (deriving from tryptophan) and the aglycone of the C₁₀ monoterpene-based iridoid glycoside secologanin. These indole derivatives range from tetracyclics to compounds with as many as eleven rings. Some of these indole alkaloids include the nicotinic acetylcholine receptor (nACh-R) antagonists *C*-curarine (quaternary amine, eleven-ring, epoxy structure), sarpagine (Phe|pyrrole|C₅N#|C₅N#[methylene]) and toxiferine (eleven-ring quaternary amine); the glycine receptor antagonist strychnine (seven compactly fused Phe, C₄N#, C₅N#, C₆O, C₆, C₄N# and C₅N# rings); the muscarinic acetylcholine receptor antagonist usambarensine (Phe|pyrrole|C₅N#|C₅N#-CH₂-|pyridine|pyrrole|Phe); the anti-addictive and hallucinogenic glutamate receptor antagonist ibogaine (Phe|pyrrole|C₆N|C₆ N-methylene); the α-adrenergic and 5HT receptor antagonist yohimbine

(Phe|pyrrole|C5N#|C5N#|C6); the *Rauwolfia* species (Apocynaceae) antipsychotic and neurotransmitter transport inhibitor reserpine (Phe|pyrrole|C5N#|C5N#|C6-O-CO-Phe); and the anti-mitotic, tubulin-binding antitumour agents vinblastine and vincristine (Phe|pyrrole|C8N#|C5N#-Phe|pyrrole|C6*|C4N*#|C5N*#).

The hallucinogenic tetracyclic ergine (lysergic acid amide) (Phe*|pyrrole*|C6*|DHpyridine carboxamide) is found (like chanoclavine) in *Rivea corumbosa* and *Ipomoea* species (ololiuqui) (Convolvulaceae). Ergine is also found in the fungal ergot (*Claviceps purpurea*) that infects Poaceae (such as rye) as are a variety of hallucinogenic ergine derivatives namely the tetracyclic elymoclavine (a teratogen) and ergometrine and hallucinogenic compounds involving ergine substituted with polycyclic substituents namely ergocornine, ergocristine, ergocryptine, ergosine and ergotamine. The ergot alkaloids are hallucinogens that act as serotonin receptor (5HT-R) agonists and block prolactin release in herbivores. Ergot consumption has had a tragic history in susceptible regions of Western Europe and North America because consequent behavioural alteration was construed as “devil possession” leading to appalling torture and execution of as many as 100,000 victims as “witches”.

viii. Isoquinoline (IQ) alkaloids include a variety of bioactive compounds variously deriving from the amino acids phenylalanine and tyrosine and including IQ (benzo[c]pyridine) (Phe|pyridine; Phe|C5N) or its derivatives as part of their structure. In many cases the pyridine moiety is reduced to give tetrahydroisoquinoline and the benzo moiety is often substituted with a MD (–O–CH₂–O–) to form an additional ring. This very large group of alkaloids includes many compounds which are psychoactive and/or which affect muscle function. Chemically the IQ alkaloids are classified into structural subgroups named for key members (e.g. morphine-related morphinans) or structural complexity (e.g. simple IQs, ring-opened IQs and benzyloisoquinolines).

Many opium-derived and other IQs are psychoactive, the best known being the analgesic, addictive, narcotic, opium-derived morphinan alkaloids codeine and morphine (heroin being the semi-synthetic diacetate of morphine). The tertiary or quaternary amine structural component is important for the activity of some *Erythrina* alkaloids and bisbenzyloisoquinolines (notably the major curare component (+)-tubocurarine) as antagonists of the nACh-R involved in neuronal excitation of skeletal muscle. The planar disposition of some polycyclic benzophenanthridines enables intercalation (parallel interleaving) between the base pairs of DNA. A variety of naturally occurring and synthetic IQ compounds are protein kinase inhibitors.

The chemical and pharmacological complexity of the various IQ alkaloid sub-groups is sketched below with pharmacological and other attributes for each compound given in parentheses. Some of the better-known IQ alkaloids derive from opium, the dried milky latex from the unripe seed pods of *Papaver somniferum* (opium poppy) (Papaveraceae) and accordingly whether a substance is opium-derived is also indicated. Selected representative examples are given for each IQ alkaloid subgroup.

Simple isoquinolines (IQs) (–)-pellotine (IQ) (*Lophophora williamsii* (peyote) (Cactaceae) paralytic convulsant); (–)-salsolinol (IQ) (*Musa paradisiaca* (banana) (Musaceae) and *Theobroma cacao* (cocoa) (Sterculiaceae) dopamine antagonist linked to chocolate craving).

Ring-opened isoquinolines Narceine (MD–Phe–CH₂–CO–Phe amine) (opium-derived antitussive).

Aporphines Magnoflorine (IQ*|C6*|Phe) (a weak neuromuscular blocker of widespread occurrence); xylopinine (MD–IQ*|C6*|Phe) and xylopinine (Phe|C5N*|C5N*|Phe) (*Xylopi*a spp. (Annonaceae) α -adrenergic antagonists).

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Cularines Cularicine, cularidine, cularimine and cularine (Fumariaceae cytotoxics) (IQ*|C6O*|Phe-MD).

Morphinans (compactly fused Phe, C6, C5N, C6 and C4O rings) Codeine (opium-derived addictive, analgesic, antitussive, spasmolytic narcotic); morphine (opium-derived addictive, analgesic, antitussive, sedative, spasmolytic narcotic; heroin is the semi-synthetic diacetate); thebaine (non-analgesic, toxic, convulsant narcotic and semi-synthesis precursor of the anti-addiction drug naltrexone).

Phthalideisoquinolines α -narcotine and narcotoline (MD-IQ-C4L|Phe) (opium-derived spasmolytics); (+)-bicuculline (MD-IQ-C4L|Phe-MD) (*Corydalis* species (Papaveraceae) GABA receptor antagonist).

Rhoedans Rhoeadine (MD-Phe|C9ON|Phe-MD) (*Papaver rhoeas* (red poppy) (Papaveraceae) narcotic).

Pavines (-)-argemonine (Phe|C8[CH₃N<]|Phe) (*Argemone* species (Papaveraceae) weak analgesic).

Benzylisoquinolines (IQ-CH₂-Phe) Ethaverine and laudanosine (L-type Ca²⁺ channel blockers from opium); papaverine (cAMP phosphodiesterase inhibitor and smooth muscle relaxant derived from opium and *Rauwolfia serpentina* (Apocynaceae)); protopine (MD-Phe|C9N|Phe-MD); opium-derived smooth muscle relaxant); (+)-reticuline (opium-derived adrenergic receptor ligand and hair growth accelerant).

Emetines (Phe|C6N#|C6N#-CH₂-C5N|Phe) Emetine, emetamine and psychotrine (from *Cephaelis ipecacuanha* (Rubiaceae), ipecacuanha being used as an emetic and expectorant due principally to its content of emetine, a DNA-binding compound).

Protoberberines Berberine (umbellatine) (MD-Phe|C5N#|C5N#|Phe) (DNA-binding cytotoxic, adrenergic receptor antagonist and AChE inhibitor from *Berberis vulgaris* (Berberidaceae) and other plants).

Benzophenanthridines (IQ|Phe|Phe) Fagaronine (*Fagara xanthoxylum* (Rutaceae) DNA-binding antibacterial); palmatine (calystigine) (Berberidaceae and Papaveraceae adrenergic ligand and AChE inhibitor); sanguinarine (pseudochelerythrine) (MD-IQ|Phe|Phe-MD) (antibacterial, DNA-binding protein kinase inhibitor derived from *Chelidonium majus* (Papaveraceae) and opium); chelerythrine (MD-IQ|Phe|Phe) (*C. majus* (Papaveraceae) protein kinase inhibitor).

Bisbenzylisoquinolines (macrocylic or linear, formed by 2 benzylisoquinolines) (+)-tubocurarine (macrocylic) (acetylcholine (nicotinic) receptor antagonist and skeletal muscle relaxant; major component of *Chondrodendron* species (Menispermaceae) pareira bark-derived “curare” arrow poison); dauricine (linear) (Menispermaceae curare-like anaesthetic); rodiasine (macrocylic) (*Ocotea venenosa* (Lauraceae) curare-like skeletal muscle relaxant); cepharanthine (macrocylic) (*Stephania* species (Menispermaceae) antimycobacterial active against leprosy and tuberculosis).

Erythrina isoquinolines (Phe|C5N*#|C4N*#|C6*) Erysonine, erysotrine, erythratidine, α -erythroidine and β -erythroidine (*Erythrina* species (Fabaceae) curare-like neuromuscular blockers).

ix. Pyrrolidine alkaloids are based on tetrahydropyrrole (pyrrolidine, C4N), a five-membered ring containing one N atom, that is, the fully reduced derivative of pyrrole (Section 1, Appendix). Examples include cuscohygrine, hygrine and hygroline from *Erythroxylum coca* (coca) (Erythroxylaceae); the anti-schistosomiac cucurbitine from *Cucurbita moschata* (Cucurbitaceae); the antimicrobial tricyclic gerrardine from *Cassipourea* species (Rhizophoraceae); the renal osmoprotectant stachydrine (proline betaine) and 3-hydroxystachydrine from *Capparis* species (Capparidaceae); and the anti-inflammatory (-)-betonicine

(achillein or 4-hydroxyproline betaine) from *Betonica officinalis* (Lamiaceae) and *Achillea* species (Asteraceae).

DMDP (2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine) from *Derris elliptica* and *Lonchocarpus sericeus* (Fabaceae) and the related homoDMDP and several homoDMDP glycosides from *Scilla campanulata* and *Hyacinthoides non-scripta* (Hyacinthaceae) are variously active as inhibitors of particular glycosidases (enzymes cleaving glycosidic linkages in sugar oligosaccharides and polysaccharides). These polyhydroxypyrrolidine compounds are structurally similar to so-called furanose sugars (see Section 1.9 and Chapter 2).

Myosmine (3[2-pyrrolidinyl]pyridine) and nicotine (3[1-methyl-2-pyrrolidinyl]pyridine) and a variety of related pyrrolidinylpyridine compounds notably occur in *Nicotiana tabacum* (tobacco) (Solanaceae) and are discussed in Section xii under pyridine alkaloids.

x. Pyrrolizidine alkaloids (C4N# | C4N#) have an N atom shared between two fused five-membered rings. Some pyrrolizidine alkaloids are α -glycosidase inhibitors, namely (sources in parentheses) alexine (*Alexa leiopetala* (Fabaceae)), australine (*Castanospermum australe* (Fabaceae)) and casuarine (*Casuarina equisetifolia* (Casuarinaceae)). 1,2-Dihydroxy-3,5-dihydroxymethylpyrrolizidine (hyacinthacine B2) from *Scilla campanulata* (Hyacinthaceae), its C-5 epimer (hyacinthacine B1) from *Scilla campanulata* and *Hyacinthoides non-scripta* (Hyacinthaceae) and 3-hydroxymethyl-5-methyl-1,2,6,7-tetrahydroxyquinolizidine (hyacynthacine C1) from *Hyacinthoides non-scripta* all inhibit various glycosidases.

The highly poisonous *Senecio* species (ragworts) (Asteraceae) have a major role in global livestock poisoning through the elaboration of hepatotoxic pyrrolizidines including the angelic acid ester O⁷-angelylheliotridine and a variety of related compounds having a lactone (cyclic ester) ring (angularine, isatidine, jacobine, retrorsine, riddelline, senecionine, seneciophylline and senecivernine). Senecionine is a teratogen as are other pyrrolizidines (namely fulvine and heliotrine), these compounds having unwanted developmental effects connected with mutagenicity and toxicity. Other variously hepatotoxic and carcinogenic pyrrolizidines derive from *Crotalaria* species (Fabaceae) (including the lactones fulvine (a teratogen), monocrotaline, riddelline and usaramine); *Heliotropium* species (Boraginaceae) (heliosupine, heliotridine, heliotrine (a teratogen), indicine, intermedine, lasiocarpine, lycopsamine and supinine); and from *Symphytum* (comfrey) species (Boraginaceae) (echimidine, heliosupine, lasiocarpine, lycopsamine and symlandine). The diester echimidine also occurs in *Echium plantagineum* (Paterson's curse or Salvation Jane) (Boraginaceae), a pretty plant that covers 33 million hectares of Southern Australia from Western Australia to northern New South Wales and costs the Australian livestock industry US\$125 million per annum.

xi. Indolizidine alkaloids (C5N# | C4N#) have an N atom shared between a five-membered ring and a six-membered ring. Castanospermine from *Castanospermum australe* (Fabaceae) inhibits α - and β -glucosidases and swainsonine from *Swainsona* species (Fabaceae) inhibits α -mannosidase. The indolizidine slaframine (produced on *Trifolium repens* (red clover) (Fabaceae) by the fungal pathogen *Rhizoctonia leguminicola*) is a muscarinic acetylcholine receptor (mACh-R) agonist (i.e. an acetylcholine "mimic" on such receptors) and is hence a parasympathetic stimulant causing salivation and diarrhoea in livestock.

xii. Pyridine and piperidine alkaloids. Piperidine alkaloids are based on piperidine (hexahydropyridine) which has a six-membered saturated ring including an N atom (C5N). An example of a simple pyridine compound is trigonelline (*N*-methylpyridine 3-carboxylic acid), a hypoglycaemic compound from *Trigonella foenum-graecum* (fenugreek), *Medicago sativa* (alfalfa) (Fabaceae) and *Coffea* species (Rubiaceae). Piperidine- and pyridine-based alkaloids often have more than one ring and the degree of saturation can vary. Thus, (–)-anabasine (3-(2-piperidinyl)-pyridine) involves a piperidine (six-membered ring) linked to

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pyridine and is an analogue of nicotine (3[1-methyl-2-pyrrolidinyl]pyridine) which involves a pyrrolidine (five-membered ring) linked to pyridine.

Myosmine (3[2-pyrrolidinyl]pyridine) and nicotine (3[1-methyl-2-pyrrolidinyl]pyridine) (Section 1, Appendix) and a number of related bioactive alkaloids occur in *Nicotiana tabacum* (tobacco) (Solanaceae) and variously in other Solanaceae such as *Duboisia* species. Nicotine and the related tobacco compounds nicotyrine and (–)-nornicotine are agonists (neurotransmitter “mimics”) of the so-called (nicotine binding) nACh-R involved in neurotransmission and in neuromuscular transmission for skeletal muscle. The extraordinary addictiveness of nicotine derives from nACh-R agonists causing dopamine release and activating the mesolimbic dopamine system yielding “reward” effects. The antidepressant (–)-cotinine is the major nicotine metabolite in humans and a nicotinic agonist.

(–)-Anabasine (3-(2-piperidinyl)-pyridine) from *Nicotiana* and *Duboisia* species (Solanaceae) is an nACh-R agonist used to discourage tobacco smoking as is the *N*-methylated tricyclic piperidine (–)-lobeline from *Lobelia* species (Campanulaceae). Lobeline-related compounds from *Lobelia* species include the bicyclic *N*-methyltetrahydropyridines isolobinine and lobinine and the tricyclic *N*-methylpiperidines lobelanine and lobelanidine. Anabasine-related compounds include anatabine (2-(3-pyridyl)-1,2,3,6-tetrahydropyridine) from *N. tabacum* and (+)-ammodendrine (*N*-acetyltetrahydroanabasine) from *Ammodendron* and *Sophora* species (Fabaceae).

Apart from nicotine, the best-known piperidine alkaloid is (+)-coniine (2-propylpiperidine) from *C. maculatum* (hemlock) (Apiaceae) and *Sarracenia flava* (carnivorous pitcher plant) (Sarraceniaceae). Hemlock was drunk in the judicial murder of Socrates (Athens, 399 BC). Coniine is a paralysis-inducing nACh-R agonist as are (+)-*N*-methylconiine and γ -coniceine from the same source, the latter also deriving from *Aloe* species (Liliaceae). Coniine and γ -coniceine are teratogenic as well as being highly toxic. Other piperidine-related teratogens include (–)-anabasine from *Nicotiana* species, mimosine from *Leucaena leucocephala* and *Mimosa pudica* (Fabaceae) and (+)-ammodendrine, *N*-methylammodendrine and *N*-acetylhystrine from toxic *Lupinus* (lupine) species (Fabaceae) that can give rise to “crooked calf disease”.

Seeds of *Areca catechu* (betel nut) (Palmae) contain the simple *N*-methyltetrahydropyridine 3-carboxylic acid (*N*-methyl- Δ^3 -tetrahydronicotinic acid) arecaidine and arecoline (arecaidine methyl ester) (Section 1, Appendix) that are mACh-R agonists and accordingly parasympathetic stimulants. Betel nut also yields guvacine (Δ^3 -tetrahydronicotinic acid) that is an anti-epileptic GABA transport inhibitor. Conversely the *N*-methyl dihydropyridone derivative ricinine from seeds of *Ricinus communis* (castor seed) (Euphorbiaceae) is a stimulatory agonist acting at the benzodiazepine site of the GABA(A) receptor.

The simple piperidine pelletierine from *Punica granatum* (pomegranate) (Punicaceae) and *Duboisia myoporoides* (Solanaceae) is an anthelmintic. The simple piperidine derivatives deoxymannojirimycin (DMJ) and deoxynojirimycin (DNJ) from *Lonchocarpus* species (Fabaceae) are glycosidase inhibitors because they are structurally similar to the pyranose (six-membered ring) sugar moieties of the glycosidase disaccharide substrates.

xiii. Quinoline alkaloids are based on a benzo[b]pyridine (quinoline) nucleus (Phe|pyridine) and are biosynthetically derived from 2-aminobenzoic acid (anthranilic acid), a key intermediate in the biosynthesis of the indole-containing amino acid tryptophan. Quinoline alkaloids can be simple or composed of a quinoline nucleus fused with other moieties to yield polycyclic derivatives. Thus, quinoline fused with benzene is acridine (dibenzo[b,e]pyridine) (Phe|pyridine|Phe); furoquinolines have a fused furan ring (a five-membered ring with an O) (Phe|pyridine|C4O); and pyranoquinolines have a fused pyran ring (a six-membered ring with an O) (Phe|pyridine|C5O). Quinazolines have two N atoms

in the same ring. The anticancer quinoline-based compound camptothecin has a structure involving fused quinoline, indolizidine and pyran lactone rings. Simple and more complex quinolines can have an additional ring formed by an MD substituent. The structural and pharmacological complexity of quinoline alkaloids is sketched below.

Simple quinolines (Phe|pyridine) include the *Cinchona* and *Remijia* species (Rubiaceae) antimalarials cinchonidine (α -quinidine), cinchonine (a stereoisomer of cinchonidine), hydroquinidine (quinotidine), quinine and quinidine (β -quinine), these compounds all having a quinuclidinemethanol (1,4-ethylpiperidinylmethanol) substituent. Quinine is also an extremely bitter tasting compound. Of a range of other simple quinolines, eduline and its *O*-methyl derivative japonine, both from *Orixa japonica* (Rutaceae), are notable for being intestinal smooth muscle relaxants and echinopsine from *Echinops* species (Asteraceae) is psychotropic.

Furoquinolines (Phe|pyridine|C4O) notably derive from the Rutaceae and include a variety of antibacterial and antifungal compounds. Thus, *O*-methylptelefolonium and pteleatine from *Ptelea trifoliata* (Rutaceae) and veprisinium from *Vepris louisii* (Rutaceae) are antimicrobial. Ribalinium from *Ruta graveolens* (Rutaceae) is anti-mycobacterial. The Rutaceae furoquinolines dictamnine(dictamine), γ -fagarine, haplopine, isodictamnine, kokusaginine, maculosidine and skimmianine (β -fagarine) are phototoxic antimicrobials. Dictamnine, γ -fagarine (8-methoxydictamnine) and skimmianine (7,8-dimethoxydictamnine) from *Ruta graveolens* (rue) (Rutaceae) are photomutagenic, forming DNA monoadducts in a light-dependent process and thus contributing to the phototoxic phytodermatitis of rue. Confusameline, kokusaginine and skimmianine (β -fagarine) are 5-hydroxytryptamine (5HT, serotonin) receptor (5HT-R) antagonists and platelet aggregation inhibitors. Haplophyllidine and robustine are psychoactive.

Pyranoquinolines (Phe|pyridine|C5O) include the antimicrobials flindersine and *N*-methylflindersine from *Flindersia* and *Glycosmis* species (Rutaceae).

Acridines (Phe|pyridine|Phe) include arborinine from *Ruta graveolens* and other Rutaceae (a spasmolytic and A1 adenosine receptor antagonist) and the pyranoquinoline acronycine (with cytotoxic and antitumour activity) from *Acronychia* species and *Melicope leptococca* (Rutaceae) and which has become a useful lead compound for the synthesis of other anti-cancer compounds. A variety of synthetic acridines are DNA binding anticancer compounds.

Quinazoline alkaloids (Phe|C4N2) include a variety of bioactive compounds from a number of plant families. Febrifugine (Phe|C4N2-C₃-HHpyridine) and the hemiacetal isofebrifugine (Phe|C4N2-CH₂-C4OH-HHpyridine) are potent antimalarials from *Dichroa febrifuga* and *Hydrangea* species (Saxifragaceae). The quinazolines deoxypeganine, deoxyvasicinone and peganine (Phe|C4NN#|C4N#) from *Peganum* species (Zygophyllaceae) are AChE inhibitors. The structurally related vasicinol (7-hydroxypeganine) from *Adhatoda vasica* (Acanthaceae) and *Sida cordifolia* (Malvaceae) is also an AChE inhibitor and the related vasicinone from the same sources is bronchodilatory. Tryptanthrine (couroupitine A) (Phe|C4NN#|C4N#|Phe) from *Strobilanthes cusia* (Acanthaceae), *Isatis tinctoria* (woad) (Brassicaceae) and *Polygonum tinctorum* (Polygonaceae) is a potent inhibitor of inducible cyclooxygenase (COX) 2, inhibits inducible nitric oxide synthase (iNOS) expression and is an agonist of the xenobiotic-responsive element-interacting aryl hydrocarbon receptor (dioxin receptor).

Camptothecins. The alkaloid camptothecin from *Camptotheca acuminata* (Nyssaceae) and *Mappia foetida* (Icacinaceae) has a pyranoindolizoquinoline structure (Phe|pyridine|C4N#|C5N#|C5L) involving the fusion of quinoline (Phe|pyridine), indolizidine (C4N#|C5N#) and C5 lactone (C5L) rings. Camptothecin is a topoisomerase I inhibitor and is a potent cytotoxic and antitumour compound that is used clinically as an anticancer

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compound and has been the “lead compound” for the synthesis of a variety of anticancer compounds such as irinotecan, topotecan and 9-aminocamptothecin.

xiv. Tropane alkaloids are alicyclic compounds containing an N atom and structurally based on the bicyclic aliphatic tropane (8-methyl-8-azabicyclo[3.2.1]octan-3- α -ol) (C7[CH₃-N<]), which can be simply viewed as a cycloheptane (C7) cross-linked by a methylamino (CH₃-N<) group. Pseudotropine is the corresponding 3- β -ol isomer, nortropine lacks the *N*-methyl and tropane lacks the 3-hydroxy. Ecgonine (tropine 2-carboxylic acid) is the precursor of the important narcotic cocaine (ecgonine benzoate methyl ester). The highly toxic anticholinergic atropine (tropine tropate), a potent antagonist of mACh-Rs, is an ester of tropine and tropic acid (α -(hydroxymethyl)phenylacetic acid) (Section 1, Appendix). The tropane moiety derives biosynthetically from ornithine and the tropic acid from the amino acid phenylalanine.

Tropine derivatives are typically found in certain highly poisonous Solanaceae species, most notably *Atropa belladonna* (deadly nightshade), *Datura stramonium* (thornapple), other *Datura* species, *Duboisia myoporoides* (corkwood elm), *Hyoscyamus niger* (henbane) and other *Hyoscyamus* species. Other sources include *Convolvulus* species (Convolvulaceae), *Erythroxylum coca* (coca), other *Erythroxylum* species (Erythroxylaceae) and *Bruguiera species* (Rhizophoraceae).

Hyoscyamine (duboisine) and the racemate atropine are mACh-R antagonists and a number of atropine derivatives also have this property, namely anisodamine (6 β -hydroxyhyoscyamine), 7 β -hydroxyhyoscyamine, hyoscyne (6,7-epoxyhyoscyamine or scopolamine), benzoyltropein (tropine benzoate), littorine (tropine α -hydroxyphenylpropionate), tigloidine (pseudotropine tiglate) and tropacocaine (pseudotropine benzoate). The further derivatives apoatropine (α -dehydrohyoscyamine) and tropine are very toxic.

The stimulant narcotic cocaine (benzoylmethylecgonine) from *Erythroxylum coca* (coca) and other *Erythroxylum* species (Erythroxylaceae) inhibits serotonin (5HT) and dopamine reuptake. Related bioactive tropane alkaloids from *Erythroxylum* species include benzoylecgonine, benzoyltropeine (tropine benzoate), cinnamoylcocaine (cinnamoylmethylecgonine) and ecgonine.

A variety of other tropane alkaloids have been isolated of which the most important is anatoxin-A, a highly toxic nACh-R agonist and depolarizing neuromuscular blocking agent deriving from *Anabaena* cyanobacterium species that can contaminate inland waters.

xv. Quinolizidine and Lycopodium alkaloids. Quinolizidine alkaloids have two fused six-membered rings sharing an N atom, the simplest such entity being the saturated two-ring compound quinolizidine (C5N#|C5N#). More complex entities are formed by the addition of further N-containing rings through addition of substituents such as -CH₂-NH-CH₂-, -(CH₂)₃-NH- and -(CH₂)₄-NH- as well as other ring and “side chain” substituents. The major source of quinolizidine alkaloids are the legumes (Fabaceae). However, various quinolizidine and related alkaloids have been isolated from *Lycopodium* species (club mosses) (Lycopodiaceae).

Legume quinolizidines. The simplest legume quinolizidine is the toxic lupinine (quinolizidine-1-methanol) from *Lupinus* (lupine) species as well as from *Anabasis aphylla* (Chenopodiaceae). Quinolizidine-based legume toxicity is a significant agricultural problem. Other toxic legume quinolizidines (other attributes in parentheses) include anagryne (C5N#|C5N#||C5N#|CN5# i.e. quinolizidine||quinolizidine) (teratogen), cytosine (C5N#|C5N#||C5N) (nACh-R agonist, hallucinogen and teratogen), *N*-methylcytosine (nACh-R agonist and teratogen), (-)-sparteine (lupinidine) (quinolizidine||quinolizidine)

(which blocks voltage-gated Na⁺ channels and ATP-regulated K⁺ channels), lupanine (2-oxo-11 α -sparteine) (weak sedative and Na⁺ channel blocker), and 13-hydroxylupanine (anti-arrhythmic and hypoglycaemic). Sophoramine (C5N*#|C5N*#||C5N*#|CN5#) is also anti-arrhythmic. (+)-Matrine (C5N*#|C5N*#||C5N*#|CN5#) inhibits lipopolysaccharide-induced cytokine expression in immune cells and is anti-nociceptive by acting through μ and κ opiate receptors. (+)-Allomatrine (the C-6 epimer of (+)-matrine) is anti-nociceptive, acting through κ opiate receptors.

Lycopodium alkaloids. The *Lycopodium* (or club moss) alkaloids include quinolizidine alkaloids in which N atoms are variously shared between two or three six-membered rings. The toxic alkaloid lycopodine (C5N*#|C5N*#||C6*[isobutyl<]) is a tetracyclic alkaloid with an N shared between two six-membered rings. The toxic alkaloid carolinianine (C5N*#|C5N*#||C5N*#N#|CN5#) is a tetracyclic with two Ns shared between three and two six-membered rings, respectively. Other such alkaloids, such as lycodine (C5N|C6[isobutyl<]|C5N), have Ns that are associated with only one ring.

xvi. Amaryllidaceae alkaloids derive from the bulbs of plants such as amaryllis or belladonna lily (*Amarillus belladonna*), daffodil and narcissus (*Narcissus* species) and snowdrop (*Galanthus nivalis*). These alkaloids are typically tetracyclic with a five- or six-membered N-containing ring as a common feature, many having a further ring created by an MD bridge (–O–CH₂–O–).

Many Amaryllidaceae alkaloids are toxic and are of interest as anticancer and selective anti-protozoal agents because of their cytotoxicity. Examples (some source genera in parentheses) include: the cytotoxic antimalarials augustine (MD–Phe|C5N[OH–CH–CH₂<]|C6) (*Crinum*), crinamine (MD–Phe|C5N[OH–CH–CH₂<]|C6) (*Crinum*), lycorine (MD–Phe|C5N|C6) (*Brunsvigia*, *Lycoris*), 1,2-di-*O*-acetyllycorine (*Brunsvigia*); the related antineoplastic cytotoxic alkaloids ambelline (MD–Phe|C5N[OH–CH–CH₂<]|C6), acetylcaranine and anhydrolycorinium (*Amaryllis*); the cytotoxics tazettine, hippeastrine (MD–Phe|C5L|C6|C4N) and haemanthidine (*Hymenocallis*); the specific anti-microsporidium (*Encephalitozoon intestinalis*) antimitotics pancratistatin (MD–Phe|C5N|C6) (*Pancreatum*) and 7-deoxynarciclasine (*Narcissus*); and the further toxic alkaloids 3-acetylnerbowdine (*Nerine*), candimine (MD–Phe|C5L|C6|C4N) (*Hippeastrum*) and caranine (MD–Phe|C5N*#|C4N*#|C6*) (*Amaryllis*).

The phenanthridine alkaloid lycorine (narcissine, galanthidine) (MD–Phe|C5N|C6) has a widespread occurrence and inhibits protein synthesis. Like lycorine, the structurally similar alkaloids dihydrolycorinine, haemanthamine, narciclasine, pretazettine and pseudolycorine also inhibit protein synthesis at the level of peptide bond formation. Galanthamine (lycorimine) (Phe*|C6N**'|C4O**'|C6*'), from daffodil bulbs but also of widespread occurrence, is both a nACh-R allosteric modulator and an inhibitor of AChE. Galanthamine is clinically employed in the treatment of Alzheimer's disease (dementia linked to deficiency in acetylcholine-mediated signalling in the central nervous system).

xvii. Other polycyclic alkaloids not covered above include the following groups of alkaloids:

Benzofuranone tetrahydropyrrole alkaloids. Shihunidine (Phe|C4OL·C4N) and shihunine (Phe|C4OL·C4N) from *Dendrodium* species are inhibitors of the Na⁺, K⁺-ATPase (sodium pump).

Benzoxazolinone alkaloids include some types of phytoalexins (compounds produced by plants in response to microbial infection), examples including *Avena sativa* (oats) (Poaceae) avenalumin I (β OH–Phe|C4NOL–CH=CH–Phe– β OH), *Triticum aestivum* (wheat)

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and *Zea mays* (maize) (Poaceae) 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA) (Phe|C4NO) and DIMBOA glucoside and *Dianthus caryophyllus* (carnation) (Caryophyllaceae) dianthalexin (Phe|C4NOL-Phe).

Cephalotaxine alkaloids are based on cephalotaxine which has a pentacyclic system including a seven-membered ring and a five-membered ring sharing an N atom (MD-Phe|C6N*#|C4*N#|C5*). Cephalotaxine alkaloids include the cytotoxic, anticancer protein synthesis inhibitors cephalotaxine, harringtonine and homoharringtonine.

Imidazole-containing alkaloids related to the amino acid histidine include histamine (imidazole-4-ethanamine) (C3N2) (from numerous plant sources) and casimiroedine (an *N*-glycoside), *N*-methylhistamine and *N,N*-dimethylhistamine from *Casimiroa edulis* (Rutaceae) that are hypotensive through interaction with histamine receptors.

Imidazolylmethylfuranones include the parasympathetic agonist pilocarpine (C4OL-CH₂-C3N2) and pilosine (carpidine) (Phe-CH₂-C4OL-CH₂-C3N2) from *Pilocarpus* species (Rutaceae), narcotic compounds that are agonists of muscarinic acetylcholine receptors (mACh-Rs) and accordingly stimulate salivation and tear secretion.

Isoxazole alkaloids involve a five-membered unsaturated ring having an O and an N atom (C3NO). Isoxazole alkaloids notably include ibotenic acid (C3NO-CH(NH₃⁺)COO⁻) and muscimol (OH-C3NO-CH₂-NH₂) from the reputedly aphrodisiac, hallucinogenic and extremely toxic *Amanita* species mushrooms. Ibotenic acid (= α-amino-3-hydroxy-5-isoxazoleacetic) is neurotoxic and an agonist of excitatory NMDA- and non-NMDA ionotropic glutamate receptors and of inhibitory ionotropic glutamate receptors. Muscimol (3-hydroxy-5-aminomethyl-isoxazole) is an hallucinogenic GABA(A) receptor agonist.

Phenanthroindolizidine and phenanthroquinolizidine alkaloids involve a phenanthrene (Phe|Phe|Phe (angular)) fused with an indolizidine or quinolizidine, respectively. The phenanthroindolizidines tylophorine (phenanthrene|C5N#|C4N#) and tylocrebrine (phenanthrene|C5N#|C4N#) and the phenanthroquinolizidine cryptopleurine (phenanthrene|C5N#|C5N#) are toxic, cytotoxic protein synthesis inhibitors. The phenanthroindolizidines tylophorine and pergularinine are thymidylate synthase inhibitors.

Taxine alkaloids are complex polycyclic compounds in which N is present but not as an integral part of a ring. The taxines are found in *Taxus* (yew) species (Taxaceae). Taxine A (C6|C10|C6-O-CO-CH(OH)-CH(N(CH₃)₂)-Phe) is substantially responsible for yew toxicity. The related polycyclic amide taxol (paclitaxel) and the closely related docetaxel are tubulin-binding, antimetabolic cytotoxics that are used clinically as anticancer drugs. A variety of taxines have been isolated from *Taxus* species.

Other alkaloids include: the **quinine-like chloroalkaloids** (C5·ChloroC5*·*′ (-CH₂*CH₂-NH*′-)|C6*·*′) acutumine, acutumidine, dauricumine and dauricumidine from *Menispermum dauricum* (Menispermaceae); **tricyclic pyrazole alkaloids** (THpyrrole#|C3NN#-Phe) from *Newbouldia laevis* and *Withania somnifera* (Solanaceae) including withasomnine, newbouldine and the 4′-hydroxy and 4′-methoxy derivatives of these alkaloids; **pyrrolidinoquinolines** variously from *Calycanthus* species (Calycanthaceae) and *Psychotria* species (Rubiaceae) including calycanthine (Phe|C5N*·*′(||C4N*)|C5N*·*′(||C4N*)|Phe), isocalycanthine, and tetrahydroisocalycanthine; **pyrazine alkaloids** (pC4N2), namely the antibiotic mycotoxin aspergillilic acids from *Aspergillus* species (fungi); **polycyclic quinolizidine lactones** include the anti-inflammatory prostaglandin synthetase inhibitors cryogenine (Phe|C11OL(Phe|)|C5N#|C5N#) and nesodine from *Heimia* species (Lythraceae); **various diverse peptide macrocyclic alkaloids** including the DNA-binding RNA- and DNA-polymerase inhibitor pithecolobine from *Pithecolobium*

saman (Fabaceae) and the potent cytotoxic, antitumour, antitubulin compounds maytansine (from *Maytenus* species (Celastraceae)) and cryptophycin A (a cyclic depsipeptide from the cyanobacterium (blue-green alga) *Nostoc*); **colchicine-related** antimitotic alkaloids variously from *Androcymbium*, *Colchicum* and *Gloriosa* species (Liliaceae) and including androcymbine, *O*-methylandrocymbine, colchicine (Phe|C7(NH-CO-CH₃)|C7) and demecolcine (colchicine being used to treat gout); and **securinine** (in which piperidine shares an N with a pyrrolidine (five-membered ring) and a seven-membered ring) (C5N#|C6N#(-CH₂-)|C4OL); securinine derives from *Securinega suffruticosa* (Euphorbiaceae) and *Securidaca longepedunculata* (Fabaceae) and is a GABA(A) receptor antagonist.

xvii. Pseudoalkaloids. As indicated previously, for the sake of consistency and simplicity, all heterocyclics with a ring N have been included here in the category of “alkaloids” including a variety of “universal” biochemically important derivatives of pyrimidine (a six-membered ring with two Ns) and purine (pyrimidine fused with a five-membered ring with two Ns). Unsaturated pyrimidine (*m*C4N2) and purine (*m*C4N2|C3N2; pyrimidine|imidazole) derivatives are involved in RNA and DNA structure and biosynthesis as well as related compounds used in signalling and for “defensive” purposes.

The bases found in RNA (ribonucleic acid) are the purine heterocyclics adenine (6-aminopurine) and guanine (2-amino-6-oxypurine) and their “complementary” pyrimidine bases uracil (2,4-dioxypyrimidine) and cytosine (2-oxy-4-aminopyrimidine), respectively (Section 1, Appendix). In RNA double-stranded duplexes adenine (A) base-pairs with uracil (U) via two hydrogen bonds (A=U) and guanine base-pairs with cytosine (C) via 3 hydrogen bonds (G≡C). Adenine forms the nucleoside adenosine by an N-glycosidic link with the 5-carbon (C5) sugar ribose. Adenosine can be successively modified by phosphorylation to yield the nucleotides adenosine 5'-monophosphate (5'-AMP), adenosine 5'-diphosphate (5'-ADP) and adenosine 5'-triphosphate (5'-ATP). The other bases form the corresponding nucleosides (and nucleotides) guanosine (5'-GMP, 5'-GDP and 5'-GTP), uridine (5'-UMP, 5'-UDP and 5'-UTP) and cytidine (5'-CMP, 5'-CDP and 5'-CTP).

The bases found in DNA (deoxyribonucleic acid) are adenine and guanine and the corresponding base-pairing complements thymine (T) (5-methyluracil, 2,4-dioxy-5-methylpyrimidine) and cytosine (C) that hydrogen bond in double-stranded (duplex) DNA thus: A=T and G≡C. The corresponding nucleosides (deoxyribonucleosides) are formed via *N*-glycosidic links with 2'-deoxyribose (2'-deoxyadenosine, 2'-deoxyguanosine, 2'-deoxythymidine and 2'-deoxyuridine) and thence the corresponding deoxyribonucleotides (5'-dAMP, 5'-dADP, 5'-dATP, 5'-dGMP, 5'-dGDP, 5'-dGTP, 5'-dTMP, 5'-dTDP, 5'-dTTP, 5'-dCMP, 5'-dCDP and 5'-dCTP).

The 3',5'-cyclic nucleoside monophosphates 3',5'-cyclic AMP (cAMP) and 3',5'-cyclic GMP (cGMP) are so-called “second messengers”, the cytosolic levels of which rise in response to binding of particular “primary messengers” (such as hormones or neurotransmitters) to plasma membrane receptors (Chapters 5 and 7). Both cGMP and cAMP have been found in plants. ATP is the so-called “energy currency” of cells. UDPglucose is involved in protein glycosylation and in synthesis of sucrose, cellulose (a β-1,4-glucan), callose (a β-1,3-glucan) and glycogen (an α-1,4-glucose polymer). Synthesis of starch (an α-1,4-glucose polymer) involves ADP-glucose, CDP-glucose and GDP-glucose as precursors (Chapter 2).

In addition to the bases outlined above, transfer RNA (tRNA) (involved in amino acid-specific codon recognition in protein synthesis) contains unusual chemically modified bases (e.g. 6-methylaminopurine). DNA can be modified by methylation yielding 5-methylcytosine. A number of other adenine (6-aminopurine) derivatives are plant growth regulator “cytokinins” having mitogenic and anti-senescent activity in plants including plant-derived

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dihydrozeatin (N^6 -isopentanoladenine), N^6 -(Δ^2 -isopentenyl)adenine and zeatin (N^6 -(Δ^2 -isopentenol)adenine) and the semi-synthetics N^6 -furfuryladenine (kinetin) and N^6 -benzyladenine.

Critical N-containing heterocyclics are chlorophyll a and chlorophyll b, Mg^{2+} -chelated cyclic tetrapyrroles that are involved in light harvesting in the chloroplast photosystems. The Fe^{3+} (Fe^{2+})-complexed tetrapyrrole haems are involved as the prosthetic groups of cytochromes in mitochondrial and chloroplast electron transport chains and of cytochrome P450 of the endoplasmic reticulum (ER)-associated xenobiotic detoxification system. The non-cyclic tetrapyrrole phytochrome is the key chromophore in red/far red light perception and signalling in plants. Haem is the prosthetic group of the oxygen-binding protein haemoglobin.

Vitamins are plant-derived compounds that we cannot synthesize ourselves and which accordingly must be ingested for survival. Vitamins are typically ring structures involving one or more ring Ns. **Thiamine (vitamin B₁)** (pyrimidine-CH₂-(N)-thiazole) involves a pyrimidinylmethyl (*mC4N2*) linked to a thiazole (C3NS) ring and as the thiamine pyrophosphate (TPP) coenzyme derivative is involved in pyruvate dehydrogenase, α -ketoglutarate dehydrogenase and transketolase function. Good vitamin B₁ sources are leafy vegetables, grain and legumes and deficiency causes beri beri (diarrhoea and fatigue). **Riboflavin (vitamin B₂)** is a riboside of isoalloxazine (Phe|pyrazine|pyrimidine) (Phe|*pC4N2*|*mC4N2*) (Section 1, Appendix) and is part of the redox coenzymes flavin adenine dinucleotide (FAD/FADH₂) and flavin mononucleotide (FMN/FMNH₂) (oxidized/reduced forms). Riboflavin is present in leafy vegetables and cereals and deficiency is associated with growth retardation. **Pyridoxine (vitamin B₆)** (1-methyl-3-hydroxy-4,5-dicarboxymethylpyridine) is the precursor of pyridoxal phosphate, a coenzyme involved in transaminase and lysyl oxidase. Vitamin B₆ is found in cereals and legumes and deficiency is associated with dermatitis, depression and particular infantile convulsions. **Biotin (vitamin H or coenzyme R)** (C4S|C3N2) involves fused, fully reduced (saturated) thiophene and imidazole rings and is involved in carboxylation reactions (e.g. fatty acid synthesis). **Folic acid** (pteroylglutamate) has a pteridine (*mC4N2*|*pC4N2*) (pyrimidine|pyrazine) heterocyclic ring and is involved in methylation reactions crucial for DNA precursor (thymine) synthesis. Folate is present in green leafy dietary vegetables and maternal folate deficiency is associated with occurrence of spina bifida. **Cyanocobalamin (vitamin B₁₂)** (5,6-dimethylbenzimidazolyl cyanocobamide), produced by colonic bacteria, is a cobalt ion-chelated tetrapyrrole, the coenzyme derivatives of which are involved in C–C bond breakage and re-formation in methionine (C₅) and succinyl-CoA (C₄) formation from homocysteine (C₄) and methylmalonyl-CoA (C₄), respectively. Vitamin B₁₂ deficiency is associated with pernicious anaemia. **Niacin** (nicotinic acid, pyridine 3-carboxylic acid) is the precursor of nicotinamide which is part of the nicotinamide adenine dinucleotide redox coenzymes NAD⁺/NADH and NADP⁺/NADPH (oxidized/reduced forms). Niacin is found in grain and legumes and niacin deficiency is associated with pellagra (involving mental and physical weakness).

Methyl derivatives of xanthine (2,3-dioxypurine) namely caffeine (1,3,7-trimethylxanthine), theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine) (Section 1, Appendix) are variously found in plants used for stimulatory drinks such as *Ilex paraguayensis* (maté) (Aquifoliaceae), *Coffea* species (coffee) (Rubiaceae), *Paullinia cupana* (guarana) (Sapindaceae), *Cola acuminata* (cola) and *Theobroma cacao* (cocoa) (Sterculiaceae) and *Camellia sinensis* (tea) (Theaceae). These methylxanthines are variously active as inhibitors of

cAMP phosphodiesterase or as adenosine receptor antagonists. Caffeine also activates the ryanodine receptor Ca^{2+} channel.

The pyrimidine nucleosides convicine (3,6-diamino-2,4,5-trihydroxypyrimidine 5-*O*- β -glucoside) and vicine (divicine- β -glucoside, 2,6-diamino-4,5-dihydroxypyrimidine 5-*O*- β -glucoside) derive from *Vicia fava* (fava beans) (Fabaceae) and give rise to Favism in people with glucose-6-phosphate dehydrogenase (G6PDH) deficiency (typically in Mediterranean countries in which this deficiency was selected for as a protectant against malaria). The aglycones (non-glycosylated pyrimidines) are involved in oxidative reactions resulting in glutathione deficiency, red blood cell haemolysis and anaemia in G6PDH-deficient individuals.

1.7 Plant phenolics

Plant phenolics represent a very large group of defensive compounds defined here as having a phenol (hydroxybenzene) moiety. In some instances substances having a phenolic precursor (e.g. methoxybenzene derivatives) have conveniently also been included in this category. Phenolics derive biosynthetically from hydroxycinnamoyl coenzyme A (yielding a phenylpropanoid moiety).

The phenolics range in complexity from simple phenolics and quinones (with one ring), through chalcones and stilbenes (with two rings) to a range of phenolics with three rings namely anthocyanins, anthochlors, benzofurans, chromones, chromenes, coumarins, flavonoids, isoflavonoids, neoflavonoids, stilbenoids and xanthones (see Section 2, Appendix). More complex polycyclic phenolics exist, notably the hydrolysable tannins (gallotannins and ellagitannins) and the condensed tannins.

The phenolic ring system (Phenyl-OH, or for aromatics in general, Aryl-OH) is planar and electron-rich. The planar benzene ring is hydrophobic but the phenolic OH confers polarity and water-solubility and the capacity for hydrogen bonding, for example, Phenyl-OH \cdots $^-\text{OOC-X}$ and Phenyl-OH $\cdots\text{H}_2\text{N-X}$ (these properties permitting phenolic-protein interactions that are stronger, the greater the number of interactions involved). The phenolic group can be deprotonated (to form the phenolate (Phenyl-O $^-$) and can be oxidized yielding a quinone (Aryl=O) and the radical Aryl-O \cdot . Accordingly, phenolics have antioxidant properties that are biologically important. Because of the extensive conjugated double bond systems found in the more complex phenolics (e.g. Aryl-(CH $_2$ -CH=CH) $_n$), such compounds absorb light well in the visible part of the spectrum, that is, they are coloured.

The above properties of phenolics provide molecular rationales for phenolic compound functions. Thus, coloured phenolics act as pollinator-attractants and complex polyphenolics (tannins) bind tightly to proteins and act as herbivore deterrents through being bitter tastants. The planar ring systems of flavonoids and related compounds can mimic key enzyme substrates such as ATP and the key redox coenzymes NADPH, NADH, FMNH $_2$ and FADH $_2$. Many phenolics can act as anti-inflammatory antioxidants through covalent reaction with free radicals, notably ROS such as superoxide (O $_2^-$). Conversely, many phenolics have antimicrobial (antibacterial or antifungal) properties. The complex structure and function features of the various groups of phenolics are sketched below. The structures of a variety of simple and more complex polycyclic phenolics are presented in the order of increasing complexity in the Appendix (Section 2).

i. Simple phenols include a variety of compounds noted because of their antimicrobial, topical antimicrobial, antiseptic, dermatitic and odorant properties. The denaturant, irritant, odorant and antiseptic properties of the parent compound phenol are familiar.

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Antiseptic plant-derived phenols include phenol (Phe-OH, hydroxybenzene, carbolic acid), *p*-cresol (4-methylphenol), catechol (1,2-dihydroxybenzene), resorcinol (1,3-dihydroxybenzene) and pyrogallol (1,2,3-trihydroxybenzene). Other simple phenols with antimicrobial properties include some related to benzoic acid (benzenecarboxylic acid), namely salicylic acid (2-hydroxybenzoic acid), ginkgoic acid (2-hydroxy-6-(pentadec-8-enyl)benzoic acid), gentisic acid (2,5-dihydroxybenzoic acid), pyrocatechuic acid (3,4-dihydroxybenzoic acid) and gallic acid (3,4,5-trihydroxybenzoic acid). Other plant-derived phenol-related compounds include 4-methylcatechol, 1,3-dihydroxy-5-(heptadec-12-enyl)benzene, hydroquinone (1,4-dihydroxybenzene), 1,4-dihydroxy-2-geranyl (di-isoprenyl)benzene and 4-methoxybenzaldehyde (*p*-anisaldehyde).

The non-specific biocidal properties of phenols give rise to dermatitic properties. Noted plant phenol dermatitics include anacardic acids (2-hydroxy-6-(long chain alkyl)-benzoic acids), catechol (1,2-dihydroxybenzene), ginkgol (3-(pentadec-8-enyl)phenol), *Grevillea robusta* (Proteaceae) grevillol (1,3-dihydroxy-5-tridecylbenzene), salicylic acid (2-hydroxybenzoic acid), sesamol (3,4-methylene dioxyphenol), *Turricula parryi* (poodle dog bush) (Hydrophyllaceae) turricolol E (1,4-dihydroxy-2-(tri-isoprenyl)benzene) and the *Toxicodendron radicans* (poison ivy) (Anacardiaceae) 3-(long chain alkenyl)-catechols.

Phenols have distinct odours. Notable simple phenol-related odorants/tastants include 4-methoxybenzaldehyde (*p*-anisaldehyde), guaiacol (2-methoxyphenol), 4-hydroxybenzaldehyde, phenethyl alcohol, piperonal (heliotropin, 3,4-methylenedioxybenzoic acid) and *Vanilla planifolia* (vanilla) (Orchidaceae) pod vanillin (3-methoxy-4-hydroxybenzaldehyde) (Chapter 10).

Some simple phenolics inhibit COX (prostaglandin synthetase) and/or 5-lipoxygenase (5-LOX). COX inhibitors include the anacardic acids, 2,6-dimethoxyphenol and *Ginkgo biloba* (Ginkgoaceae) ginkgoic acid (2-hydroxy-5-pentadec-8-enyl)benzoic acid) and ginkgol (3-(pentadec-8-enyl)phenol). Simple phenol 5-LOX inhibitors include ginkgol and grevillol. The acetyl ester of salicylic acid (2-hydroxybenzoic acid) is the synthetic COX-inhibitory anti-inflammatory aspirin (Chapter 14).

ii. Phenolic ketones. Phenolic ketones typically have a phenol-related benzene (unsaturated C₆) ring with a 2-carbon (C₂) sidechain as exemplified by the phenolic precursor acetophenone (Phe-CO-CH₃). Such compounds derive from phenylpropanoids (Phe-C₃). A variety of such phenolic ketones are based upon phloroglucinol (1,3,5-trihydroxybenzene) including: the COX and 5-LOX inhibitors, 2,6-dimethoxy-4-hydroxyacetophenone and xanthoxylin (4,6-dimethoxy-2-hydroxyacetophenone; phloroacetophenone 4,6-dimethyl ether) and the *Humulus lupulus* (hops) (Cannabaceae) bitter-tasting, isoprenylated antibacterials humulone (α-lupulic acid) and lupulone (β-lupulic acid). The non-aromatic, hops-derived, tricyclic ketone tricyclodehydrohumulone is also a bitter tastant. Other phenolic ketones include acetosyringone (3',5'-dimethoxy-4'-hydroxyacetophenone) (the tobacco inducer of *Agrobacterium tumefaciens* virulence gene expression required for infection), the phloroglucinol benzophenone maclurin, the benzophenone tubulin-binding anti-mitotic xanthochymol and the oestrogenic macrocyclic mycotoxin zearalenone from the fungus *Gibberella zeae*.

iii. Phenylpropanoids. The phenylpropanoids derive biosynthetically from phenylalanine (Phenyl-CH₂-CH(NH₂)-COOH) through deamination. The phenylpropanoids (Phe-C₃) in turn give rise to lignans in which benzene rings are linked by a C-C bond (Phe-Phe) and coumarins in which ring closure by a lactone grouping (-O-CO-) creates a benzopyran-2-one (Phe | C5OL).

Major simple phenylpropanoids include cinnamic acid (Phe-CH=CH-COOH), *p*-coumaric acid (*p*-hydroxycinnamic acid), *o*-coumaric acid (*o*-hydroxycinnamic acid), caffeic

acid (3,4-dihydroxycinnamic acid), ferulic acid (3-methoxy-4-hydroxycinnamic acid) and isoferulic acid (3-hydroxy-4-methoxycinnamic acid). These parent compounds can in turn be altered through reduction of the sidechain double bond or of the carboxyl (to yield aldehydes and alcohols); formation of glycosides with sugars; formation of carboxylic acid esters with sugars and other compounds (notably quinic acid and shikimic acid); formation of amides; decarboxylation (to yield phenylpropenes and phenylpropanes); methylation of phenolic hydroxyls; and formation of an MD ring from phenolic hydroxyls.

Some non-polar phenylprop-2-ene (allylbenzene (AB); $\text{Phe-CH}_2\text{-CH=CH}_2$) derivatives can form 2,3-epoxides and thence covalent adducts with DNA, such genotoxic (and potentially mutagenic and carcinogenic) compounds including elemicin (3,4,5-trimethoxyAB), estragole (3-methoxyAB), methyleugenol (4,5-dimethoxyAB) and safrole (4,5-methylenedioxyAB), noting that such compounds occur in plant material ingested by humans. While the phenylprop-1-ene (prop-1-enebenzene; PB) compounds *trans*- and *cis*-asarone (2,4,5-trimethoxyPB) form DNA adducts, a range of other plant-derived PB or AB compounds are not genotoxic including eugenol (4-hydroxy-5-methoxyAB), isosafrole (4,5-methylenedioxyPB), methylisoeugenol (4-hydroxy-5-methoxyPB) and myristicin (3-methoxysafrole) (which forms such adducts poorly). Epoxide hydrolases provide some protection from genotoxic phenylpropenes.

A variety of **phenylpropanoid ketones** are anti-inflammatory inhibitors of COX and 5-LOX, enzymes that are involved in the formation of prostaglandins and leukotrienes, respectively. Thus, the dihydroferulic acid-derived ketone [6]-Gingerol (4'-hydroxy-5'-methoxyphenylpropane-CO-CH₂-CH(OH)-(CH₂)₄-CH₃) (Phe-alkyl ketone) inhibits both COX and 5-LOX as variously do the corresponding [2]-, [4]-, [8]-, [10]-, [12]-, [14]- and [16]-gingerols and the diketones [6]- and [8]-gingerdione, all of these compounds deriving from the rhizome of *Zingiber officinale* (ginger) (Zingiberaceae). The structurally related **diarylheptanoids** are ketones (R-CO-R') from *Alpinia* species (Zingiberaceae) rhizomes in which the aryl R-CO- and R'- groups are phenylpropanoid (Phe-C₃) and phenylpropanoid-related (Phe-C₄), respectively. The diarylheptanoids are variously COX and 5-LOX inhibitors.

A variety of other phenylpropanoids have been shown to inhibit particular enzymes including (target enzyme in parentheses): coniferyl aldehyde and the amide fagaramide (COX); the biphenylpropanoid glycosides forsythiaside, hellicoside and suspensaside (5-LOX and cAMP phosphodiesterase); the allylbenzene myristicin (monoamine oxidase); the tricaffeic acid salvianolic acid A (gastric H⁺ secreting H⁺-ATPase); the caffeic acid esters vanicosides A and B and the diferuloyl curcumin (protein kinases); curcumin and caffeic phenethyl ester (HIV-1 integrase); caffeic acid (xanthine oxidase); and ferulic acid, curcumin, the diarylheptanoid yakuchinone B and 4-hydroxy-3-methoxy cinnamaldehyde (tyrosinase).

iv. Lignans. Simple lignans derive from dimerization of phenylpropanoids (Phe-C₃), typically through a sidechain (C₃) C-C link, that is, $\text{Phe-C}_3 + \text{Phe-C}_3 \rightarrow \text{Phe-C}_3\text{-C}_3\text{-Phe}$ (typically $\text{Phe-CH}_2\text{-CH(CH}_3\text{)-CH(CH}_3\text{)-CH}_2\text{-Phe}$). However, alternative linkages could be phenyl C-C links (i.e. $\text{Phe-C}_3 + \text{Phe-C}_3 \rightarrow \text{C}_3\text{-Phe-Phe-C}_3$). In monoepoxylic lignans, a tetrahydrofuran (THF) (C₄O) is formed linking the two phenyls, that is, $\text{Phe-CH}_2\text{-CH(CH}_3\text{)-CH(CH}_3\text{)-CH}_2\text{-Phe} + \text{O} \rightarrow \text{Phe-CH}_2\text{-C}_4\text{O-CH}_2\text{-Phe}$ or $\text{Phe|C}_4\text{O-Phe}$ (in which the THF moiety is fused with one of the phenyls). Further oxidation yields lignanoides in which there is a central tetrahydrofuranone (C₄OL) lactone ring ($\text{Phe-CH}_2\text{-C}_4\text{OL-CH}_2\text{-Phe}$) and bisepoxylic lignans in which phenyl (Phe-) moieties are linked by two fused THF rings ($\text{Phe-C}_4\text{O|C}_4\text{O-Phe}$). In the more complex podophyllotoxin-related cyclolignans, there is sidechain cyclization to form a ring system fused with one of the

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phenyl groups and further cyclolignan possibilities exist. These various structural types are further varied by substitutions with hydroxyl, methoxy, methylenedioxy and *O*-glycosyl groups. Lignans are mostly found in wood and many have cytotoxic properties.

Simple lignans involving a Phe-C₃-C₃-Phe structure are illustrated by the antioxidant and Ca²⁺ channel blocker nordihydroguaiaretic acid (NDGA) (3,4-dihydroxyphenyl-CH₂-CH(CH₃)-CH(CH₃)-CH₂-(3',4'-dihydroxyphenyl)), the bitter-tasting phyllanthin and the cAMP phosphodiesterase inhibitor *cis*-hinokiresinol. Simple lignans of the C₃-Phe-Phe-C₃ kind are illustrated by the antibacterials honokiol and the protein kinase inhibitor magnolol.

Lignanoides (Phe-CH₂-C₄OL-CH₂-Phe) include the Ca²⁺ channel blocker trachelogenin, the cytochrome P450-linked oxygenase inhibitor cubebin, the cAMP phosphodiesterase inhibitor (-)-arctigenin and the antimetabolic glycoside podorhizol-β-D-glucoside from *Podophyllum* species (Podophyllaceae).

Monoepoxylic lignans include the Ca²⁺ channel blockers fargesone A and fargesone B (Phe|C₄O-Phe(MD)); the antitumour compound burseran ((MD)Phe-CH₂-C₄O-CH₂-Phe); the platelet activating factor (PAF) receptor antagonists grandisin, magnosalicin, saucernetin and (+)-veraguensin (Phe-CH₂-C₄O-CH₂-Phe); and the PAF antagonists kadsurene and kadsurin A (DHPhe|C₄O-Phe).

Bisepoxylic lignans (Phe-C₄O|C₄O-Phe) include the 1-acetoxypinoresinol and pinoresinol (cAMP PDE inhibitors), (-)-eudesmin (Ca²⁺ channel blocker), sesamolol (antioxidant) and sesartemin (an inhibitor of cytochrome P450-linked oxygenase).

Podophyllotoxin-related cyclolignans include the important antitumour antimetabolic podophyllotoxin ((MD)Phe(Phe)|C₄OL) from *Podophyllum* species (Podophyllaceae) that inhibits topoisomerase and binds to tubulin. Podophyllotoxin-related compounds with antimetabolic, cytotoxic and antitumour activity include 4'-demethylpodophyllotoxin, 4'-demethyldeoxypodophyllotoxin and deoxypodophyllotoxin. A variety of other kinds of cyclolignans and polycyclic neolignans have been characterized.

v. Benzoquinones, naphthoquinones and anthraquinones. The benzoquinone parent compound quinone (*p*O=Phe=O) (Q) is an oxidant which is readily reduced to *p*-hydroxyphenol (hydroquinone) (HO-Phe-OH). Quinone is a cytotoxic antimicrobial found in plants. A variety of simple antimicrobial hydroquinone-based phenolics are elaborated by plants as also outlined in Section i above. The reactivity of quinones in terms of redox reactions, hydrogen bonding (-C=O...H-X-) and hydrophobic binding in relation to proteins in general contributes to their irritant, cytotoxic and antimicrobial effects.

The naphthoquinones are fused benzene and quinone rings (Phe|Q) and the anthraquinones involve a quinone ring fused with two benzene rings (Phe|Q|Phe). Furanobenzoquinones and furanonaphthoquinones involve a furan ring (C₄O) fused with a benzoquinone or naphthoquinone ring, respectively. Similarly, pyranoquinones involve fusion of quinones with a pyran (C₅O) ring. Binaphthoquinones and bianthraquinones derive from C-C links between the monomeric precursors. Substituents include hydroxy, hydroxymethyl methoxy, alkyl (notably isoprenyl), *C*-glycosyl and *O*-glycosyl groups. The compounds with more extensive conjugated systems (e.g. the anthraquinones) are coloured.

Benzoquinones (Q) include the bicyclic COX inhibitor arnebinone (DHPhe|Q) and the leukotriene receptor antagonists ardisianone and cornudentanone, which are 6'-methoxy-2'-alkylbenzoquinones (Q-alkyl) where the long chain alkyl substituents are 3-acetoxypentadecyl and 3-acetoxytridecyl, respectively. A number of benzoquinones are allergens including acamelin, 2,6-dimethoxybenzoquinone, geranylbenzoquinone,

prenylbenzoquinone and primin. The universal isoprenylated benzoquinone ubiquinones (e.g. coenzyme Q₁₀; benzoquinone-2-methyl-5,6-dimethoxy-3-(isoprenyl)₁₀) are key redox components in the mitochondrial electron transport chain and coenzyme Q₁₀ is used as an anti-aging nutraceutical. The plastoquinones are analogous 3-isoprenylated 5,6-dimethylbenzoquinone redox components in the chloroplast photosynthetic electron transport chain.

Naphthoquinones (Phe|Q). The benign isoprenylated naphthoquinones alkanin and shikonin are used for red lipstick and lawsone (1-hydroxynaphthoquinone) is the henna principle used to dye hair and for painting hands in Indian ceremonies. A variety of naphthoquinones are antimicrobials. Juglone, naphthazarin and plumbagin are protein kinase inhibitors. The widespread isoprenylated naphthoquinone vitamin K₁ (phyloquinone) is required for the formation of γ -carboxyglutamate residues in prothrombin, this permitting Ca²⁺ binding, prothrombin activation and subsequent blood clotting.

Anthraquinones (Phe|Q)|Phe). Alizarin (1,2-dihydroxyanthraquinone) is the orange-red compound of *Rubia tinctorum* (madder) (Rubiaceae), a longstanding dyestuff in human history. A range of anthraquinones are variously cathartic, antimicrobial and cytotoxic. A variety of anthraquinones are protein kinase inhibitors including alizarin, chrysazin, damnacanthal, emodin and purpurin.

Binaphthoquinones include the phototoxic phytotoxin cercosporin from the fungus *Cercospora* (two Phe|Q moieties linked by two Phe-Phe links and an MD link). Hypericin (two anthraquinones linked by three Phe-Phe linkages) is a **bianthraquinone** from *Hypericum* species (Hypericaceae). Hypericin is a phototoxic protein kinase inhibitor that causes light-dependent ovine facial eczema. **Benzonaphthoquinones** include the dermatitic cypripedin (Phe|Phe|Q). Lichen 7-chloroemodin is a novel **chloroanthraquinone** and the fused tricyclic **pyrano- α -naphthoquinone** β -lapachone (Phe|*o*Q|C5O) is a reverse transcriptase inhibitor with antimicrobial and cytotoxic activity.

vi. Stilbenes, bisbenzyls and phenanthrenes. Stilbenes (Phe-CH=CH-Phe) derive from the phenylpropanoid *p*-hydroxycinnamic acid (Phe-C₃; *p*OH-Phe-CH=CH-CO₂⁻) and malonylCoA (C₃^{*}; ⁻O₂C-CH₂-CO-S-CoA) with loss of CO₂ (C₁): Phe-C₃ + 3 C₃ → Phe-C₂-Phe + 4C₁). A further C-C link between the phenyl rings yields the three fused benzene rings of phenanthrene (the non-linear isomer of the linear anthracene, Phe|Phe|Phe). Stilbene reduction yields bisbenzyls (Phe-CH₂-CH₂-Phe). Stilbenoid compounds can be modified by reduction and by hydroxyl, methoxy, isoprenyl and glycosyl ring substituents. Stilbenes are often found as antifungal agents in wood.

Simple stilbenes (Phe-CH=CH-Phe) include the *Vitis vinifera* (grape) (Vitaceae) cytotoxic resveratrol (4,3',5'-trihydroxystilbene), the mitochondrial electron transport inhibitor oxysesveratrol (3,5,2',4'-tetrahydroxystilbene) and the protein kinase inhibitor piceatannol (3,4,3',5'-tetrahydroxystilbene), all these compounds having antifungal activity. The isoprenylated stilbene chlorophorin (4-geranyl-3,5,2',4'-tetrahydroxystilbene) is an antioxidant free radical scavenger (AO/FRS).

Bisbenzyl (Phe-CH₂-CH₂-Phe) compounds include dihydroresveratrol (4,3',5'-trihydroxybisbenzyl) and the allergenic benzopyranone hydrangenol from *Hydrangea macrophylla* (Saxifragaceae).

Phenanthrenes (angular Phe|Phe|Phe) include the antifungal methoxyphenanthrenes batatasin I and isobatatasin I from bulbs of *Dioscorea* species (Dioscoraceae). The pyrano-phenanthrenes have a tetracyclic structure (involving linkage of the outer phenanthrene rings with an -O-CH₂- group), examples including the spasmolytic compounds coelogen and flavidin from *Coelogyne* species (Orchidaceae).

vii. Anthochlors (chalcones and aurones), anthocyanidins and anthocyanins. Anthochlors (chalcones and aurones), anthocyanidins and anthocyanins provide colour to flowers that is required for attracting pollinating herbivores. The anthochlors are yellow but the anthocyanins (and the corresponding aglycone anthocyanidins) have colours ranging from blue to red.

Chalcones. The parent compound is chalcone (1,3-diphenyl-2-propen-1-one or benzylideneacetophenone; $\text{Phe}-\text{CH}=\text{CH}-\text{CO}-\text{Phe}$), the ring numbering being 1–6 (benzylidene phenyl) and 1'–6' (acetophenone phenyl). Chalcone variants derive from hydroxy, prenyl (isopentenyl) and glycosyl substituents. Phenols are weak acids and as such can act as “protonophores” to increase the proton (H^+) permeability of the mitochondrial inner membrane and hence act as “uncoupling” inhibitors of the key ATP-providing process of oxidative phosphorylation. Butein (2',4',3,4-tetrahydrochalcone), isoliquiritigenin (2',4',4-trihydroxychalcone) and okanin (2',3',4',3,4-pentahydroxychalcone) are uncouplers of oxidative phosphorylation. Various chalcones inhibit the following particular enzymes (in parentheses): abyssinone VI (3,5-isoprenyl-2',3',4-trihydroxychalcone) (steroid aromatase); butein (receptor tyrosine kinase and NADH and succinate dehydrogenases); liquiritigenin and isoliquiritigenin (monoamine oxidase); and chalconaringenin (2',4',6',4-tetrahydroxychalcone) (iodothyronine deiodinase).

Dihydrochalcones. The parent compound is dihydrochalcone (1,3-diphenylpropan-2-one). Phloretin (4,2',4',6'-tetrahydroxydihydrochalcone) is an uncoupler and an inhibitor of iodothyronine deiodinase and protein kinase. Phloridzin (phloretin 2'-*O*-glucoside) is a bitter tastant and an inhibitor of glucose transport. Odoritol (α -hydroxy-4,4'-dimethoxy-6'-hydroxydihydrochalcone) is a *Lathyrus odoratus* (sweet pea) (Fabaceae) phytoalexin. Various methylated dihydrochalcones including loureirins B and D from *Dracaena loureiri* (Agavaceae) are oestrogen receptor agonists.

Aurones (Phe | C4O(=O)=CH-Phe). Aurones (2-benzylidenebenzofuranones) derive from oxidation and cyclization of chalcone precursors to yield the corresponding benzofuranone (benzene fused with a five-membered furanone ring): $\text{Phenyl}-\text{CO}-\text{CH}=\text{CH}-\text{Phenyl} + \text{O}_2 \rightarrow \text{Benzofuranone} = \text{CH}-\text{Phenyl}$. Various aurones inhibit iodothyronine deiodinase, namely (numbering 1–9 in the bicyclic benzofuranone and 1'–6' in the benzylidene phenyl) aureusidin (4,6,3',4'-tetrahydroxyaurone), bracteatin (4,6,3',4',5'-pentahydroxyaurone), maritimetin (6,7,3',4'-tetrahydroxyaurone) and sulfuretin (6,3',4'-trihydroxyaurone).

Anthocyanins and anthocyanidins. Anthocyanidins are the aglycones of the corresponding anthocyanins, the parent compound being 2-phenylbenzopyrylium (flavylium) ($\text{Phe} | \text{pyrylium}^+-\text{Phe}$). The benzopyrylium moiety is benzene fused with an unsaturated six-membered pyrylium ring containing five Cs and a positively charged O. Cyanidin (ring numbering 1–10 in the benzopyrylium ring and 1'–6' in the phenyl ring) is 3,5,7,3',4'-pentahydroxyflavylium and is very widespread, particularly as the anthocyanin cyanidin 3-*O*-glucoside. Other anthocyanidins include apigeninidin, delphinidin, hirsutidin, luteolinidin, malvidin, pelargonidin, peonidin and petunidin, the structural variations arising from differing patterns of hydroxy and methoxy substitution (and thence of differing glycosylation in the corresponding anthocyanins).

Cyanidin inhibits epidermal growth factor receptor tyrosine kinase (EGF-RTK), α -glucosidase and COX-1 and COX-2. Delphinidin (3,5,7,3',4',5'-hexahydroxyflavylium) also inhibits EGF-RTK. Anthocyanidins and anthocyanins can be anti-inflammatory antioxidants by acting as free radical scavengers. Thus, nasunin (delphinidin-3-(*p*-coumaroylrutinoside)-5-glucoside) scavenges OH (hydroxyl), O_2^- (superoxide) and lipid peroxy radicals and inhibits lipid peroxidation.

viii. Benzofurans. The parent compound benzofuran (Phe|furan) involves a fused benzene (unsaturated C6 ring) and furan (unsaturated five-membered ring including four Cs and one O). In addition to simple benzofurans there are dibenzofurans (Phe|furan|Phe) in which the furan ring is fused with two benzenes to make a tricyclic nucleus. The simple benzofurans and dibenzofurans are generally toxic with antimicrobial and notably antifungal activity.

Simple benzofurans (Phe|furan) involve benzofuran variously having acetoxy, hydroxy, methoxy or more complex substituents on the benzo moiety and typically a 2-phenyl or 2-(2-propenyl) substituent on the furan moiety. Asteraceae benzofurans with a 2-propenyl substituent include toxol and toxyl angelate (from *Haplopappus heterophyllus*) and dehydrotremetone and tremetone (from *Eupatorium* (snakeroot) species); ingestion of these plants by cows gives rise to “milk sickness”. Snakeroot “milk sickness” involves blockage of glucose-supplying gluconeogenesis (see Chapter 2) and was responsible for the death of Abraham Lincoln’s mother Nancy. The *Penicillium*-derived tricyclic chlorobenzofuran metabolite griseofulvin (Phe|C4O(=O)·C6) is an antifungal drug that interferes with microtubule tubulin and is used against tinea capitis (cradle cap) in children. The 2-phenylbenzofurans include *Morus* species (mulberry) (Moraceae) albanol A (mulberrofuran G) (Phe|furan-polycyclic) and mulberrofuran A (Phe|furan-Phe-isoprenyl) (COX inhibitors); lithospermic acid (aryl-Phe|furan-Phe) (from Boraginaceae) (a free radical scavenger and inhibitor of prolyl hydroxylase and collagen hydroxylation); and *Morus alba* (mulberry) (Moraceae) antifungal phytoalexins moracins A–Z and chalcomoracin (Phe|furan-Phe) (superoxide scavengers).

Dibenzofurans (Phe|furan|Phe) include various fungal infection-induced plant antifungal compounds (phytoalexins) such as the Rosaceae-derived cotonefuran (from *Cotoneaster lactea*) and α -pyrofurans (from *Pyrus communis*). Usnic acid from lichens (notably *Usnea* species) is anti-mycobacterial, anti-mitotic, an uncoupler and a potent inhibitor of plant protoporphyrinogen synthetase and 4-hydroxyphenylpyruvate dioxygenase.

ix. Chromones and chromenes. Chromones and chromenes involve a benzene ring fused with pyran (an unsaturated six-membered ring containing five Cs and one O). In chromenes (Phe| α -pyran), the heterocyclic ring is an unsaturated α -pyran (1,2-pyran) moiety (C5O, two asymmetric double bonds) and in chromones (Phe| γ -pyran-4-one), the O-containing ring is an unsaturated γ -pyran-4-one (1,4-pyran-4-one) moiety (C5, O, two symmetrically placed double bonds and a keto O). The flavonoids (2-phenylchromones), isoflavonoids (3-phenylchromones) and xanthenes (Phe| γ -pyran-4-one|Phe) will be dealt with in Sections xi–xvi. The chromones and chromenes are variously condensed with other ring systems and substituted with hydroxy, methoxy, alkyl and aryl groups. A number of these compounds are variously antimicrobial and cytotoxic.

Simple chromones (Phe| γ -pyran-4-one) include the glucoside biflorin (a cAMP phosphodiesterase inhibitor and free radical scavenger) and the 2-phenoxychromone capillarisin (an aldose reductase inhibitor) as well as a number of variously cytotoxic and antimicrobial compounds.

Furanochromones (furan|Phe| γ -pyran-4-one) have a furan ring fused with the benzene moiety of the chromone. Khellin, the related khellol glucoside and visnagin (dehydrokhellin) derive from seeds of *Ammi visnaga* (Apiaceae), both khellin and visnagin being phototoxic and vasorelaxant cAMP phosphodiesterase inhibitors.

Pyranochromones (α -pyran|Phe| γ -pyran-4-one) have an α -pyran ring fused with the benzene ring of the chromone and include the *Cneorum* species (Cneoraceae) antibacterial and cytotoxic compounds pulverochromenol (having an α -pyran fused with

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a benzochromone) and spatheliabischromene (α -pyran | Phe(α -pyran) | γ -pyran-4-one) (having two α -pyran rings condensed with a benzochromone).

Chromenes (Phe | α -pyran) include enecalinal (a phototoxic antimicrobial from various Asteraceae) and the phloroglucinol derivative mallotochromene (cytotoxic and an HIV-1 reverse transcriptase inhibitor). Precocene 1 (7-methoxy-2,2-dimethylchromene) and precocene 2 (6,7-dimethoxy-2,2-dimethylchromene) produced by *Ageratum* species (Asteraceae) inhibit the production of insect juvenile hormone (JH) as a result of “suicidal” conversion of these “pro-toxins” to cytotoxic derivatives by the JH-producing insect cells.

x. Coumarins. The parent compound coumarin (benzopyran-2-one; 1,2-benzopyrone) (Phe | pyran-2-one) involves the fusion of benzene (Phe-H) and pyran-2-one (C5, O, two double bonds and a 2-keto; unsaturated C5OL). Coumarin is responsible for the smell of newly cut grass. In addition to simple coumarins, there are furanocoumarins (in which a five-membered furan ring is fused with the benzo moiety of coumarin in either an angular or linear fashion) and pyranocoumarins (in which a six-membered pyran ring is fused with the benzo moiety of coumarin in either an angular or linear fashion). These coumarins are variously substituted with hydroxy, methoxy, methyl, acetoxy, glycosyl and other groups.

Simple coumarins (Phe | pyran-2-one) include coumarin and a variety of antibacterial derivatives including ammosesin (7-hydroxy-3-geranylgeranylcoumarin), daphnetin (7,8-dihydroxycoumarin), esculetin (6,7-dihydroxycoumarin), esculin (esculetin 6-*O*-glucoside), herniarin (7-methoxycoumarin) and umbelliferone (7-hydroxycoumarin). Fraxetin and 4-methyldaphnetin (6,7-dimethoxycoumarin) are antioxidant ROS scavengers and 5-LOX inhibitors. Esculetin, 7-hydroxy-4-methylcoumarin and umbelliferone are xanthine oxidase inhibitors. Coumarins inhibiting other enzymes (enzyme target in parentheses) include: osthol (7-methoxy-8-isopentenylcoumarin) (cAMP phosphodiesterase) and the antioxidant scoparone (6,7-dimethoxycoumarin) (tyrosine kinase). Dicoumarol (3,3'-methylenebis(4-hydroxycoumarin); dicoumarol) is a haemorrhagic anticoagulant from *Melilotus alba* (sweet clover) (Fabaceae) hay. Dicoumarol acts by being an antagonist of vitamin K₁ (a quinone that is required for prothrombin carboxylation and consequent Ca²⁺ binding and activation leading to blood clotting).

Furanocoumarins (furan | Phe | pyran-2-one) include a variety of angular and linear furanocoumarins as exemplified by the respective parent compounds isopsoralen and psoralen. Many furanocoumarins and the parent compounds themselves bind to DNA and form covalent adducts with DNA in a light-activated process involving alkylation of pyrimidine bases. Such photoactivatable compounds include the angular furanocoumarin isopsoralen (angelicin) and the linear furanocoumarins psoralen, bergapten (5-methoxypsoralen), 4,5',8-trimethoxypsoralen and xanthotoxin (8-methoxypsoralen). Xanthotoxin (8-hydroxypsoralen) is an antioxidant ROS scavenger. A variety of angular and linear furanocoumarins inhibit inducible NO synthase expression, including isopsoralen, pimpinellin, sphondin, byakangelicol, oxypeucedanin, cnidilin and xanthotoxin. Isopsoralen and psoralen inhibit both monoamine oxidases A and B.

Pyranocoumarins (C5O | Phe | pyran-2-one) include a variety of angular and linear compounds. A number of angular pyranocoumarins are spasmolytic and vasodilatory, notably the Ca²⁺ channel blocker visnadin. The inophyllums B and P from *Calophyllum ionophyllum* (Guttiferae) are inhibitors of HIV-1 reverse transcriptase.

xi. Flavones and flavonols. Flavones, biflavones and flavone-3-ols (flavonols) are derivatives of the parent 2-phenylchromone, flavone (2-phenyl-1-benzopyran-4-one);

2-phenyl- γ -benzopyrone), the ring numbering system being 1 (pyrone ring O), 4 (pyrone ring keto C), 5–8 (benzo ring Cs) and 1'–6' (2-phenyl ring Cs). Flavones and flavonols (3-hydroxyflavones) contribute to petal colour (especially as perceived by insects) together with anthocyanins and also function in UV protection and defence against herbivores.

Flavones. Flavone structural variation derives from hydroxylation, *O*-methylation and *O*-glycosylation. In addition, there can be C6- and C8-linked *C*-glycosides, isoprenyl (isopentenyl, C₅) substituents and C–C or C–O–C links to form biflavones. Methylation of the phenolic OHs decreases polarity to permit an external location such as in the waxy leaf or fruit surface.

Flavones with a widespread occurrence include apigenin (5,7,4'-trihydroxyflavone), luteolin (5,7,3',4'-tetrahydroxyflavone) and the corresponding derivatives apigenin 7,4'-dimethylether, apigenin 7-*O*-glucoside (cosmosiin), apigenin 8-*C*-glucoside (vitexin), apigenin 6,8-*C*-diglucoside (vicenin-2), luteolin 7-*O*-glucoside, luteolin 6-*C*-glucoside (isoorientin), luteolin 6-*C*-glucoside (orientin) and luteolin 6,8-*C*-diglucoside (lucenin-2).

Some bioactive flavones include: aldose reductase inhibitors (apigenin 4'-methyl ether (acacetin), apigenin 7-*O*-apioside (apiin), 5,7-dihydroxyflavone (chrysin) and luteolin); anti-inflammatory 5-LOX inhibitors (5,6,7-trihydroxyflavone (baicalein), 5,6,3',4'-tetrahydroxy 7-methoxyflavone (pedalitin), 5,3',4'-trihydroxy 6,7-dimethoxyflavone (cirsiolol, 6-*O*-methylpedalitin) and flavone); a COX inhibitor (flavone); iodothyronine deiodinase inhibitors (acacetin, chrysin and luteolin); a NADH and succinate dehydrogenase inhibitor (luteolin); millet-derived, goitrogenic inhibitors of thyroid peroxidase (flavone *C*-glycosides orientin and vitexin); and protein kinase inhibitors (acacetin, apigenin, baicalein, flavone, luteolin, 5,7,3',4',5'-pentahydroxyflavone (trictetin) and trictetin 3',4',5'-trimethyl ether).

A variety of flavones are anti-inflammatory (apigenin, apigenin 7,4'-dimethylether, baicalein, 8-hydroxyluteolin and luteolin); insect feeding attractants (notably the *C*-glycosides carlinoside, isoorientin, isoscoparin, neocarlinoside, schaftoside and neoschaftoside); oestrogenic (wogonin); and oviposition stimulants (luteolin 7-(6''-malonylglucoside) and vicenin-2).

Biflavones. A number of biflavones are formed via C–C linkages, notably the cAMP phosphodiesterase (cAMP PDE) inhibitory biapigenins agathisflavone (6,8''-biapigenin), amentoflavone (3',8''-biapigenin), cupressiflavone (8,8''-biapigenin) and robustaflavone (3',6''-biapigenin). The 4'-C–O–6''-C-linked biapigenin hinokiflavone is also a cAMP PDE inhibitor.

Flavonols. The most common flavonols (3-hydroxyflavones) include kaempferol (3,5,7,4'-tetrahydroxyflavone), quercetin (3,5,7,3',4'-pentahydroxyflavone), myricetin (3,5,7,3',4',5'-hexahydroxyflavone), quercitrin (quercetin 3-*O*-rhamnoside), isoquercitrin (quercetin 3-*O*-glucoside), isorhamnetin (quercetin 3'-methyl ether) and rutin (quercetin 3-rutinoside). A large number of other flavonols variously have hydroxy, methoxy, isoprenyl, *O*-glycoside and other substituents.

Some bioactive flavonols include: aldose reductase inhibitors (axillarin (5,7,3',4'-tetrahydroxy-6-methoxyflavone), 2,3-dihydroquercetin (taxifolin), 6-hydroxykaempferol (galetin), hyperin (quercetin 3-*O*-galactoside), isoquercetrin, morin (3,5,7,2',4'-pentahydroxyflavone), quercetin, quercitrin and rutin); anti-inflammatory 5-LOX inhibitors (fisetin (3,7,3',4'-tetrahydroxyflavone), kaempferol, morin, myricetin, quercetin and rutin); a COX inhibitor (galangin (3,5,7-trihydroxyflavone)); iodothyronine deiodinase inhibitors (fisetin, kaempferol and morin); NADH and succinate dehydrogenase inhibitors (fisetin and myricetin); and protein kinase inhibitors (fisetin, galangin, isorhamnetin, kaempferide

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(kaempferol 4'-methyl ether), morin, quercetagenin (6-hydroxyquercetin), quercetin, quercitrin and rutin).

Flavonols are variously good ROS scavengers (e.g. kaempferol and quercetin). Particular flavonols are insect feeding attractants or stimulants (quercetin, quercetin 7-*O*-glucoside (quercimeritrin), isoquercitrin, quercitrin and rutin).

xii. Dihydroflavonoids. Dihydroflavonoids are flavonoids in which the 2,3 double bond of the chromene ring has been reduced. Such compounds include the flavanones (2,3-dihydroflavones such as naringenin or 2,3-dihydroapigenin) and 2,3-dihydroflavonols (such as taxifolin or 2,3-dihydroquercetin). Related compounds include flavan-3-ols, 2,3-dihydrochalcones (1,3-diphenylpropan-1-ones) and flavans. Further, more complex flavan-based compounds include the biflavans and biflavanones. The basic skeleton in each case can be modified with hydroxyl, methoxy, glycosyl, isopentenyl (isoprenyl) and other groups. The condensed tannins derive from C-C-linkage of flavan-3-ols such as afzelechin, (+)-catechin and (−)-epicatechin and are considered separately in Section xiii.

Flavanones. Widespread flavanones (2,3-dihydroflavones) include the 2,3-dihydroflavones eriodictyol (5,7,3',4'-tetrahydroxyflavanone; 2,3-dihydroluteolin), naringenin (5,7,4'-trihydroxyflavanone; 2,3-dihydroapigenin) and pinocembrin (5,7-dihydroxyflavanone; 2,3-dihydrochrysin). Eriodictyol and eriodictyol 4'-methyl ether (hesperetin) induce *Rhizobium* nodulation gene expression; hesperetin and eriodictyol 3'-methyl ether are insect feeding deterrents; and several hesperetin glycosides are oviposition stimulants. The 7-*O*-neohesperidosides of naringenin, eriodictyol and hesperetin are bitter tasting. The flavanolignan flavanone derivatives silandrin, silybin and silychristin from *Silbum marianum* (Asteraceae) are antihepatotoxic. Sanggenon C and sanggenon D bind to the phorbol ester binding site on protein kinase C (PKC).

Dihydroflavonols. Widely distributed 2,3-dihydroflavan-3-ols include the antioxidant 2,3-dihydroflavonols aromadendrin (3,5,7,4'-tetrahydroxyflavanone; 2,3-dihydrokaempferol), ampelopsin (3,5,7,3',4',5'-hexahydroxyflavanone; 2,3-dihydromyricetin), fustin (3,7,3',4'-tetrahydroxyflavanone; 2,3-dihydrofisetin) and taxifolin (3,5,7,3',4'-pentahydroxyflavanone; 2,3-dihydroquercetin). Some flavanols are sweet-tasting, notably 6-methoxyaromadendrin 3-*O*-acetate, 6-methoxytaxifolin and taxifolin 3-*O*-acetate. Taxifolin and fustin inhibit NADH and succinate dehydrogenases and taxifolin inhibits 5-LOX.

Flavans. A number of flavans are variously antimicrobial or dermatitic. The isoprenyl flavans kazinolins A, Q and R from *Broussonetia* species (Moraceae) are cytotoxic.

Biflavanoids. Biflavanoids are linked by C-C bonds. Biflavanones include isochamaejasmin (3,3'-binaringenin), kolaflavanone (3',8''-binaringenin) and the aldose reductase inhibitor manniflavanone (3',8'-bieriodictyol). The *Camellia sinensis* (tea) (Theaceae) biflavanol theasinensin A (6',6''-bi(5,7,3',4',5'-pentahydroxyflavan 3-*O*-galloyl ester), a theaflavin precursor, is apoptotic, cancer chemopreventative and an inhibitor of squalene epoxidase.

Flavan-3-ols. Flavan-3-ols include afzelechin (3,5,7,4'-tetrahydroxyflavan), (+)-catechin, (−)-epicatechin, (−)-epicatechin, (+)-catechin ((+)-3,5,7,3',4'-pentahydroxyflavan), (−)-epicatechin ((+)-3,5,7,3',4'-pentahydroxyflavan), epigallocatechin (EGC; 5'-hydroxyepicatechin), epicatechin-3-*O*-gallate (ECG), (−)-epigallocatechin-3-*O*-gallate (EGCG) and (−)-galocatechin-3-*O*-gallate (GCG). These polyphenols are variously antioxidant ROS scavengers and the monomeric units of condensed tannins (see Section xiii). Enzymes variously inhibited by these flavan-3-ols include squalene epoxidase, protein kinase, aldose reductase, COX and 5-LOX.

xiii. Tannins. The tannins are widely distributed defensive compounds in plants and fall into two major categories, the condensed tannins and the hydrolysable tannins. The condensed tannins essentially derive from the polymerization of the flavan-3-ols (+)-catechin, (-)-epicatechin and their derivatives via C-C links, thus generating flavan oligomers (flavolans). The hydrolysable tannins, defensive compounds confined to dicots, involve a glucose esterified to gallic acid (gallotannins) or ellagic acid-derived hexahydroxydiphenic acid (ellagitannins). The multiplicity of phenolic hydroxy groups enables tannins to hydrogen bond extensively with protein peptide links (-CO-NH-) and protonatable R groups, this property being the basis of "tanning" animal skins to generate leather. Tannins have anti-oxidant activity as ROS scavengers. Various condensed and hydrolysable tannins are cytotoxic with antitumour activity. Notwithstanding the general avidity of tannins for polypeptides, there are many examples of specificity in tannin-protein interactions.

Condensed tannins derive from the polymerization of flavan-3-ols such as (+)-catechin (C; (+)-3,5,7,3',4'-pentahydroxyflavan), (-)-epicatechin (E; (+)-3,5,7,3',4'-pentahydroxyflavan), EGC; 5'-hydroxyepicatechin) and ECG, this typically involving 4 → 8 and 6 → 8 C-C links. The condensed tannins are classified on the basis of the mauve- to red-coloured monomeric anthocyanidin products produced by heating the tannin in acid, for example, as indicated in parentheses as follows: procyanidins (product cyanidin, 3,5,7,3',4'-pentahydroxyflavylium), prodelphinidins (delphinidin, 3,5,7,3',4',5'-hexahydroxyflavylium), propelargonidins (pelargonidin, 3,5,7,4'-tetrahydroxyflavylium) and proluteolinidins (luteolinidin, 5,7,3',4'-tetrahydroxyflavylium).

A variety of condensed tannins are antagonists of particular hormone receptors or inhibitors of particular enzymes, most notably protein kinases.

Hydrolysable tannins involve a glucose esterified to gallic acid (gallotannins) or ellagic acid-derived hexahydroxydiphenic acid (ellagitannins). These complex structures can be described simply in essence by representing galloyl (Phe), galloyl variants and hexahydroxydiphenoyl (Phe-Phe) as G, G' and H, respectively, noting that glucose has five hydroxy groups that can potentially form ester linkages (X-CO-O-Y) with these acids, diesters being formed with H and monoesters with G and G'. Thus, pentagalloyl-β-D-glucose can be represented as G₅-glucose and casuarinin as H₂-glucose-G. The more complex coriariin A can be represented as HG₂-glucose-G'-G'-glucose-HG.

A variety of hydrolysable tannins have been shown to act as hormone receptor antagonists or inhibitors of particular enzymes. The inhibition of protein kinases by various hydrolysable tannins becomes more potent as the number of phenolic groups increases.

xiv. Isoflavonoids. Isoflavonoids have a common structural element of a 3-phenyl chromane which is thence modified by oxidation and substitution to yield the different classes within this group, namely the isoflavones, isoflavanones, isoflavans, pterocarpanes, rotenoids and coumestans. The isoflavonoids are very largely confined to the legumes (Fabaceae) and many such compounds have antifungal activity. Many isoflavonoids are phytoalexins, that is, antifungal compounds synthesized in response to fungal infection of the plant. The structural and functional complexity of the isoflavonoids is briefly sketched below.

Isoflavones are derivatives of the parent compound isoflavone (3-phenylchromone; 3-phenylbenzopyran-4-one). The dietary isoflavone phytoestrogens (notably from soya bean) that bind to the oestrogen receptor are the best known, namely: daidzein (7,4'-dihydroxyisoflavone), genistein (5,7,4'-trihydroxyisoflavone) and glycitein (7-hydroxy-6-methoxyisoflavone) and their respective "pro-phytoestrogen" 7-O-glucoside precursors daidzin,

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glycitin and genistin, respectively, that are inactive or poor as ligands for the oestrogen receptor but which are hydrolysed to the active aglycones after ingestion. Formononetin (daidzein 4'-methylether) is also a "pro-phytoestrogen". The further postprandial 2,3-dihydro products dihydrodaidzein (equol), dihydroglycitin and dihydrogenistein are also active as oestrogen receptor ligands. Isoflavone *C*-glycosides include the anti-atherosclerotic genistein 8-*C*-glycoside, and daidzein 8-*C*-glycoside (puerarin). The isoprenylated isoflavones licoisoflavone A (5,7,2',4'-tetrahydroxy-3'-isopentenylisoflavone), luteone (5,7,2',4'-tetrahydroxy-6-isopentenylisoflavone) and wighteone (5,7,4'-trihydroxy-6-isopentenylisoflavone) are phytoalexins.

Isoflavanones are 2,3-dihydroisoflavones and a number of such compounds are antifungal phytoalexins. Thus, kievitone (2',4',5,7-tetrahydroxy-8-isopentenylflavanone) and the related compounds cyclokievitone, dalbergioidin and 5-deoxykievitone are antifungal phytoalexins induced in *Phaseolus vulgaris* (bean) and other Fabaceae species by fungal infection.

Isoflavans are analogues of the isoflavanones that lack the 4-keto, that is, they are 3-phenylchromanes. The simple isoflavans sativan and vestitol from *Lotus* species (Fabaceae) are antifungal phytoalexins. The pyranoisoflavans glabridin and hispaglabridin are antimicrobials from *Glycyrrhiza glabra* (liquorice) (Fabaceae) roots.

xv. Polycyclic isoflavan-related compounds (neoflavonoids). Pterocarpanes, pterocarpenes, coumestans and rotenoids are polycyclic compounds related to isoflavans and coumarins through the formation of an additional fused furan or pyran ring as a result of introduction of an ether (C–O–C) link between the chromane ring and a 3-phenyl substituent.

Pterocarpanes and pterocarpenes. Pterocarpanes (Phe|C5O|C4O|Phe) are isoflavonoids involving a fusion of chromane and benzofuran rings, that is, they are isoflavans in which a furan ring is formed through generation of an ether link between the chromane and the 3-phenyl. Pterocarpenes are 2,3-dehydropterocarpanes. The phytoalexins anhydroglycinol and phaseollidin are examples of a pterocarpene and a pterocarpan, respectively. Glyceollins I and II (C5O|Phe|C5O|C4O|Phe) from *Glycine* species (Fabaceae) and phaseolin (Phe|C5O|C4O|Phe|C5O) from *Phaseolus* species are pyranopterocarpan phytoalexins.

Coumestans are benzofuranocoumarins. Coumestrol (Phe|C5OL|furan|Phe; coumarin|furan|Phe) is a phytoalexin in *Glycine max* and *Phaseolus* species (Fabaceae). Coumestrol is also oestrogenic as is the pyranocoumestan phytoalexin sojagol (coumarin|furan|Phe|C5O) from *Glycine max*.

Rotenoids have a basic structural element involving fused chromone and chromane rings. The best-known rotenoid is the furanorotenoid rotenone (C5O|Phe|pyran-4-one|C5O|Phe) from *Derris* and *Lonchocarpus* species (Fabaceae), a potent inhibitor of the mitochondrial electron transport chain NADH dehydrogenase (complex I).

xvi. Xanthones. Xanthones have a basic parent tricyclic ring structure, namely that of xanthone (dibenzo- γ -pyrone) (Phe|(4-keto)C4O|Phe). This structure arises from phenylpropanoid (Phe–C₃) and malonyl-coenzyme A (C₃–CoA, ⁻O₂CCH₂CO–S–X) precursors (Phe–C₃ + 2C₃O₃ → Phe–CO₂–Phe + 2CO₂). Xanthones are grouped below into simple xanthones, prenylated xanthones, xanthone-*O*-glycosides, xanthone-*C*-glycosides and pyranoxanthones. In addition, these compounds differ in hydroxy, methoxy, glucosyl, methyl and alkyl substituents.

Simple xanthones include various mutagenic and antibacterial compounds such as bellidifolin (3-methoxy-1,5,8-trihydroxyxanthone). A number of simple xanthones are inhibitors of monamine oxidase A (bellidifolin, demethylbellidifolin, gentiacaulin, isogenitisin and swerchirin), protein kinase (norathyriol) and of xanthine oxidase (athyriol, isoathyriol and norathyriol).

Prenylated xanthenes include α -mangostin (2,8-di-isoprenyl-1,3,6-trihydroxy-7-methoxyxanthone) and γ -mangostin from the fruit of *Garcinia mangostana* (Guttiferae). α -Mangostin inhibits various protein kinases, Ca^{2+} ATPase and HIV-1 protease and binds to the oestrogen receptor and the histamine receptor. γ -Mangostin inhibits HIV-1 protease and various protein kinases.

Glycosylated xanthenes include xanthone-*O*-glycosides such as the antibacterial bellidifolin 8-*O*-glucose (swertianolin) and the widely distributed xanthone-*C*-glycoside mangiferin (1,3,6,7-tetrahydroxyxanthone 2-*C*-glucoside).

Pyranoxanthenes have a pyran ring fused with a xanthone, an example being the antimicrobial isomangostin (C5O | Phe | (4-keto)C4O | Phe) that is structurally related to the prenylated xanthone α -mangostin (2,8-di-isoprenyl-1,3,6-trihydroxy-7-methoxyxanthone) through cyclization involving the 1-hydroxy and 2-isoprenyl. The furanoxanthone psorospermin (C4O | Phe | (4-keto)C4O | Phe) derives from cyclizing involving adjacent C5 side chain and hydroxy substituents yielding a fused furan ring.

1.8 Plant terpenes

Terpenes are composed of isoprenyl (C_5) units and are conveniently grouped as monoterpenes (skeletal basis $\text{C}_{10} = 2 \times \text{C}_5$), sesquiterpenes ($\text{C}_{15} = 3 \times \text{C}_5$), diterpenes ($\text{C}_{20} = 4 \times \text{C}_5$), triterpenes ($\text{C}_{30} = 6 \times \text{C}_5$) and tetraterpenes ($\text{C}_{40} = 8 \times \text{C}_5$). The structures of some representative terpenes are shown in the Appendix (Section 3). Terpenes ultimately derive biosynthetically from acetate (C_2) via the activated acetyl thioester ($\text{CH}_3\text{-CO-S-X}$) acetyl-coenzyme A (acetylCoA; $\text{CH}_3\text{-CO-S-CoA}$) as outlined below (enzymes catalysing key steps being indicated in parentheses).

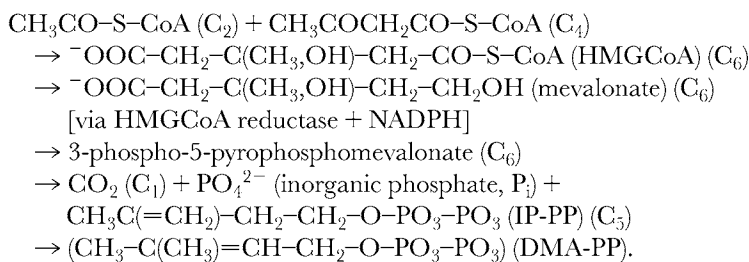
Acetate (C_2) is generated as a result of primary “catabolic” “energy metabolism” involving glucose (C_6) oxidation to pyruvate (C_3) (by the enzymes of the ATP-yielding glycolysis pathway) and subsequent pyruvate decarboxylation (loss of CO_2 , C_1) and oxidation to yield acetylCoA and reduced coenzymes. AcetylCoA (C_2) condenses with oxaloacetate (C_4) to yield the tricarboxylic acid citrate (C_6) which is ultimately oxidized via a succession of C_6 , C_5 and C_4 intermediates to yield oxaloacetate (C_4), CO_2 (C_1), ATP and reduced coenzymes (catalysed by the enzymes of the tricarboxylic acid (or citric acid, Krebs) cycle). The reduced coenzymes (NADH and FMNH₂) are oxidized via the mitochondrial respiratory chain (oxygen being the ultimate electron acceptor), this being coupled to the formation of the “energy-rich” “cellular energy currency” ATP (catalysed by the ATP synthase ($\text{F}_0\text{-F}_1$) complex of oxidative phosphorylation).

Excess acetate (C_2) can be converted to the “mobile” ketone body energy source acetoacetate (C_4) and thence its reduced form hydroxybutyrate (C_4) for transport throughout the body. Excess acetate can be carboxylated (via acetylCoA carboxylase) to form malonylCoA (C_3), the donor for further C_2 additions (with CO_2 elimination) in the “anabolic” synthesis of long chain fatty acids. Fatty acids are components of the phospholipids of cellular membranes and are also stored as triacylglycerols (triglycerides) for subsequent hydrolysis and “catabolic” fatty acid oxidation to yield reduced coenzymes and thence ATP (see Chapter 2).

AcetylCoA (C_2) can also react with acetoacetylCoA (C_4) to generate hydroxymethylglutarylCoA (HMGCoA) (C_6) and thence the isoprenoid precursor mevalonate (C_6). Mevalonate (C_6) ultimately yields the key C_5 isoprenoids isopentenylpyrophosphate ($\text{CH}_3\text{C(=CH}_2\text{)-CH}_2\text{-CH}_2\text{-O-PO}_3\text{-PO}_3$) (IP-PP) and dimethylallylpyrophosphate ($\text{CH}_3\text{-C(CH}_3\text{)=CH-CH}_2\text{-O-PO}_3\text{-PO}_3$) (DMA-PP), the immediate precursors of cholesterol and

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steroid hormones in animals and of a wide range of terpenes in plants. These reactions are summarized below:



IP-PP and DMA-PP can yield volatile C₅ hemiterpenes. At the other extreme, extensive polymerization of the C₅-pyrophosphates (with release of pyrophosphate, PP_i) yields the formation of the plant latex polymers such as *cis*-polyisoprenes (rubber) and *trans*-polyisoprenes (gutta-percha). In between these extremes, a variety of monoterpenes, sesquiterpenes, triterpenes and C₄₀ carotenes derive from these C₅-pyrophosphate precursors.

Head to tail condensation of IP-PP (C₅) and DMA-PP (C₃) with release of PP_i forms geranylpyrophosphate: CH₃-C(CH₃)=CH-CH₂-CH₂-C(CH₃)=CH-CH₂-O-PO₃-PO₃, that is, H(CH₂-C(CH₃)=CH-CH₂)₂-O-PO₃-PO₃ (C₁₀-PP), the starting point for plant monoterpenes. Further, head-to-tail reaction of geranylpyrophosphate (C₁₀-PP) with isopentenylpyrophosphate (C₅-PP) yields farnesylpyrophosphate H(CH₂-C(CH₃)=CH-CH₂)₃-O-PO₃-PO₃ (C₁₅-PP), the parent of plant sesquiterpenes. Head to tail condensation of farnesylpyrophosphate (C₁₅-PP) with IP-PP (C₅-PP) yields geranylgeranylpyrophosphate H(CH₂-C(CH₃)=CH-CH₂)₄-O-PO₃-PO₃ (C₂₀-PP), the parent of plant diterpenes.

Representing the PP-end as the “head”, head-to-head condensation of two geranylgeranylpyrophosphate (C₂₀-PP) molecules ultimately yields phytoene (C₄₀), that is, if one represents the isoprenylpyrophosphate polarities as IP-PP and PP-PI, one could represent phytoene as (IP)₄-(PI)₄.

Head-to-head condensation of two farnesylpyrophosphate (C₁₅-PP) molecules yields a C₁₃-cyclopropane (C₃)-C₁₄ intermediate which is then reduced to yield squalene: H(CH₂-C(CH₃)=CH-CH₂)₃-(CH₂-CH=C(CH₃)CH₂)₃ (C₃₀), that is, if one represents the isoprene polarities as IP and PI, one could represent squalene as (IP)₃-(PI)₃. Squalene is subsequently oxidized [via a squalene monooxygenase] to yield squalene 2,3-epoxide which is cyclized to the tetracyclic sterol terpene lanosterol (C₃₀) [via squalene cyclase].

If as above we simply represent alicyclic rings sharing two Cs by a vertical line, then we can represent the basic tetracyclic structure of lanosterol as C₆|C₆|C₆|C₅ (noting that there are two double bonds and various alkyl substituents and also a 3-hydroxyl on the first of the alicyclic rings). Many subsequent reactions yield cholesterol, a major triterpene membrane component that modifies the fluidity of animal cell membranes and is a precursor for synthesis of animal bile acids (fat solubilizing amphipathic detergents); plant triterpenes; and steroid hormones such as the corticosteroids cortisol and cortisone, the mineralocorticoid aldosterone and the sex hormones testosterone and 17-β-oestradiol. The structure and bioactivity of the plant terpenes is sketched below.

i. Monoterpenes. The monoterpenes (di-isoprenes) are typically strong smelling oils and part of the so-called “essential oils” of odoriferous plants.

Non-cyclic monoterpenes are unsaturated, pleasant-smelling, C₁₀ aliphatic compounds including aldehydes such as citronellal and citral (lemon-scented); the sweet-rose

scented alcohols geraniol and nerol; esters such as geranyl acetate and linalyl acetate (bergamol); and alkenes such as myrcene and β -ocimene.

Monocyclic monoterpenes include the fully saturated menthol (5-methyl-2-isopropylcyclohexanol) (C6) (peppermint smell), the fully unsaturated analogue thymol (5-methyl-2-isopropylphenol) (C6) (smell of thyme) and the partially unsaturated α -terpinene (5,6-dihydro-4-isopropyltoluene) (C6) (lemon odour). Variants derive from different degrees of unsaturation and substitution and from different functional groups (e.g. alkyl, hydroxyl, aldehyde, peroxy and keto groups).

Bornane monoterpenes are exemplified by camphene (2,2-dimethyl-3-methylenebicyclo[2,2,1]heptane), a structure in which two fused cyclopentane rings share three Cs. We can simply represent the camphene skeleton as a cyclohexane with a methylene ($-\text{CH}_2-$) cross-link (C6($-\text{CH}_2-$)). The keto derivative camphor (camphor smell), the ether eucalyptol (eucalyptus smell) and the simple bornene α -pinene (pine smell) are familiar examples.

Tropolone monoterpenes include the antifungals β - and γ -thujaplicin (4- and 5-isopropyltropolones, respectively, tropolone being 2-hydroxycycloheptatrienone (C7)). The antioxidant β - thujaplicin (hinokitiol) is an inhibitor of 5-, 12- and 15-LOXs.

Thujane monoterpenes are based on the bicyclic (C3|C5) monoterpene thujane and include umbellone (thujan-2-one) and the neuroactives α -thujone and β -thujone (thujan-3-one isomers) that can cause convulsions. Thujones are GABA(A) receptor antagonists and are the active constituents in oil of wormwood from *Artemisia absinthium* (Asteraceae) used in the alcoholic drink absinthe that was eventually banned because of its deleterious neurotoxic effects.

Chrysanthemum carboxylic acid esters. Chrysanthemum monocarboxylic acid (CMC) and dicarboxylic acid (CDC) esters include the toxic cinerins and pyrethrins from *Pyrethrum* (*Chrysanthemum cinerarifolium*) (Asteraceae) namely cinerin I (CMC cinalone ester), cinerin II (CDC monomethyl ester cinerolone ester), pyrethrin I (CMC pyrethrolone ester) and pyrethrin II (CDC monomethyl ester pyrethrolone ester). The chrysanthemum carboxylic acids are cyclopropane-based monoterpenes and cinalone and pyrethrolone are cyclopentanone monoterpene alcohols. The pyrethrins (and their insecticidal synthetic derivatives) are toxic to insects through keeping cell membrane voltage-gated Na^+ channels open and thus impairing neurotransmission.

ii. Iridoids. Iridoids are monoterpenes deriving biosynthetically from geranylpyrophosphate (C_{10}) and are typically bicyclic hemiacetals (C5|C5OH) or lactones (C5|C5OL). The heterocyclic ring is typically a hemiacetal, ring closure deriving from intramolecular reaction between an aldehyde ($-\text{CHO}$) and another aldehyde or a hydroxyl ($-\text{OH}$) to yield a $-\text{CH}(\text{OH})-\text{O}$ -linkage in the iridoid (i.e. C5|C5OH). Alternatively, heterocyclic ring closure involves lactone formation involving reaction of a carboxyl ($-\text{COOH}$) with an hydroxyl ($-\text{OH}$) to form an intracyclic ester or lactone linkage ($-\text{CO}-\text{O}-$) as in nepetalactone (C5|C5OL). The lactone and hemiacetal rings are denoted below as C_nOL and C_nOH , respectively, (where n is the number of C atoms in the ring). The hemiacetal hydroxyl can be glycosylated. The hemiacetal structure is unstable and ring opening of the aglycone (e.g. generated by acid hydrolysis) yields an aldehyde that is very reactive (yielding coloured polymeric forms). In the seco-iridoids, the alicyclic C5 ring is opened or expanded by oxygen insertion.

Simple iridoids are volatile iridoids of which the best known is the cat-exciting nepetalactone (C5|C5OL) from *Nepeta cataria* (catnip) (Lamiaceae). The lactone nepetalactone, the hemiacetal neomatatabiol (C5|C5OH), iridodiol (in the ring opened bi-aldehyde

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OHC-C5-CH(CH₃)-CHO) and ring-closed (C5|C5OH) forms) and the ring-opened bi-aldehyde dolichodial are volatile simple iridoids variously having insect repellent and attractant activity. The iridoid hemiacetal valtratum from the roots of *Valeriana* (valerian) and *Centranthus* is an anxiolytic psycholeptic and related valepotriates such as isoaltrate may also contribute to the tranquillizing, anxiolytic and anti-insomnia effects of valerian (noting that the baldrinal and homobaldrinal aldehyde products are mutagenic).

Iridoid glycosides include the bitter hemiacetal glucosides (C3|C5|C4OH-O-glucoside) catalpol, harpagoside and loganin (loganoside). The hemiacetal glucoside aucubin (aucuboside) is toxic because the aglycone C5OH ring can open and thence react with proteins to form imine adducts.

Seco-iridoids involve opening of the C5 ring and include the glucoside swertiamarin (C5OL|C5OH-O-glucoside) (the aglycone of which, erythrocentaurin, is very bitter) and oleuropein (aryl-C5OH-O-glucoside) which can form covalent adducts with proteins through reaction with a readily oxidized alkene side chain. Secologanin is similarly reactive through the aldehyde and ethylenyl substituents on the residual heterocyclic ring and is a precursor for particular alkaloids through reaction with amines.

Non-glycoside iridoids include aglycones stabilized through formation of a cyclic ether ring involving the hemiacetal hydroxy, examples including the antimicrobials plumericin and isoplumericin (C4OL*|C4O*,*' |C5*,*' |C5O*,*') (where the superscripts * and *' indicate that three Cs are respectively shared by the three rings thus denoted). The tranquillizing iridoid hemiacetals didrovaltratum and valtratum from *Valeriana officinalis* (valerian) (Valerianaceae) have isobutyric acid esterified on the hemiacetal hydroxy and another hydroxy.

iii. Sesquiterpenes. Sesquiterpenes derive from farnesylpyrophosphate (C₁₅) having three isoprene units (C₅) linked head-to-tail and occur in plant essential oils. Sesquiterpenes include a huge variety of cyclic compounds as well as simple non-cyclic farnesyl derivatives. The cyclic sesquiterpenes include monocyclic, bicyclic and tricyclic compounds and the sesquiterpene lactones. The sesquiterpene lactones are a particularly large group and are dealt with separately in Section iv.

Non-cyclic sesquiterpenes include the volatiles α- and β-farnesene (which have alarm pheromone activity) and pleasant odorants from *Citrus sinensis* (orange) (Rutaceae), namely α- and β-sinensal (mandarin peel odour) and nerolidol from orange flower oil (oil of neroli). The epoxide JH III is produced by *Cyperus iria* (Cyperaceae) and acts critically on insect development.

Monocyclic sesquiterpenes typically have an alkylated C6 ring but macrocyclic examples include the insect antifeedant shiromodiol diacetate (C10) and the insect attractant odorants α-humulene from *Humulus lupulus* (hops) (Cannabaceae) (C11 ring) and germacrene B from *Citrus* peel (C10 ring). Monocyclic sesquiterpenes with a C6 ring include: juvabione (that has insect JH activity); the important plant growth regulator abscisic acid (that regulates stomatal opening, bud dormancy and leaf abscission); the odorants curcumen and zingiberene from the oil of both *Curcuma aromatica* (turmeric) and *Zingiber officinale* (ginger); the sweet compounds hernandulcin and 4β-hydroxyhernandulcin; the anti-inflammatory bisabolol (that promotes wound healing); and the *Viola* (Violaceae) violet scents, the α- and β-irone isomers.

Bicyclic sesquiterpenes include a variety of bioactive compounds including: the Solanaceae phytoalexins capsidiol (C6|C6) from *Capsicum frutescens* (pepper) and the *Solanum tuberosum* (potato) antifungals rishitin (C6|C6) and solavetivone (C6-C5); the *Ipomoea batatas*

(sweet potato) (Convolvulaceae) furanoid phytoalexin ipomeamarone (THfuran-furan); the hepatotoxic furanoid sesquiterpenes dehydromyodesmone (C6-C5) and dehydrongainone (THfuran-furan) from the toxic shrub *Myoporum deserti* (Myoporaceae); the piscicidal 5-LOX inhibitors buddledin A, B and C (C4|C6); and the spasmolytic cAMP PDE inhibitor petasin (C6|C6).

Neuroactive bicyclic sesquiterpenes include the antifeedant cinnamodial (C6|C6) (a vanilloid (capsaicin) receptor agonist), α -eudesmol (C6|C6) (a Ca^{2+} channel blocker) and valerenic acid (C5|C6) (which inhibits GABA breakdown). Odorant bicyclic sesquiterpenes include α -vetivone (C6|C6) and β -vetivone (C6·C5) from *Vetiveria zizanoides* (vetiver grass) (Poaceae) roots. The anti-inflammatory antioxidants chamazulene (C5|C7) and guaiazulene (C5|C7) derive post-extraction from steam distillation of leaves of *Matricaria chamomilla* (chamomile) (Asteraceae). The dialdehyde warburganal (C6|C6) is toxic because of its reactivity with thiols and the amino groups of proteins. The dimeric, bicyclic, sesquiterpene phenolic aldehyde gossypol (Phe|Phe-Phe|Phe) from *Gossypium hirsutum* (cotton) (Malvaceae) seed oil is a potent inhibitor of various protein kinases and of the Ca^{2+} -dependent protein phosphatase calcineurin.

Non-lactone tricyclic sesquiterpenes include the *Juniper* (Cupressaceae) odorants α -cedrol and α -cedrene (C5|C5|C6); the *Piper cubeba* (cubeb fruit) (Piperaceae) flavours α - and β -cubebene (C5|C3|C6); and the fragrant patchouli alcohol (tetramethyl-1,6-methano-octahydronaphthalene) (C6|C6(-CH(OH)-(CH₃)₂-)) from *Pogostemon patchouli* (Lamiaceae) patchouli oil. The carcinogenic DNA alkylating and breaking norsesquiterpene pterisin B (C3·C6|C5) occurs as a glucoside ptaquiloside in *Pteridium aquilinum* (bracken fern) (Dennstaedtiaceae) (the fern “fiddlehead” sprouts are eaten in New Brunswick, Canada and elsewhere in the region and are toxic if insufficiently cooked).

iv. Sesquiterpene lactones. The sesquiterpene lactones are a large class of C₁₅-based terpenes having a common five-membered γ -lactone ring system (a tetrahydrofuranone) involving cyclization through esterification of a carboxy with a γ -hydroxy of the precursor HO-CH(X)-CH(Y)-CH(Z)-COO⁻. Sesquiterpene lactones are typically unsaturated di- or tri-cyclics and many have a reactive methylene (=CH₂) substituent. Many of these terpenes derive from Asteraceae (Compositae) plants and are variously bitter tasting, insect antifeedants, cytotoxic and antineoplastic. These compounds can be grouped based on the various fused ring structure arrangements. In summarizing, the sesquiterpene lactone structures below the common C4 lactone ring element will be represented as C4OL and the corresponding C5 lactone as C5OL. Similarly, the commonly occurring C4 and C5 cyclic ethers are represented as C4O and C5O, respectively. Where condensed rings share three Cs, a double vertical line (||) is used and remember that an asterisk (*) indicates that a ring is part of a tricyclic structure in which all rings share one C.

Elemanolides. The elemanolide sesquiterpene lactones (C5OL|C6|C4OL) are exemplified by the antifeedants vernodalin (C5OL|C6|C4OL) and vernodalol (C5OL|C6) (in which the C4OL lactone ring is opened and the carboxy methylated). Vernodalin contributes to the bitter taste of *Vernonia amygdalina* (Asteraceae) ingested by parasite-infected chimpanzees.

Eudesmanolide sesquiterpene lactones (C6|C6|C4OL) include a variety of variously cytotoxic compounds. The antifeedants alantolactone and isoalantolactone (helenin being a mixture of the two) (C6|C5|C4OL=CH₂) are antimicrobial. The pro-apoptotic activity of these compounds may derive from the reactivity of the α -methylene- γ -butyrolactone ring

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(C4OL=CH₂). Santamarin may form a covalent adduct in inhibiting transcription factor NFκB binding to DNA.

Guaianolides (C5|C7|C4OL) include many cytotoxic and antineoplastic compounds. Various guaianolides are bitter tasting and insect antifeedants. Zaluzanin inhibits bacterial lipopolysaccharide-induced NFκB-mediated expression of iNOS by immune cells and cynaropicrin inhibits similar induction of TNF-α expression through formation of a covalent protein adduct. Costunolide, 7-hydroxycostunolide and 3,4-epoxydehydroleucodin act in a similar manner to inhibit NFκB binding to DNA.

Other notable guaianolides include achillin, artabsin and matricin (that can be converted on heating to the anti-inflammatory radical scavenger and COX inhibitor chamazulene); the cytotoxic and antineoplastic chloroguaianolides eupachlorin, eupachlorin acetate and eupachloroxin; the cytochrome P450 aromatase inhibitors 10-epi-8-deoxycumambrin, dehydroleucodin and ludartin; and thapsigargin, thapsivillosin and trilobolide (inhibitors of the transmembrane Ca²⁺ pumping Ca²⁺ ATPase).

Pseudoguaianolides (C5|C7|C4OL) differ from the guaianolides in having a 5-methyl substituent (at the junction of the C5 and C7 rings) and this group includes many insect antifeedants and compounds with cytotoxic and antineoplastic activity. Ambrosin and hymenin trigger apoptosis in leukaemia cells. The anti-inflammatory helenalin alkylates the p65 subunit of NFκB, thereby inhibiting the function of this inflammation-related transcription factor. Glutathione adducts of helenalin and 11α,13-dihydrohelenalin acetate inhibit glutathione S-transferase and helenalin inhibits 5-LOX. 2,3-Dihydrohelenalin and *bis*-helenaliny malonate inhibit IMP dehydrogenase.

Germacranolides have a common bicyclic (C10|C4OL) structure but some (e.g. budlein A) have an additional fused furan ring through an ether linkage across the larger ring. Many germacranolides are cytotoxic and antineoplastic. Parthenolide (C10|C4OL) from the antimigraine herb *Tanacetum (Chrysanthemum) parthenium* (feverfew) (Asteraceae) is a serotonin receptor (5HT-R) antagonist. Parthenolide and costunolide inhibit the phosphorylation of IκB that is required for pro-inflammatory activation of NFκB.

Tutinanolide sesquiterpene lactones are epoxides having a common C6|C5epoxide bicyclic element to which is appended a five-membered lactone structure involving three Cs of the C6 ring through an ester (–CO–O–) cross-link across the ring (this is denoted as a (C4OL*|C6*(–CO–O–)|C5*epoxide) structure). Important compounds of this kind include the *Menispermum oculus* (Menispermaceae) GABA(A) receptor and glycine receptor antagonists picrotin and picrotoxinin (C4OL*|C6*(–CO–O–)|C5*epoxide). Other excitatory tutinanolides that are GABA(A) receptor antagonists include coriamyrtin (C6(–CO–O–)|C5epoxide) and tutin (2-hydroxycoriamyrtin) from *Coriaria* species (Coriariaceae) and the Euphorbiaceae mellitoxin (C6(–CO–O–)|C5epoxide) that also derives from the honey of bees feeding on *Coriaria* species.

Other sesquiterpene lactones include the toxic Asteraceae seco-pseudoguaianolides hymenoxon (P|C7|C4OL) (from the toxic *Hymenoxys* and *Helenium* species) that alkylates DNA and vermeerin (C5OL|C7|C4OL) (from the toxic *Geigeria* species) that forms adducts with protein cysteines; the seco-guaianolides (xantholides) (C7|C4OL) xanthinin and xanthumin that have auxin antagonist and antifeedant activity, respectively; and the GABA(A) receptor antagonist anisatin (C5|C6(C3OL)|C5OL).

Artemisinin (qinghaosu) (3,12-peroxyC6O*|C5OL*|C6*) from *Artemisia annua* (Asteraceae) is of major importance as an antimalarial because of extensive resistance of *Plasmodium falciparum* to antimalarials such as chloroquine. Artemisinin has a 3,12-peroxy (–O–O–) substituent spanning the C6O ring. Artemisinin alkylates and inhibits glutathione S-transferase.

v. Diterpenes. Diterpenes derive from the C₂₀ isoprenoid geranylgeranylpyrophosphate (four head-to-tail-linked isoprenes). Geranylgeraniol and the chlorophyll moiety phytol are acyclic diterpenes (Section 3, Appendix). Cyclic diterpenes vary in the number, nature and disposition of the ring structures. The core alicyclic skeleton of the various diterpenes usually involves fused C3, C4, C5, C6 and C7 alicyclic rings that are typically (but not always) completely saturated. Carboxy and hydroxymethyl groups (or carboxymethyl and hydroxy groups) on adjacent Cs can cyclize to form a fused five-membered lactone ring (C4OL). A fused, reduced six-membered lactone ring (C5OL) derives from lactone formation from, for example, carboxymethyl and hydroxymethyl groups on adjacent Cs. In addition, epoxides can be formed from oxidation of double bonds.

The diterpenes are a structurally diverse group of natural products, of which many are toxic or otherwise bioactive. In the following sketch, diterpene structural complexity has been simplified as before by representing fused rings sharing two Cs as C_n|C_n. Ring systems with more than two fused rings are mostly angular (cf. fully reduced phenanthrene) rather than linear (cf. fully reduced anthracene). In some cases, furan and pyran rings are involved that have different degrees of saturation. The different classes of diterpenes are dealt with below in alphabetical order for ease of reference.

Abietane diterpenes (C6|C6|C6 with varying degrees of unsaturation) include the 5-LOX inhibitor abietane, the GABA(A) receptor antagonist taxodione and the bitter tastant carnosol.

Clerodanes involve a (C6|C6) group variously linked to furan (unsaturated C4O), pyran (unsaturated C5O), methyleneoxy and methylenedioxy rings. Clerodanes include bitter tastants and antifeedants as exemplified by the extremely bitter component columbin of the bitter tonic made from roots of *Jateorhiza columba* (columba root) (Menispermaceae).

Daphnanes (C5|C7|C6) include a variety of cytotoxic, irritant, inflammatory and toxic compounds from the Thymelaeaceae and the Euphorbiaceae. Of particular note are the highly inflammatory PKC activators resiniferatoxin and tinyatoxin from *Euphorbia* species (Euphorbiaceae) and thymeleatoxin from *Thymelea hirsuta* (Thymelaeaceae). While the non-ester resiniferonol is inactive, the ester (X-CO-O-Y) resiniferatoxin is both an anti-nociceptive vanilloid receptor (capsaicin receptor) agonist and a PKC activator, as is the ester tinyatoxin.

Gibbanes have a complex (C6*|C4OL*|C5*'|C6*'|C5*') structure (noting that the central C5*' shares a common C with both C6*|C4OL* rings and the C6*'|C5*' rings, respectively). The gibbanes include a large number of plant growth regulators called gibberellins of which the best known is gibberellic acid (gibberellin A₃ or GA₃) which controls growth and seed dormancy. Gibberellic acid is produced by the rice pathogen *Gibberella fujikuroi* (*Fusarium moniliforme*) and causes greatly increased, spindly rice stalk growth. Gibberellic acid is used to induce barley seed aleurone α-amylase production in malting prior to brewing beer.

Ginkgolides (C4OL|C5^{3*,4*}|C4OL^{3*,4*}(|C4O^{3*,3*,4*}|C4OL^{3*})|C5^{3*,4*}) (noting – in the worst case you will encounter in this chapter – that the superscripts 3*, 3'* and 4* indicate three separate C atoms shared by 3, 3 and 4 rings, respectively, as denoted). Ginkgolides are anti-inflammatory, bitter antifeedants from *Ginkgo biloba* (Ginkgoaceae). Ginkgolide A is a PAF antagonist and consequently anti-inflammatory.

Grayanotoxins (C5|C7*|C6*||C5*) are highly toxic Ericaceae compounds of which grayanotoxin I is the best known. Grayanotoxin I opens voltage-gated Na⁺ channels from the inside of the cell thus causing depolarization, impairment of neurotransmission and interference with proper cellular signalling.

Ingenanes (C5*|C7*||C7*|C3) include irritants and secondary tumour promoters (co-carcinogens) from *Euphorbia* species (Euphorbiaceae) that activate PKC. While the non-ester

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precursor ingenol is active, 17-hydroxyingenol 20-hexadecanoate, ingenol 3-benzoate, ingenol 3,20-dibenzoate and ingenol 20-hexadecanoate all interact with PKC.

Jatrophanes (C5|C12) are cytotoxic, antitumour compounds from *Jatropha* species (Euphorbiaceae). Jatrophane binds to DNA and also has activity as a glutamate receptor antagonist.

Kauranes (common structural element C6|C6*|C6*||C5*) and related compounds include natural products that are variously antifeedants, bitter and otherwise bioactive. Thus, the glycoside toxin atractyloside inhibits the mitochondrial ADP/ATP translocator, the sweet glycoside stevioside blocks Ca²⁺ channels and the antifeedant inflexin inhibits aromatase. Some kauranes having a fused furan ring (i.e. skeletal structure furan|C6|C6*|C6*||C5*) include the very bitter glycoside mascaroside and the coffee components cafestrol (cafesterol) and kahweol ($\Delta^{1,2}$ -cafestrol). Cafestrol and kahweol (present in boiled (unfiltered) coffee) raise plasma low density lipoprotein (LDL)-associated cholesterol (by decreasing expression of LDL receptors) but are also chemopreventative by decreasing expression of the cytochrome P450-linked CYP oxygenases that generate genotoxic metabolites from precursors (e.g. genotoxic aflatoxin B1-8,9-epoxide from the consumed *Aspergillus flavus* (fungal) coumarin procarcinogen aflatoxin B1).

Labdanes (core C6|C6 linked to variously reduced furan or pyran moieties) include the Lamiaceae (Labiatae) diterpenes forskolin (C6|C6|pyran) (that activates adenylyl cyclase, the enzyme catalysing cyclic AMP formation from ATP) and premarrubiin (C4OL*|C6*|C6*·furan-furan) that converts to the bitter non-opiate antinociceptive marrubiin (C4L*|C6*|C6*-(CH₂)₂-furan).

Tigliane (C5|C7|C6|C3) diterpenes include the highly irritant, toxic, co-carcinogenic, PKC activating phorbol esters from Euphorbiaceae plants. While not being activated by the parent compound phorbol, PKC is activated by plant-derived esters of phorbol, 4-deoxyphorbol and 12-deoxyphorbol (e.g. 12-*O*-palmitoyl-16-hydroxy-phorbol 13-acetate, 12-deoxyphorbol 13-benzoate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate-20-acetate, sapintoxin A (4-deoxyphorbol 12-(2-methylamino)benzoate-13-acetate) and 12-tetradecanoylphorbol 13-acetate (TPA)), as well as by synthetic phorbol esters.

Other diterpenes include the antifungal phytoalexin casbene (C3|C14); the PKC-binding dihydroxyatisanone and trihydroxyatisane (C6|C6|C6|C6); the toxic totarane diterpenes hallactones A and B (C4OL*|C6*|C6*|C5OL); the pimarane pimaric acid (C6|C6|C6); the labour-inducing oxepane macrocyclic ethers montanol and zoapatanol (C7O); portulal (C7|C5); lathyrol (C5|C11|C3) and the macrocyclic insect trail pheromone neocembrene (C14) that is also found in certain plants.

vi. Triterpenes. Triterpenes derive from cyclization of the linear C₃₀ precursor squalene, remembering that if we denote isoprene (C₅) as IP (to indicate structural head and tail polarity) then squalene has the structure (IP)₃-(PI)₃. Triterpenes are polycyclic and often glycosylated. The non-glycosylated aglycones usually have about thirty Cs, but some have more or fewer C atoms. Thus, one can distinguish between the C₃₀ triterpenoid saponin aglycones (saponin aglycones), the cucurbitacin aglycones and other C₃₀ triterpenes as opposed to the C₂₇ spirastane-based steroid saponin aglycones, C₂₄ bufadienolides, C₂₃ cardenolides, nortriterpenoid C₂₆ limonoids and C₁₉-C₂₀ quassinoids. Further, the phytosterols are structurally very similar to cholesterol (C₂₇) but the major phytosterols have 1-2 more Cs in the side chain furthest removed from the 3-hydroxy. The structural and functional complexity of the terpenes is briefly sketched below.

C₃₀ triterpenoid saponins and sapogenins. Saponins are terpenoid amphipathic compounds having water-soluble sugar residues linked (via glycosidic links formed between the sugar hemiacetal and terpenoid OHs) and a relatively hydrophobic (water repelling) triterpenoid aglycone part. Amphipathic compounds (i.e. compounds having both hydrophilic and hydrophobic regions) typically foam (by accumulating at an air–water interface) and can act as detergents (by solubilizing hydrophobic compounds such as phospholipids). Accordingly, saponins have detergent properties and can be haemolytic through solubilizing the cell membrane of red blood cells.

The C₃₀ sapogenins (the aglycone moieties) typically have a non-linear (i.e. reduced phenanthrene-like) 3-OH-C6|C6|C6|C6 skeletal structure with glycosylation often at the 3-OH but also occurring at OHs more distal to the 3-OH. Unless indicated otherwise, the compounds discussed below have this skeletal structure. An illustrative exception is the nucleoside transport inhibitor cimicifugoside which has a 3-*O*-glycosyl (Glyc)-C6|C6|C6|C5|pyran·furan-epoxide structure.

Some triterpenoid saponins are bitter tastants (e.g. helianthoside A) and others are sweet tasting, most notably the 3-*O*-glycosides abrusosides A–D (C6|C6|C6|C5-CH(CH₃)-C5L 3-*O*-glycosides) from *Abrus* species (Fabaceae) and glycyrrhizin (glycyrrhizic acid) from the rhizomes and roots of *Glycyrrhiza glabra* (licorice) (Fabaceae). In contrast, the 3-*O*-glycoside gymnemic acid, the 3-*O*-glycoside of barringtonenol (from tea) and jegosaponins A–D have antisweet activity (i.e. abolish a sweet tastant response) (Chapter 10).

Glycyrrhetic acid (glycyrrhetic acid) (the aglycone of glycyrrhizic acid) inhibits 11β-hydroxysteroid dehydrogenase (thus impairing cortisol oxidation to cortisone and causing hyper-mineralocorticosteroidism when licorice is taken in excess). Glycyrrhetic acid, oleanolic acid and ursolic acid inhibit protein kinases. Gypenosides (C6|C6|C6|C5 glycosides) and saikosaponin A inhibit the Na⁺ pump (Na⁺, K⁺-ATPase). α-Hederin (sapindoside A) and oleanolic acid inhibit chitin synthetase II. Oleanolic acid and ursolic acid inhibit DNA polymerase.

Other C₃₀ triterpenoids have been shown to interact with specific biochemical targets. Such triterpenes are classified in terms of their skeletal arrangement, for example, cycloartanes, friedelanes, oleanane, taraxanes and ursanes (C6|C6|C6|C6|C6), fernanes, hopanes and lupanes (C6|C6|C6|C6|C5), dammaranes and euphanes (C6|C6|C6|C5-C₈), and protolimonoids (C6|C6|C6|C5-P). The friedelane tingenone binds to DNA and inhibits DNA-dependent RNA and DNA synthesis. The ursane α-amyrin, the lupane lupeol and fatty acid esters of these triterpenes inhibit cyclic AMP-dependent protein kinase (PKA) and the serine proteases trypsin and chymotrypsin. A range of Asteraceae cycloartane, dammarane, oleanane and taraxane triterpenoids that inhibit phorbol ester-induced inflammation are also inhibitors of trypsin and chymotrypsin.

Steroid saponins are glycosides of spirostane triterpenoid sapogenins that have a basic 3-OH-C6|C6|C6|C5|THfuran·THpyran skeleton. Steroid saponins are in general non-toxic but have a foaming and detergent propensity. The steroid glycoside digitonin and its aglycone digitogenin derive from seeds of *Digitalis purpurea* (foxglove) (Scrophulariaceae). Digitonin is widely used in biochemical investigations as a “gentle” non-ionic detergent to solubilize membranes, for example, to prepare submitochondrial particles from the mitochondrial inner membrane. The steroid glycoside officinalisin I from the roots of *Asparagus officinalis* (asparagus) (Liliaceae) is bitter whereas the glycoside osladin is sweet. The steroid glycoside gitonin from foxglove leaves is a cyclic AMP phosphodiesterase inhibitor.

Cucurbitacins are oxygenated triterpenes (C₃₀; typical skeletal structure C6|C6|C6|C5-C₈) that can be glycosylated. Cucurbitacins are typically bitter tastants and

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antifeedants present in plants of the Cucurbitaceae in particular as well as having been found in some other plant families. Cucurbitacins are in general bitter tastants and antifeedants. However, some cucurbitacins such as the glycosides bryodulcoside and carnosifloside VI are sweet tastants. The aglycones cucurbitacins B and D are ecdysone antagonists and can act both as antifeedants and as insect attractants. Cucurbitacins can be toxic and cytotoxic. The aglycone cucurbitacin E disrupts the cellular actin cytoskeleton. Some cucurbitacin glycosides from *Picria fel-terrae* (Scrophulariaceae) inhibit both the classical and alternative pathways of the complement system.

Phytosterols are structurally very similar to cholesterol and the major phytosterols (campesterol, sitosterol and stigmasterol) have the same kind of membrane viscosity modulating function in plants that cholesterol (C₂₇; 3-OH-C6|C6|C6|C5-C₈) has in animals. Campesterol (24-methylcholesterol), sitosterol (24-ethylcholesterol) and stigmasterol (Δ^{22} , 24-ethylcholesterol) are widespread phytosterols. The “animal” sterols lanosterol and cholesterol are present in particular plants. Phytosterol esters reduce cholesterol absorption and lower LDL-cholesterol.

The insect moulting hormones ecdysone and 20-hydroxyecdysone (2,3-OH-C6|C6|C6|C5-C₈) are elaborated by particular plants as are a large number of structurally very similar phytoecdysones that mimic ecdysone action in insect metamorphosis. The C₁₉ animal androgens androstenedione and testosterone (3-keto-C6|C6|C6|C5) are present in *Pinus sylvestris* (Pinaceae) and the C₁₈ oestrogens 17 β -oestradiol, oestriol and oestrone are elaborated by particular plants. The elaboration of phytoecdysones and testosterone and oestrogen receptor agonists would potentially perturb the development of herbivore pests. The plant growth regulator brassinolide (2,3-OH-C6|C6OL|C6|C5-C₈) is also active as an ecdysone antagonist.

Cardenolides, cyclic bridged cardiac glycosides and bufadienolides are extremely toxic triterpenoids that are C₂₃ and C₂₄, respectively, as aglycones and derive from a C₃₀ triterpene precursor. The cardenolides (3-OH-C6|C6|C6|C5-C₄OL) (fused rings successively denoted A, B, C and D) can have a *cis*-configuration at the junction of the A and B rings (5 β -cardenolides such as digoxigenin) or a *trans*-configuration (5 α -cardenolides such as aspeciogenin from *Asclepias* species (Asclepiadaceae)). The cardenolides are typically glycosylated and the cardiac-active compounds are referred to as cardiac glycosides. The cardiac glycosides inhibit the Na⁺ pump (Na⁺, K⁺-ATPase) that is responsible for maintaining a low cytosolic Na⁺ and high cytosolic K⁺ concentration critical for cell excitability, maintenance of low cytosolic Ca²⁺ concentration and for neurotransmission.

Among the best-known cardenolide glycosides (aglycones in parenthesis) are digitalin (gitoxigenin), gitoxin (gitoxigenin), digitoxin (digitoxigenin) and digoxin (digoxigenin) from *Digitalis* species (Scrophulariaceae), notably *Digitalis purpurea* (foxglove). The foxglove leaf extract (digitalis) has been used for several centuries for cardiac insufficiency, inhibition of the Na⁺ pump successively lowering the Na⁺ gradient across the cell membrane, decreasing Na⁺-dependent Ca²⁺ pumping out of the cell, increasing cytosolic Ca²⁺ concentration and increasing cardiac muscle contraction. Other important cardiotoxic cardiac glycosides (aglycones in parenthesis) are ouabain (ouabagenin) and strophanthin-K (strophanthidin) from *Strophanthus* species (Apocynaceae). Ouabain has been found to be an endogenous Na⁺ pump regulator and signalling compound in animals.

Various Asclepiadaceae 5 α -cardenolides (C₂₃; 2,3-di-OH-C6|C6|C6|C5-C₄OL) form cyclic bridged glycosides linking the sugar via the 2- and 3-hydroxyls of the aglycone, an example being asclepin from *Asclepias* species. Bufadienolide (C₂₄; 3-OH-C6|C6|C6|C5-C₄OL) glycosides include (aglycone in parenthesis) scillaren A (scillarenin) from *Scilla maritima* (Liliaceae) and hellebrin (hellebrigenin) from *Helleborus niger* (Ranunculaceae).

Limonoids are C_{26} nortriterpenoids deriving from a C_{30} triterpene precursor. The best known limonoids are the *Azadirachta indica* (neem tree) antifeedant azadirachtin ($C5OL^*|C4O^*|C6^*-C6O(\text{epoxide}; \text{methylene cross-link})|furan$) and the *Citrus* species (Rutaceae) bitter antifeedant limonin ($C5OL^*|C4O^*|C6^*|C6|C5OL(\text{epoxide})-furan$). Limonin gives a delayed bitter taste to *Citrus* fruit. The limonoids are typically bitter compounds with insect antifeedant activity.

Quassinoids are typically C_{19} and C_{20} nortriterpenoids deriving from processing of a C_{30} triterpene precursor. These compounds typically have a basic $C6|C6^*|C6^*||C4O^*|C5OL^*|$ skeleton as typified by the cytotoxic bruceines from *Brucea* species (Simaroubaceae). Other quassinoids include the very bitter tastants quassin ($C6|C6^*|C6^*|C5OL^*$) from *Quassia amara* (Simaroubaceae) and nigakihemiacetal A ($C6|C6^*|C6^*|C5OH^*$). Many quassinoids are bitter tastants and cytotoxic. Chaparrinone and related quassinoids from *Hannoa* species (Simaroubaceae) are antimalarials.

vii. Carotenes. Carotenes derive from geranylgeranylpyrophosphate $H(CH_2-C(CH_3)=CH-CH_2)_4-O-PO_3-PO_3$ (C_{20} -PP). Representing the PP-end as the “head”, head-to-head condensation of two geranylgeranylpyrophosphate (C_{20} -PP) molecules ultimately yields phytoene (C_{40}), that is, if one represents the isoprene polarities in isopentylpyrophosphate (IP-PP) as IP (tail-head) and PI (head-tail), one could represent phytoene as $(IP)_4-(PI)_4$. Because of the extensive conjugated double bond systems (i.e. $(-C=C-C=C-)_n$) the carotenes are coloured, the colour ranging from yellow to red. Accordingly, carotenes are important for pollination (attracting insects to flowers) and seed dispersal (attracting herbivores to fruit).

The most abundant carotene is β -carotene which after ingestion gives rise to vitamin A (all-*trans*-retinol) (C_{20}) that is involved in proper development (via the cytoplasmic retinoid receptors that switch on expression of specific sets of genes). The aldehyde derivative retinal is involved in vision as the chromophore covalently linked to opsin proteins and which initiates a G protein-linked signalling pathway after undergoing light-dependent isomerization. The signalling pathway in vision successively involves conformational change of the opsin-retinal complex (rhodopsin), release of G α -GTP from the G protein complex, activation of cyclic GMP phosphodiesterase by G α -GTP, decreased cyclic GMP, closure of cyclic GMP-gated Na^+ channels and transmembrane potential hyperpolarization (see Chapters 3 and 5). Vitamin A ((all *E*)-2,3,7-dimethyl-9-(2,6,6-trimethyl)-1-cyclohex-1-yl)-2-4,6,8-nonatetraen-1-ol) can be simply represented as cyclic $(IP)_2-(IP)_2-OH$ and β -carotene as cyclic $(IP)_2-(IP)_2-(PI)_2$ -cyclic $(PI)_2$. Accordingly, oxidation of β -carotene yields two molecules of vitamin A.

In addition to β -carotene there are a variety of other C_{40} pro-vitamin A carotenes that differ from β -carotene in the nature of the terminal cyclic moieties. Thus, representing the “right” cyclic moiety as X, we can represent β -carotene as $X-(IP)_2-(PI)_2-X$ that yields two molecules of vitamin A or $X-(IP)_2-OH$. Carotenes can have different cyclic moieties X' (where $X' \neq X$) or no cyclic isoprene dimer moieties. Other C_{40} pro-vitamin A carotenes that yield only one vitamin A molecule on oxidation include α -carotene, β -cryptoxanthin, β -carotene epoxide, echinenone and mutachrome (generalized structure $X-(IP)_2-(PI)_2-X'$) and γ -carotene and torulene ($X-(IP)_2-(PI)_4$).

A variety of C_{40} carotenes do not yield vitamin A on oxidation and these variously have altered cyclic groups or no cyclic groups at all and can be variously oxidized or reduced. Good examples are the widespread lutein ($X'-(IP)_2-(PI)_2-X'$) (yellow) and the non-cyclic carotenes lycopene (Ψ, Ψ -carotene; the orange-red colour of tomatoes and other fruits), ζ -carotene (7,8,7',8'-tetrahydro- Ψ, Ψ -carotene; yellow) and lycoxanthin (Ψ, Ψ -caroten-16-ol; yellow).

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Crocetin (C₂₀) is a yellow (IP)₂-(PI)₂-derived dicarboxylic acid (generalized structure -OOC-C₁₈-COO-) from the styles of *Crocus sativus* (Iridaceae) (the saffron of Indian cooking and Buddhist robes). Crocin, the digentiobiose ester of crocetin, is water soluble, unlike other carotenoids which are lipophilic (fat soluble). Crocetin is a protein kinase inhibitor. Excess vitamin A (or excess pro-vitamin A) ingestion is toxic (dog liver consumption having caused the death of Sir Douglas Mawson's explorer companions in the Antarctic by this mechanism).

1.9 Other plant compounds

A variety of other plant compounds are bioactive as toxins, pro-toxins, sweet or bitter tastants, odorants, semiochemicals, enzyme inhibitors, receptor agonists, receptor antagonists or psychoactive agents. The structure and bioactivity of non-alkaloid, non-phenolic and non-terpenoid plant compounds is briefly reviewed below. Some selected structures of cyclic compounds in this category are shown in the Appendix (Section 4).

i. Sugars. Sugars such as monosaccharides (e.g. glucose and fructose) and disaccharides (e.g. sucrose) are typically sweet tastants, this pleasant animal perception having been selected evolutionarily because of the energy-rich, catabolizable nature of sugars. However, sugars are often linked to toxic defensive compounds as glycosides and such compounds can be bitter. Sugars can have a general structure of HOCH₂-(CH(OH))_n-CHO (aldoses) or HOCH₂-(CH(OH))_n-CO-CH₂OH (ketoses). A C atom having four different substituents can give rise to two possible mirror image isomers (stereoisomers) that as configurational isomers can only be interconverted by breaking and re-forming bonds. The stereoisomers of sugars due to these C atom "chiral centres" were detected by differential "optical activity" (rotation of the plane of polarization of plane polarized light in a polarimeter) and the absolute configurations have been established. Most of the sugars of living organisms have a so-called D configuration (as with the key metabolite D-glucose) as opposed to an L-configuration (as with the 5-carbon sugar L-arabinose).

Sugars are further classified by the number of carbons. Thus, aldoses include aldotrioses (C₃; D-glyceraldehyde, HO-CH₂-CHO), aldotetroses (C₄; D-erythrose); aldopentoses (C₅; D-ribose, D-arabinose, D-xylose) and aldohexoses (C₆; D-glucose, D-mannose, D-gulose, D-galactose). Ketoses include ketotrioses (C₃; dihydroxyacetonephosphate, HO-CH₂-CO-CH₂OH), ketotetroses (C₄; D-erythrulose), ketopentoses (C₅; D-ribulose, D-xylulose) and ketohexoses (C₆; D-fructose).

Aldose sugars (such as glucose) can exist in an open chain form as described above but in aqueous solution largely condense to form cyclic hemiacetals, the ring closure linkage being: -CH(CH₂OH)-O-CH(OH)-. Similarly, ketose sugars (such as fructose) condense to form a hemiketal, the ring closure linkage being: -CH(CH₂OH)-O-C(OH, CH₂OH)-. Glucose forms a six-membered ring containing five Cs and one O and is called a glucopyranose form after the cyclic ether tetrahydropyran (C₅O). Fructose forms a five-membered ring containing four Cs and one O and is called a fructofuranose after the cyclic ether tetrahydrofuran (C₄O).

If D-glucopyranose is drawn with the hemiacetal O going into the plane of the paper and the C-6 CH₂OH group pointing above the chain, then the C-1 hemiacetal OH can either point up (in the β anomer) or point down (in the α-anomer). Hence, we can either have β-D-glucopyranose or α-D-glucopyranose and the same anomeric possibilities exist for other sugars, for example, β-D-fructofuranose or α-D-fructofuranose (Section 4, Appendix). Hemiacetal and hemiketal OHs can react with OH groups on other molecules (HO-X) with the elimination of H₂O to form a glycosidic link: C-1-O-X, noting that this is either an α- or β-glycosidic link, for example, quercimeritrin (in which a glucoside is formed

via reaction of the hemiacetal glucose with the 7-OH of the flavonol quercetin) is quercetin 7-*O*- β -D-glucoside.

Monosaccharides can link together through glycosidic links and thence to form oligosaccharides and ultimately polysaccharides (such as starch, glycogen, cellulose and callose) (see Chapter 2). Thus, maltose (α -D-glucopyranosyl-(1 \rightarrow 4)-D-glucopyranose or α -D-Glc-(1 \rightarrow 4)-D-Glc) derives from the reaction of two glucopyranoses to form an " α (1 \rightarrow 4) bond" with the elimination of H₂O (HO-H, with OH coming from the hemiacetal C-1 OH of one glucose and H from the alcohol 4-OH of the second glucose). Note that mutarotation means that the second glucose moiety in maltose still has a hemiacetal OH (a "reducing end" because it can react with an oxidant) and could exist in either an α - or β -form.

Lactose (β -D-galactopyranosyl-(1 \rightarrow 4)- β -D-glucopyranoside; β -D-Gal-(1 \rightarrow 4)-D-Glc) involves a " β (1 \rightarrow 4) bond", noting that lactose has a "reducing end", that is, C-1 of the glucose part. Sucrose (α -D-glucopyranosyl-(1 \rightarrow 2)- β -D-fructofuranoside; α -D-Glc-(1 \rightarrow 2)- β -D-Fru) does not have a reducing end, the reducing ends of both the constituent monosaccharides being involved in glycosidic bond formation (Section 4, Appendix). Maltose, lactose and sucrose are sweet tasting. Other sweet tasting sugars include: melibiose (β -D-Gal-(1 \rightarrow 6)-D-Glc); the sulfated fucose polymer fucoidan from brown algae; the sugar alcohols (H(CH-OH)_nCH₂OH) glycerol (C₃), erythritol (C₄), D-arabitol (C₅), dulcitol (C₆), D-mannitol (C₆), D-sorbitol (C₆) and sedoheptitol (C₇); and the cyclohexanehexols (cyclitols; C₆(OH)₆) inositol and quercitol. Gentiobiose (β -D-Glc-(1 \rightarrow 6)-D-Glc) is a bitter tastant and the sulfated galactose polymer carageenan from red seaweed can induce gastric inflammation and oedema in mammals.

ii. Other aliphatics. In addition to the compounds outlined above, plants variously produce numerous aliphatic carboxylic acids, alcohols, aldehydes, fatty acids, sulfides and hydrocarbons that are variously bioactive. The structure and bioactivity of these other aliphatic plant natural products are outlined below.

Carboxylic acids. Aliphatic carboxylic acids (R-COOH) are deprotonated at physiological pH (pH 7) and are therefore represented as R-COO⁻. Thus, acetic acid (CH₃-COOH) exists as acetate (CH₃COO⁻) at pH 7. A variety of short chain mono-, di- and tricarboxylic acids are important intermediates in metabolism and may be present at low concentrations in all cells either as the acid or as a covalent adduct. Thus, acetate (C₂) and malonate (C₃) can exist as the key acyl-coenzyme A thioester intermediates acetylCoA and malonylCoA, respectively. Phosphoenolpyruvate (C₃), 1,3-bisphosphoglyceric acid (C₃) and 3-phosphoglycerate (C₃) are key metabolic intermediates.

Major monocarboxylic acids include formate (C₁; HCOO⁻), glycolate (C₂; HO-CH₂-COO⁻), glyoxylate (C₂; OHC-COO⁻), acetate (C₂; CH₃-COO⁻), pyruvate (C₃; CH₃-CO-COO⁻), lactate (C₃; CH₃-C(H,OH)-COO⁻), mevalonate (C₆), shikimate (C₇; 3,4,5-trihydroxycyclohexanecarboxylate, an intermediate in aromatic compound biosynthesis) and quinate (C₇; tetrahydroxycyclohexanecarboxylate). Dicarboxylic acids include oxalate (C₂; ⁻OOC-COO⁻), malonate (C₃; ⁻OOC-CH₂-COO⁻), tartrate (C₄; ⁻OOC-C(H,OH)-C(H,OH)-COO⁻) and the successive TCA cycle intermediates α -ketoglutarate (C₅; ⁻OOC-CO-CH₂-CH₂-COO⁻), succinate (C₄; ⁻OOC-CH₂-CH₂-COO⁻), fumarate (C₄; OOC-CH=CH-COO⁻), malate (C₄; ⁻OOC-CH₂-CH(OH)-COO⁻) and oxaloacetate (C₄; ⁻OOC-CH₂-CO-COO⁻). Tricarboxylic acids include the successive TCA cycle intermediates citrate (C₆; ⁻OOC-CH₂-C(H,COO⁻)-CH₂-COO⁻), *cis*-aconitate (C₆; ⁻OOC-CH=C(H,COO⁻)-CH₂-COO⁻) and isocitrate (C₆; ⁻OOC-C(H,OH)-C(H,COO⁻)-CH₂-COO⁻).

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Some organic acids (notably citrate and malate) may be present at high concentrations in the acid vacuoles of plant cells. Thus, in particular, desert plants having so-called Crassulacean acid metabolism (CAM plants) there is a water-saving adaptation that involves fixing CO₂ as malate [via PEP carboxylase] during the night (with leaf stomata open) and then releasing the CO₂ intracellularly for photosynthetic CO₂ fixation during the day (with leaf stomata closed and thereby minimizing H₂O loss). Thus, malate concentration increases during the night. Some fruits have a high level of organic acids such as malate, notably *Malus* species (apples) (Rosaceae).

Organic acids are sour tastants and particular organic acids accumulated in acid vacuoles contribute to the sourness of fruit, including malic acid and quinic acid (apple, apricot, pear, peach and banana fruit), citric acid (citrus fruits) and tartaric acid (grapes). Isovaleric acid (isopropylacetic acid) has a rancid smell but organic acid esters can have very pleasant smells (e.g. that of ethylbutyrate, the smell of apples). Oxalic acid is neurotoxic by chelating Ca²⁺ and malonate is a competitive inhibitor of succinate dehydrogenase. Fluoroacetic acid (FCH₂-COO⁻) is toxic because of its conversion to fluorocitrate, a potent inhibitor of the enzyme aconitase that catalyses the conversion of citrate to isocitrate in the TCA cycle (Krebs cycle, Citric acid cycle). Ascorbic acid (vitamin C) is a tetrahydroxylactone co-enzyme for collagen hydroxylation and is readily oxidized to dehydroascorbic acid. Vitamin C must be derived from plants by humans and its absence causes scurvy.

Long chain fatty acids (general structure of a saturated fatty acid: CH₃-(CH₂)_n-COOH) are key components of all living things. Fatty acids form esters (X-CO-O-Y) with glycerol (trihydroxypropane; CH₂(OH)-CH(OH)-CH₂OH) to form monacyl-, diacyl- and triacylglycerides as high density “energy stores” in animal fatty tissue and in plants, notably in the oil-rich seeds of cotton, sunflower, linseed, coconut, peanut, soya bean and canola (rapeseed). 3-Phosphodiacylglycerol (phosphatidic acid) is the parent compound for phosphodiester phospholipids (e.g. phosphatidylinositol, phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine) that are the bulk components of the molecular bilayers making up biological membranes. Plant fatty acids are typically unsaturated and membranes having a higher degree of unsaturated fatty acids in the phospholipids are more fluid (i.e. less viscous) and “freeze” at lower temperatures than membranes with more saturated fatty acyl components.

Unsaturated fatty acids generally have a *cis*-configuration of the double bonds, an exception being vaccenic acid (*trans*-11-octadecenoic acid). The most common plant saturated fatty acids are palmitic acid (C₁₆; CH₃-(CH₂)₁₄-COOH; *n*-hexadecanoic acid) and stearic acid (C₁₈; CH₃-(CH₂)₁₆-COOH; *n*-octadecanoic acid). Common plant unsaturated C₁₈ fatty acids include oleic acid (*cis*-9-octadecenoic acid; *cis*-Δ⁹-octadecenoic acid), linoleic acid (*cis*-Δ^{9,12}-octadecadienoic acid), α-linolenic acid (*cis*-Δ^{9,12,15}-octadecatrienoic acid) and γ-linolenic acid (*cis*-Δ^{6,9,12}-octadecatrienoic acid). Ricinoleic acid (12-hydroxyoleic acid) is abundant in castor oil. Arachidonic acid (C₂₀; *cis*-Δ^{5,8,11,14}-eicosatetraenoic acid) is absent in higher plants but is the precursor for the pro-inflammatory oxidized prostaglandins, thromboxanes and leukotrienes in animals.

Some plant fatty acids are notably bioactive such as erucic acid (C₂₂; *cis*-Δ¹³-docosenoic acid) which was greatly reduced by breeding in canola rapeseed because of indications of negative effects in animals (e.g. myocardial fibrosis in long-term dietary experiments with rats). “Lorenzo’s oil” (a 4 : 1 mixture of glyceroltrioleate and glyceroltrierucate) apparently does not assist X-linked adrenoleukodystrophy progression in symptomatic patients but may help pre-symptomatic patients. Chaulmoogric acid ((*S*)-13-(cyclopent-2-enyl)tridecanoic

acid) inhibits the growth of the leprosy-causing *Mycobacterium leprae*. The cotton seed oil fatty acids stercularic acid (8-(2-octylcyclopropenyl)octanoic acid; C₈-C₃-C₇-COOH) and malvalic acid (7-(2-octylcyclopropenyl)heptanoic acid; C₈-C₃-C₆-COOH) inhibit fatty acid desaturase.

Acetylenes. Plants elaborate various acetylenes having the general structure R-(C≡C)_n, where R is an alkyl, aryl or heterocyclic group (e.g. pyran, furan, thiophene or cyclic disulfide) and other functional groups include carboxyl, alcohol, amide, ester, aryl and keto groups. The plant alkynes are often toxic and antifungal. Thus, the alkynes dehydro-safynol (C₁₃), safynol (C₁₃), mycosinol (C₁₃), faltarindiol (C₁₇), faltarinone (C₁₇), wyerone acid (C₁₄) and wyerone acid methyl ester (C₁₅) are antifungal phytoalexins the synthesis of which is induced by fungal pathogen infection. The cytotoxic, antineoplastic toxins virol A, virol B and cicutoxin (C₁₇) from *Cicuta virosa* (water hemlock) (Apiaceae) are acutely toxic through binding to the GABA(A) receptor chloride (Cl⁻) channel. Crepenynic acid (C₁₈) is a COX inhibitor and the phytoalexins faltarindiol (C₁₇) and faltarinone (C₁₇) inhibit pro-inflammatory iNOS induction.

The arylacetylene phenylheptatriyne (Phe-C≡C-C≡C-C≡C-CH₃) from *Bidens*, *Dahlia* and *Coreopsis* species (Asteraceae) has phototoxic antimicrobial activity as have 5-(3-buten-1-ynyl)-2,2'-bithienyl (thiophene-thiophene-C≡C-C=CH₂) and the cyclic disulfide acetylenes thiarubrine A (C₃-(C₄S-S)-C₆) and thiarubrine B (C₅-(C₄S-S)-C₄). The photo-activation of acetylenes derives from light absorption by these conjugated systems and ready reaction with oxygen to form reactive intermediates.

Alkyl sulfides and thiols. Some alkyl thiols and sulfides, notably those from commonly ingested *Allium sativum* (garlic) and *Allium cepa* (onion) (Alliaceae), are variously bioactive as odorants and antimicrobials. Propanethial S-oxide (CH₃-CH₂-CH=S=O) is a lachrymatory irritant principle of onion. Allicin (*S*-oxodiallydisulfide; CH₂=CH-CH₂-SO-S-CH₂-CH=CH₂), diallyldisulfide (CH₂=CH-CH₂-S-S-CH₂-CH=CH₂) and diallylsulfide (CH₂=CH-CH₂-S-CH₂-CH=CH₂) are major odorants of garlic that are reactive and irritant because of the allyl groups. Dimethyl disulfide (CH₃-S-S-CH₃), dipropyl disulfide (CH₃-CH₂-CH₂-S-S-CH₂-CH₂-CH₃), methyl allyl disulfide (CH₃-S-S-CH₂-CH=CH₂) and propane-1-thiol (CH₃-CH₂-CH₂-SH) are further *Allium* odorants. Methane thiol (methyl mercaptan; CH₃-SH) is a widespread plant volatile and notably derives from anaerobic bacterial degradation of cysteine as in human flatus and bad mouth odour. The aliphatic disulfides allicin and ajoene inhibit proinflammatory expression of iNOS.

Other aliphatics. In addition to the compounds described above, plants generate a variety of hydrocarbons and other aliphatic compounds ranging from low molecular weight volatiles to high molecular weight alcohols, acids, ketones and esters found in the waxy external cuticle of leaves and fruit.

In addition to the monoterpene and sesquiterpene volatiles described earlier and the thiols and sulfides outlined above, many other low molecular weight volatiles are produced by plants that variously have attractant, repellent or other signalling functions. Cucurbitic acid (C₅-C₅-CH₂-COOH) is a volatile plant growth regulator as is jasmonic acid (C₅-C₅-CH₂-COOH), a major volatile that signals tissue wounding in plants. Volatile plant wounding signals enable herbivore damage to one plant to be communicated to an otherwise untouched plant. Leaf alcohol (*cis*-hex-3-en-1-ol; *cis*-CH₃-CH₂-CH=CH-CH₂-CH₂OH) and leaf aldehyde (*trans*-hex-2-enal; *trans*-CH₃-CH₂-CH₂-CH=CH-CHO) are major green leaf odorants. Nona-2,6-dienal (CH₃-CH₂-CH=CH-CH₂-CH₂-CH=CH-CHO) and jasmone (C₁-C₅-C₃) are the characteristic odorants of cucumber

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and jasmine, respectively, and octan-1-ol is a major orchid flower (Orchidaceae) bee attractant (Chapter 10).

Higher molecular weight tastants include the peachy flavour γ -undecalactone (C_{11} ; 4-hydroxyundecanoic acid lactone; C_7 -C4OL) and the coconut flavour γ -nonalactone (C_9 ; 4-hydroxynonanoic acid lactone; C_5 -C4OL). Very high molecular weight aliphatics include long chain fatty acids, alcohols, esters, ketones and hydrocarbons, for example, the plant growth regulator triacont-1-ol (C_{30} ; $CH_3-(CH_2)_{28}-CH_2OH$), the Crassulaceae cuticle wax component tritriacontane (C_{33} ; $CH_3-(CH_2)_{31}-CH_3$ and Eucalyptus wax (C_{33} ; tritriacontane-16,18-dione).

iii. Amino acids and other non-alkaloid amines. The structures of the twenty L-amino acids found in proteins are dealt with in detail in Chapter 2. The diversity of L-amino acids and structurally related non-alkaloid plant amines is briefly outlined below.

α -Amino acids have the general structure $^-OOC-C(H,R)-NH_3^+$. The C carrying the so-called "R group" is the α -C and is a chiral centre (optical activity centre) in all amino acids in which its four substituents are different (glycine in which $R=H$ is not optically active). The other amino acids found in proteins are exclusively L-stereoisomers but D-amino acids can be generated (i.e. through racemization) by heating plant material. D-amino acids are also present in various toxic microbial peptides. The presence of D-amino acid oxidase in animal peroxisomes indicates a need for detoxification of D-amino acid xenobiotics. D-histidine, D-asparagine, D-glutamine and D-phenylalanine are sweet tastants. *N*-Malonyl-D-alanine is present in pea seedlings.

L-Amino acid analogues such as azetidine 2-carboxylic acid (the C4 ring analogue of the C5 ring L-proline) and L-canavanine (2-amino-4-(guanidinoxy)butyric acid, an analogue of L-arginine) are plant defensive amino acids that are incorporated into protein by the pathogen or herbivore with resultant toxic or debilitating protein mis-folding. L-Homoarginine and γ -hydroxyarginine are also L-arginine analogues.

L-amino acid analogues elaborated by plants inhibit particular enzymes. Thus, L-albizziine (a L-glutamine analogue) inhibits glutamine-dependent asparagine synthase. γ -Hydroxyarginine (a L-arginine analogue) inhibits arginase (the enzyme that catalyses the critical urea cycle detoxifying reaction: arginine ($^-OOC-CH(NH_3^+)-(CH_2)_3-NH-C(=NH)-NH_3^+$) + $H_2O \rightarrow$ ornithine ($^-OOC-CH(NH_3^+)-(CH_2)_3-NH_3^+$) + urea ($H_2N-CO-NH_2$)). L-Canaline ($^-OOC-CH(NH_3^+)-CH_2-CH_2-O-NH_3^+$), an analogue of the non-protein-derived L-amino acid ornithine, inhibits ornithine transcarbamoylase, a key enzyme involved in the ammonia detoxifying urea cycle.

A variety of plant amino acids are neuroactive or neurotoxic including: GABA (γ -aminobutyric acid=4-aminobutyric acid; GABA receptor agonist); β -alanine (3-aminopropionic acid; GABA receptor agonist); glutamate receptor agonists, including glutamate, isowillardine, willardiine, the Fabaceae neurotoxic, neurolathyrism-inducing compounds L- α -amino- γ -oxalylaminobutyric acid, L- α -amino- γ -oxalylaminopropionic acid and 3-cyano-L-alanine and the cycad neurotoxin L- β -methylaminoalanine; L-dopa (3,4-dihydroxy-L-phenylalanine) (the dopamine precursor used to treat Parkinsonism); L-tryptophan and 5-hydroxytryptophan (antidepressive serotonin precursors); and L- α , γ -diaminobutyric acid (a GABA transport inhibitor).

Some further toxic plant amino acids include the *N*-methylpyridinone mimosine (DNA binding and damaging) and 2-methylenecyclopropylalanine (hypoglycin) and 2-methylenecyclopropylglycine that, respectively, yield 2-methylenecyclopropylacetylCoA and 2-methylenecyclopropylformylCoA (inhibitors of acylCoA dehydrogenases). The cancer

chemopreventative, pro-apoptotic and selenosis-inducing toxic seleno-amino acids Se-methylselenocysteine, l-selenocysteine and l-selenomethionine (from selenium accumulating plants growing on seleniferous soils) yield antimitotic methylseleninic acid ($\text{CH}_3\text{-Se(=O)-OH}$), dimethyldiselenide ($\text{CH}_3\text{-Se-Se-CH}_3$) and methylselenol ($\text{CH}_3\text{-SeH}$) (which generate apoptotic superoxide O_2^-) and SeO_2 (a pro-apoptotic inhibitor of PKC).

Other plant bioactive amines include a variety of neuroactive compounds and polyamines. Notable polyamines include cadaverine (1,5-diaminopentane), putrescine (1,4-diaminobutane), spermidine ($\text{NH}_2\text{-(CH}_2\text{)}_4\text{-NH-(CH}_2\text{)}_3\text{-NH}_2$), spermine ($\text{NH}_2\text{-(CH}_2\text{)}_3\text{-NH-(CH}_2\text{)}_4\text{-NH-(CH}_2\text{)}_3\text{-NH}_2$) and agmatine ($\text{NH}_2\text{-C(=NH)-(CH}_2\text{)}_4\text{-NH}_2$).

The following phenethylamine ($\text{Phe-CH}_2\text{-CH}_2\text{-NH}_3^+$) derivatives are neuroactive (hormone/neurotransmitter receptor interaction in parenthesis): dopamine (dopamine receptor); norepinephrine, phenethylamine, *Catha edulis* (khat) (Celastraceae) D-cathine and D-cathinone and *Ephedra* species (Ephedraceae) ephedrine and pseudoephedrine (β -adrenergic receptor agonists); *Lophophora williamsii* (Cactaceae) (peyote) hallucinogens mescaline and N-methylmescaline (serotonin (5-hydroxytryptamine) 5HT₂ receptor agonists).

iv. Cyanogenic and other toxic glycosides. Cyanogenic glycosides have the general structure glycosyl-O-C(X,Y)-CN and are inactive in themselves but break down (either spontaneously in acid conditions or in hydrolytic reactions catalysed by β -glycosidases) to generate cyanide (CN^-). CN^- is a potent inhibitor of cytochrome oxidase that catalyses the final transfer of electrons to molecular oxygen in the mitochondrial respiratory (electron transport) chain. Many cyanogenic glycosides derive biosynthetically from amino acids which have the general structure $^- \text{OOC-C(H,R)-NH}_3^+$ where R is an alkyl, aromatic or heterocyclic group (see Chapter 2).

The best known cyanogenic glycosides are those occurring in plants of economic importance including: amygdalin (gentiobiosyl-O-C(H,Phe)-CN) from *Prunus amygdalis* (almond) (Rosaceae) seeds; dhurrin (*p*-hydroxymandelonitrile glucoside; glucosyl-O-C(H, *p*-OH-Phe)-CN) from *Sorghum* species (Poaceae); linamarin (manihotoxine) (glucosyl-O-C(CH₃,CH₃)-CN) from *Linum usitatissimum* (flax) (Linaceae) seedlings and in *Manihot esculentum* (cassava) (Euphorbiaceae); linustatin (gentiobiosyl-O-C(CH₃, CH₃)-CN) and neolinustatin (gentiobiosyl-O-C(CH₃, CH₂CH₃)-CN) from flax seeds; prunasin (glucosyl-O-C(H,Phe)-CN) from bark of *Prunus* species (Rosaceae); lucumin (xylosyl-(1 → 6)-glucosyl-O-C(H,Phe)-CN) from seeds of *Calocarpum sapota* (sapote) (Sapotaceae); lotaustralin (glucosyl-O-C(CH₃,CH₂CH₃)-CN) from *Lotus australis* and *Trifolium repens* (clover) (Fabaceae), flax and *Triticum* species (Poaceae); and vicianin (vicianosyl-O-C(H,Phe)-CN) from seeds of *Vicia* species (vetches) (Fabaceae).

Variants on the above theme are provided by cyanogenic glycosides in which the nitrile (CN) group is attached to an *O*-glycosylated C within a cyclic structure, for example, a cyclopentene as in gynocardin from *Gynocardia odorata* (Flacourtiaceae) seeds and a dihydropyridone as in acalyphin from *Acalypha indica* (Euphorbiaceae) seeds. An interesting exception to the above structural generality is *p*-glucosyloxymandelonitrile (glucosyl-O-Phe-C(H, OH)-CN) from *Goodia latifolia* (Fabaceae) which can generate CN^- without cleavage of the glycosidic link.

Other toxic glycosides include the 3-nitropropanoyl glucosides cibarian and coronarian from *Astragalus* species (Fabaceae) and the *Cycas* species (cycad sago palm) (Cycadaceae) cycasin (methylazoxymethanol- β -D-glucoside; $\text{CH}_3\text{-N}^+(\text{O}^-)=\text{N-CH}_2\text{-O-glucose}$). Deglycosylation of cycasin and related *Cycas* azoxyglycosides yields methylazoxymethanol

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($\text{CH}_3\text{-N}^+(\text{O}^-)=\text{N-CH}_2\text{-OH}$), a DNA-damaging, genotoxic, mutagenic, toxic and teratogenic compound.

v. Glucosinolates. Glucosinolates are thioglucosides having the general structure $\beta\text{-D-glucosyl-S-C(R)=N-O-SO}_3^-$. Thus, $\text{R}=\text{Phe-CH}_2\text{-}$ in benzylglucosinolate. The glucosinolates derive biosynthetically from amino acids (general structure: $(^-)\text{OOC-C(H,R)-NH}_3^+$) as can be seen by comparing the structure of benzylglucosinolate (glucosyl-S-C($\text{CH}_2\text{-Phe}$)=N-O-SO₃⁻) with that of the amino acid phenylalanine ($\text{R}=\text{CH}_2\text{-Phe}$) ($(^-)\text{OOC-C(H,CH}_2\text{-Phe)-NH}_3^+$). Myrosinase (thioglucosidase) present in the glucosinolate-producing plant catalyses R-glucosinolate hydrolysis when the plant material is crushed (e.g. by herbivores) with resultant production of the corresponding isothiocyanate R-N=C=S , together with minor by-products, namely R-S=C=N^- (R thiocyanate) and R-CN (R nitrile). The Brassicaceae are a major source of glucosinolates which function as insect deterrents and antifeedants. Isothiocyanates (R-N=C=S) are chemically reactive and can react with thiol and amino groups of proteins.

Glucosinolates are found in familiar *Brassica* species (broccoli, Brussel's sprouts, cabbage, chinese cabbage, cauliflower, mustard, rape cress, swede) as well as in other familiar Brassicaceae species such as *Rapahanus sativus* (radish), *Armoracia lapathifolia* (horseradish) and *Lepidium sativum* (garden cress). Glucosinolate breakdown during cooking and ingestion gives rise to isothiocyanates with characteristic flavours and properties. Thus, methylglucosinolate (glucocapparin) yields methylisothiocyanate that is responsible for the pungent flavour of horseradish and various glucosinolate breakdown products give rise to the characteristic odour of boiled cabbage so intimately redolent of British establishments.

The various substituents (R) of glucosinolate (R-glucosinolate) compounds include alkyl, hydroxyalkyl, aryl (e.g. Phe-CH_2 , $p\text{-HO-Phe}$, $\text{Phe-(CH}_2)_2$), indol-3-yl (Phe|pyrrole), methylsulfonyl alkyl ($\text{CH}_3\text{-SO}_2\text{-(CH}_2)_n$), methylsulfinylalkyl ($\text{CH}_3\text{-SO-(CH}_2)_n$) and methylthioalkyl ($\text{CH}_3\text{-S-(CH}_2)_n$) groups. These give rise to the corresponding isothiocyanates (R-N=C=S) that can have particular bioactivities such as insect attractant, insect deterrent, cytotoxic, lachrymatory, tastant and odorant activities.

Of particular note are goitrogenic glucosinolates such as benzylglucosinolate (glucotropaeolin), 3-(methylsulfinyl)propylglucosinolate (glucocheirolin) and progoitrin (2-hydroxybut-3-enylglucosinolate) that yield goitrogenic products that impair thyroid hormone production. Goitrin ((*R*)-5-vinyl-2-oxazolidinethione) is a potent goitrogen and decreases thyroid hormones T3 and T4. Goitrin also induces glutathione S-transferase activity and increases aflatoxin detoxification. Accordingly, moderate *Brassica* consumption is advocated because of the chemopreventative, anticarcinogenic effects of glucosinolate decomposition products.

Other examples of *Brassica* species glucosinolate (R-G) compounds include prop-2-enylG (prop-2-enylglucosinolate) (sinigrin), 4-(methylsulfinyl)butylG (glucoraphanin), 3-(methylsulfinyl)propylG (glucoiberin), 4-(methylsulfinyl)pentylG (glucoalyssin), 4-(methylsulfonyl)butylG (glucoerysolin), 5-(methylthio)butylG (glucoerucin), 5-(methylthio)pentylG (glucoberteroin), indol-3-ylmethylglucosinolate (glucobrassicin), *N*-methoxybrassicin (neoglucobrassicin) and *p*-hydroxybenzylG (sinalbin).

vi. Proteins. Plants produce a number of different kinds of defensive proteins. The most complex of these are polysaccharide hydrolases such as glycan hydrolases (that can hydrolyse the cell walls of invading plant pathogenic fungi), chitinases (that can damage the chitin of the insect digestive system), monosaccharide/oligosaccharide-binding proteins called lectins (that can be potent mitogens), *c.* 40 kDa polygalacturonase-inhibiting proteins

(Chapter 12) and *c.* 20 kDa Kunitz serine protease inhibitor proteins (Chapter 13). Ribosome-inactivating proteins having purine aminoglycosidase activity can be extraordinarily toxic when associated with a lectin subunit enabling entry into the target cell, ricin from seeds of *Ricinus communis* (Euphorbiaceae) being the best known example of such toxic proteins (Chapter 9). Plant thiaminase in ingested plant material degrades thiamine (vitamin B₁) and can consequently cause beriberi from vitamin B₁ deficiency. Thiaminase in insufficiently leached nardoo seed flour (flour made from the sporocarps of the nardoo fern *Marsilea drummondii*) caused peripheral neuropathy in the starving members of the Burke and Wills expedition that crossed Australia from south to north in 1860–1861. Robert O’Hara Burke, William John Wills and Charles Gray died but the sole survivor John King had permanent peripheral neuropathy. Thiamine deficiency disease is also exhibited by livestock feeding on nardoo in “outback” western New South Wales.

Plants also produced a variety of relatively small (3–15 kDa), disulfide-rich, stable defensive proteins that are variously protease and α -amylase inhibitors (thereby inhibiting herbivore digestion and feeding activity) (Chapter 13) or membrane-active entities (such as lipid transfer proteins, defensins, thionins, napins, osmotins and thaumatins) that can damage the cell membranes of pathogenic fungi. The squash family protease inhibitor proteins are among the most potent protease inhibitors known with dissociation constants for the target enzyme-inhibitor complexes of about 10 pM (Chapter 13).

Not dealt with specifically in this book are the plant proteins of importance to humans because of their immunogenicity. Various seed proteins have been shown to cause immunological hypersensitivity after ingestion or inhalation. Thus, a napin protein from rapeseed flour (Chapter 12) causes allergic reactions. The gliadins of wheat flour gluten and the prolamins of barley and rye flour are immunogenic and resultant inflammatory responses affecting the small intestinal mucosa of genetically susceptible people give rise to coeliac disease. Grass pollen is a major outdoor cause of hay fever and allergic asthma and the culprits are protein allergens associated with pollen starch grains (allergenic starch grains released from hydrated pollen being responsible for thunderstorm-associated asthma epidemics). Hevein, a defensive chitin-binding protein present in rubber tree latex, causes allergy to rubber products (Chapter 13).

Chapter 2 deals in part with the structure and function of proteins, including plant defensive proteins and the proteins that are the principal targets of plant defensive compounds.

2 Biochemistry – the chemistry of life

2.1 Introduction – water-based life

We can define living organisms as self-replicating systems. Life on earth is water-based and involves membrane-bound cells that are self-repairing and self-replicating. These highly ordered cells exist in a universe that is inexorably randomizing and do so by “feeding” on available free energy to enable the energy-requiring synthesis, maintenance and replication of highly ordered structures in an increasingly disordered universe. These relations are “governed” by the first and second laws of thermodynamics that respectively state that (a) the energy of the universe is constant and (b) the disorder (or entropy) of the universe inexorably increases.

The bulk constituent of cells is water (H_2O). The cell membrane or plasma membrane (PM) that encloses the living cell is basically composed of a phospholipid bilayer, a 0.01 micrometre (μm) (10 nm) thick bimolecular layer of hydrophobic (or water repelling) fatty molecules. In eukaryotes (organisms having a nucleus) there is a phospholipid bilayer PM enclosing the cell. Similar membranes bound specialized intracellular organelles, namely the endoplasmic reticulum (ER), ER-associated Golgi vesicles, lysosomes, vacuoles, peroxisomes, nucleus and mitochondria (and, additionally, the chloroplasts in plant cells).

The fidelity of cellular repair and reproduction is determined by a coding system based on polynucleotides – deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). In general (with some inevitable exceptions of course), the information flow is from DNA molecules (genes) which are “transcribed” to yield RNA molecules which in turn are “translated” on complex macromolecular protein–RNA assemblies called ribosomes to yield proteins (polymers of amino acids linked by peptide bonds).

The repair and replication of cells involves “metabolism” – interconversions of hundreds of low molecular weight metabolites that ultimately yield the precursors for much larger, more complex macromolecules such as phospholipids (based on phosphatidic acids or long chain fatty acid esters of glycerol phosphate), polynucleotides such as RNA and DNA (polymers of nucleotide monomers), proteins (polypeptides or amino acid monomers linked by peptide bonds) and polysaccharides (polymers of simple sugars or monosaccharides).

Crucially, metabolism conserves chemical energy in the form of the “high energy compound” adenosine 5'-triphosphate (ATP) to “drive” the energy-dependent synthesis of the macromolecular constituents. These macromolecules exist in an aqueous environment and their synthesis involves “dehydration” or elimination of H_2O in the formation of ester bonds (as in fatty acid esters of glycerol), glycosidic linkages (between monosaccharides to form polysaccharides), amide peptide bonds (linking the amino acid monomers in polypeptides) or phosphodiester linkages (between nucleotide or nucleoside 5'-monophosphate

monomers of polynucleotides). The ultimate tendency of these macromolecules in an aqueous environment is to react with H_2O and thus to be “hydrolysed” back to the monomeric constituents.

The interconversions of specific metabolites must occur at rates consistent with the overall operation (imagine an industrial production system not merely producing one particular car model but indeed every manufactured product of a high technology society in an integrated fashion). Accordingly specific catalysts are required to suitably “speed up” these chemical reactions. However three major requirements must be satisfied. First, catalysts are required for thousands of specific reactions and accordingly there is a need for an immense functional diversity of catalysts. Second, there has had to be an evolutionary mechanism to select useful catalysts. Third, the reactions are typically occurring in an aqueous environment and hence in a restricted temperature range of about 0°C (the freezing point of H_2O) to 100°C (the boiling point of H_2O). These requirements have been met by using protein (polypeptide) catalysts (known as enzymes): there is an immense potential polypeptide structural diversity; the encoding of proteins by mutable DNA has provided an evolutionary selection mechanism; and proteins can be stable within the required temperature range.

2.2 Protein structure

a. Amino acid monomers

Proteins are polymers composed of α -amino acid monomers having a common general structure ($\text{H}_2\text{N}-\text{CH}(\text{R})-\text{COOH}$) involving a carbon atom ($\text{C}\alpha$) linked to an amino group (NH_2), a hydrogen (H), a carboxyl (COOH) and a further specific group (the R group) that provides the characteristic properties for each amino acid. Thus the amino acid glycine (literature shorthand Gly or G) has $\text{R} = \text{H}$ and alanine (Ala, A) has $\text{R} = \text{CH}_3$ (methyl).

If the four entities covalently linked to a (tetravalent) carbon atom are different, “mirror image” stereoisomers are possible and the stereoisomers can have different physical properties (notably “optical activity” or rotation of the plane of polarization of plane polarized light). Gly, having two identical $\text{C}\alpha$ substituents, does not have stereoisomers. However alanine can be either of two “mirror image” stereoisomers (so-called L or D forms) that are only interconvertible by breaking and re-forming covalent bonds (i.e. they are configurational isomers). The amino acid stereoisomers found in proteins are the L-isomers. However “mirror image” amino acid D-isomers nevertheless occur in nature as defensive natural products or as constituents of defensive natural products. It should be noted that the “classical” nomenclature of L and D stereoisomers is still widely applied to amino acids (and carbohydrates) rather than the generally used *R* and *S* nomenclature. Thus L-alanine is (*S*)-2-aminopropanoic acid.

There are 20 common amino acids that can be grouped depending upon the nature of the R group (bearing in mind the typical cellular context of an aqueous solution at about pH 7).

i. Nonpolar aliphatic R groups. Glycine (Gly, G) [$\text{R} = -\text{H}$], alanine (Ala, A) [$\text{R} = \text{methyl} = -\text{CH}_3$], valine (Val, V) [$\text{R} = \text{isopropyl} = 1\text{-methylethyl} = -\text{CH}(\text{CH}_3)_2$], leucine (Leu, L) [$\text{R} = 2\text{-methylpropyl} = -\text{CH}_2\text{CH}(\text{CH}_3)_2$], isoleucine (Ile, I) [$\text{R} = 1\text{-methylpropyl} = -\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$] and methionine (Met, M) [$\text{R} = 2\text{-methylthioethyl} = -\text{CH}_2\text{CH}_2-\text{S}-\text{CH}_3$]. These R groups are hydrophobic (water repelling) but range from being very small (with Gly and Ala) to very bulky (with Leu, Ile, Met and Val), these differences being of major importance in protein structure.

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ii. Polar uncharged R groups. Serine (Ser, S) [R = hydroxymethyl = $-\text{CH}_2\text{OH}$], threonine (Thr, T) [R = 1-hydroxyethyl = $-\text{CH}(\text{OH})\text{CH}_3$], cysteine (Cys, C) [R = thiol-methyl = $-\text{CH}_2\text{SH}$], asparagine (Asn, N) [R = amidocarboxymethyl = $-\text{CH}_2\text{CO}-\text{NH}_2$], glutamine (Gln, Q) [R = amidocarboxyethyl = $-\text{CH}_2\text{CH}_2-\text{CO}-\text{NH}_2$] and proline (Pro, P) [the R group of this cyclic imino acid is $(\text{CH}_2)_3$ linking the C_α and the $\alpha\text{-NH}$ (α -imino), that is, Pro = (*S*)-2-pyrrolidinecarboxylic acid]. These uncharged but polar R groups can be solvated by H_2O and interact with other polar groups through “hydrogen bonding” in which a hydrogen atom is “shared” between electronegative atoms, for example, $\text{X}-\text{O}-\text{H}\cdots\text{O}=\text{C}-\text{Y}$. Cys (R = $-\text{CH}_2\text{SH}$) residues in proteins can form intra- and interchain disulphide (S–S) linkages thus: $\text{X}-\text{SH} + \text{HS}-\text{X} + \text{Y}$ (oxidant) $\rightarrow \text{X}-\text{S}-\text{S}-\text{X} + \text{YH}_2$.

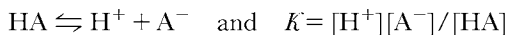
iii. Aromatic R groups. Phenylalanine (Phe, F) [R = benzyl, phenylmethyl = $-\text{CH}_2\text{Phe}$], tyrosine (Tyr, Y) [R = *p*-hydroxyphenylmethyl = $-\text{CH}_2\text{-}p\text{-OH-Phe}$] and tryptophan (Trp, W) [R = 3-indolylmethyl = $-\text{CH}_2\text{-indole}$]. Such R groups are hydrophobic and planar.

iv. Negatively charged R groups. Aspartic acid (Asp, D) [R = carboxymethyl, $-\text{CH}_2-\text{COOH}$], glutamic acid (Glu, E) [R = carboxyethyl, $-\text{CH}_2\text{CH}_2-\text{COOH}$]. At neutral pH (pH 7) the carboxyls of Asp and Glu are deprotonated (i.e. $\text{X}-\text{COOH} \rightarrow \text{X}-\text{COO}^- + \text{H}^+$) and the deprotonated amino acids are referred to as aspartate and glutamate, respectively. These negatively charged R groups can hydrogen bond with other electronegative entities and can form ionic (electrostatic) links with positively charged groups.

v. Positively charged groups. Lysine (Lys, K) [R = 4-aminobutyl, $-(\text{CH}_2)_4-\text{NH}_2$], arginine (Arg, R) [R = 4-guanidinypropyl = $-(\text{CH}_2)_3-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$] and histidine (His, H) [R = 4-imidazolylmethyl = $-\text{CH}_2\text{-imidazole}$]. At pH 7 the amino R group of Lys and the guanidiny R group of Arg are protonated and hence positively charged. The pK (see section on “Protonic equilibria of amino acids and proteins”) of the imidazole R group of His is about 6 so that at pH 7 about 10% of His R groups are positively charged. These positively charged R groups can interact electrostatically with negatively charged groups and form hydrogen bonds with electronegative entities.

b. Protonic equilibria of amino acids and proteins

Before proceeding further it is useful to briefly review protonic equilibria. The tightness of binding of a proton (H^+) to a weak acid (HA) can be described by a dissociation constant (K) where:



where $[\text{H}^+]$, $[\text{A}^-]$ and $[\text{HA}]$ are the concentrations of the indicated species at equilibrium. From this we derive the Henderson–Hasselbalch relation:

$$\text{pH} = \text{p}K + \log_{10} [\text{A}^-]/[\text{HA}]$$

or (more generally stated):

$$\text{pH} = \text{p}K + \log_{10} [\text{deprotonated}]/[\text{protonated}]$$

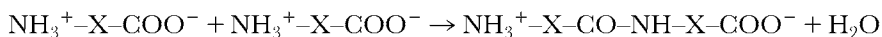
where $\text{p}K = -\log_{10} K$.

The $\text{p}K$ value for an α -amino ($-\text{NH}_2$) is about 9.5 and from the above equation we can see that at pH 7 nearly all the α -amino groups will be in the protonated ($-\text{NH}_3^+$) form. Similarly the $\text{p}K$ value for an α -carboxyl ($-\text{COOH}$) is about 2.3 and accordingly at pH 7 virtually all

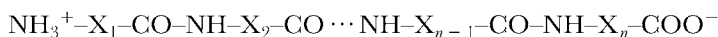
of the α -carboxyls will be in the deprotonated form ($-\text{COO}^-$). The pK values for the R group carboxyls of Asp and Glu are about 4 and accordingly these are overwhelmingly in the deprotonated form ($-\text{COO}^-$) at pH 7. The pK values for the R group ϵ -amino of Lys and the guanidinyll group of Arg are 10.5 and 12.5, respectively, and thus these groups are overwhelmingly protonated at pH 7. However the pK of 6 for the His R group imidazolyl means that only about 10% of these residues are protonated at neutral pH. Accordingly the charged residues of a polypeptide at neutral pH include the N-terminal amino that is protonated ($-\text{NH}_3^+$), the carboxyl terminal carboxyl which is deprotonated ($-\text{COO}^-$) and any R groups that can be protonated (positively charged) or deprotonated (negatively charged) at pH 7. The peptide bond amide nitrogens of the polypeptide are not protonated.

c. The peptide bond

Amino acids can form peptides with the elimination of H_2O as follows (with amino acids represented as $\text{NH}_3^+-\text{X}-\text{COO}^-$):



The resultant dipeptide in the above example has a positively charged amino terminus (N-terminus) and a negatively charged carboxy terminus (C-terminus). Extending this process we can see that a polypeptide has the following general structure:



The polypeptide structure is comprised of an N-terminal amino acid residue, a C-terminal residue and intervening amino acid residues, all of these being successively linked by peptide bonds. A critical property of the peptide bond ($\text{CO}-\text{NH}$) is that it has considerable double bond character (i.e. $-\text{C}(\text{O}^-)=\text{NH}^+-$) and accordingly no rotation occurs around this bond between the keto C and the amide N.

d. Primary structure of proteins

The primary structure of a protein is simply its linear amino acid sequence and by convention it is represented left to right, from the N-terminus to the C-terminus: N-terminus- $\text{aa}_1-\text{aa}_2 \cdots \text{aa}_{n-1}-\text{aa}_n$ -C-terminus. Thus the amino acid sequence of the endogenous peptide opiate hormone and neurotransmitter Met-enkephalin is Tyr-Gly-Gly-Phe-Met (or, in the one-letter code, YGGFM). We can consider the potential polypeptide sequence possibilities: there are 20 common amino acids that are encoded by the Genetic Code (and added to the elongating peptide in the process of protein synthesis or “translation” carried out on ribosomes) and accordingly there are 20 possibilities for position 1, 20 for position 2 and so on. Thus there are 20^{100} possible sequences 100 amino acids long. However the extant proteins – the proteins actually present in living cells – have been evolutionarily selected for specific ligand binding or catalytic functions. These considerations will greatly reduce the “functional” protein possibilities but there nevertheless still remains a huge potential complexity. A further major constraint is that proteins exist typically in an aqueous environment and must fold up in three dimensions in a compact fashion as described in the section on “Tertiary structure of proteins” so that hydrophobic R groups are located away from water.

e. Secondary structure of proteins

The secondary structure of elements of a polypeptide describes the regular folding of such sections of the polypeptide chain. The conformation of elements of the polypeptide chain is constrained by the double bond character of the peptide linkages and the nature of the R groups. If we represent the link between two successive amino acids as $C\alpha_{n-1}-CO-NH-C\alpha_n$, no rotation is possible around the peptide bond between the keto C and the amide N but rotation is possible around the $C\alpha_{n-1}$ –keto C single bond and around the amide N– $C\alpha_n$ single bond (the angles of rotation being defined as ψ and ϕ angles, respectively). These angles of rotation are constrained by the size of the R groups associated with the $C\alpha$ s, steric overlap between the various atoms being prohibited.

Two major kinds of secondary structure found in proteins are the α -helix (conventionally represented as a cylinder) and the β -strand (represented as a flat sheet with an arrow head indicating the N- to C-terminal direction). The α -helix can be envisaged as a tightly coiled, compact spring whereas the β -strand is like a spring that has been stretched out.

In the α -helix the polypeptide $C\alpha-CO-NH-C\alpha$ “backbone” coils in a “right handed” fashion (imagine thumbing a lift using your right hand) and is stabilized by hydrogen bonds between a keto (C=O) oxygen and an amide NH about three amino acid residues further along the polypeptide, these hydrogen bonds ($-CO\cdots HN-$) being oriented parallel to the long axis of the α -helix. The R groups associated with the $C\alpha$ atoms are oriented outwards, away from the α -helical cylinder, and accordingly this type of secondary structure is favoured by sequence elements containing amino acids with large, bulky R groups (e.g. Leu and Ile). The unusual imino acid Pro perturbs this regular structure and acts as an α -helix “breaker”.

The β -strand sequences are “stretched out” conformations of these polypeptide sections and are typically stabilized by inter-strand hydrogen bonds between keto (C=O) oxygens and peptide bond NHs, the strands being arrayed in an antiparallel fashion. This type of secondary structure is favoured by amino acid residues with small R groups (such as Gly, Ala and Ser) that minimize steric overlap between chains. Thus a well-known protein having this type of secondary structure is silk fibroin that has a high proportion of repeated sequences involving Gly, Ala and Ser and an extensive antiparallel “ β -pleated sheet” structure. The macroscopic properties of silk fibroin (flexibility but lack of stretchability) reflect this type of secondary structure at the molecular level.

The above description is a considerable simplification of protein secondary structure possibilities. Thus a number of helix types are possible in addition to the α -helix. Further, particular structured “ β -turns” exist that are stabilized by hydrogen bonding and link other secondary structure elements. Relatively unstructured coils, loops and “random coils” can also link α -helical and β -strand elements.

f. Tertiary structure of proteins

The tertiary structure of a protein is the overall three-dimensional structure of a protein. The three-dimensional structures of many proteins have been determined by X-ray crystallography and by nuclear magnetic resonance (NMR) spectroscopy. Such structures represented with space-filling atoms appear formidably complex. However “deconvolutions” of such structures as “ribbon diagrams” showing the arrangement of linked secondary structure elements are much more comprehensible. Some proteins have a high proportion of β -strands whereas others may have a high proportion of α -helices with all kinds of combinations and arrangements in between. While some specialized filamentous proteins (e.g. collagen, silk fibroin and hair α -keratin) are rope-like, most soluble proteins are “globular”.

A typical globular protein adopts a unique minimum energy conformation that is compact with few or no internal water molecules. Hydrophobic (nonpolar) R groups tend to be on the inside (away from water) and most hydrophilic (polar) R groups tend to be on the outside where they can be solvated by hydrogen bonding with H₂O. In the case of enzymes (proteins that catalyse specific chemical reactions) there may be special structural features of which the best known are “active site” depressions or grooves on the surface that bind the chemical substrates of the enzyme-catalysed reaction.

The major driving force for a polypeptide to adopt (and remain in) its unique three-dimensional conformation are hydrophobic interactions that keep nonpolar R groups away from H₂O. However other interactions include hydrogen bonding, electrostatic interactions, dipole–dipole interactions and weak, interatomic Van der Waals forces (e.g. involving packed hydrophobic aliphatic chains in the protein interior). In addition, disulphide bonds (S–S bonds from the oxidation of cysteines (Cys)) can provide covalent linkages between different parts of the polypeptide chain. Disulphide links are of major importance for the stability of ectoproteins, proteins functioning outside the reducing environment of the cytosol. Indeed many small, extracellular plant defensive proteins are extraordinarily stable to heat, acid and organic solvents because of a high incidence of intra- and interchain disulphide bonds (see Chapters 12 and 13).

g. Quaternary structure of proteins

The quaternary structure of proteins is the subunit complexity. Proteins can be monomeric, that is, they are composed of only one polypeptide. Homodimers are composed of two identical polypeptides while heterodimers are composed of two non-identical subunits. The oxygen-transporting haemoglobins are heterotetrameric proteins with a subunit complexity summarized as $\alpha_2\beta_2$. Very large multienzyme complexes include fatty acid synthase, mitochondrial pyruvate dehydrogenase, the mitochondrial ATP synthase and the mitochondrial electron transport chain. Extremely large multienzyme complexes are the small and large ribosomal subunits (that are composed of particular RNA molecules together with numerous ribosomal proteins) and the tobacco mosaic virus (TMV, that involves an RNA core encapsulated by a complex of 2200 identical coat protein subunits).

h. Protein complexity

Most of the targets of plant defensive compounds are proteins and indeed many plant defensive agents are also proteins. Accordingly it is useful to briefly outline the various types of proteins encountered. Most proteins are water soluble but some function associated with membranes. The membrane-bound proteins can be firmly embedded in the phospholipid bilayer of the membrane (intrinsic or integral proteins) or are less intimately associated (extrinsic or peripheral membrane proteins). As outlined above, proteins may be monomeric, multisubunit or associated with large multisubunit complexes.

While proteins are synthesized on ribosomes the translation product is often subject to considerable “post-translational modification” that can involve proteolytic processing of the initial proprotein and covalent modification of the processed protein by glycosylation (addition of sugar residues), acylation (e.g. with fatty acids), methylation and phosphorylation. Unconjugated proteins are those in which there is no non-amino acid substituent and conjugated proteins are those that have been modified with non-amino acid entities.

The completion of the sequencing of the human genome has revealed some 35,000 genes encoding proteins. However some structural motifs have proven to be particularly useful and

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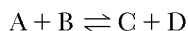
proteins can be classified into about 1000 superfamilies that each contain sets of proteins related by sequence (homologous proteins) and structure. A brief list of functionally different types of proteins includes: enzymes (catalysts); hormone, neurotransmitter and other receptors; transmembrane solute translocators; blood solute transporters (e.g. haemoglobin); blood protective proteins (e.g. immunoglobulins); peptide hormones and toxins; contractile proteins (e.g. tubulin associated with microtubules and actin and myosin associated with muscle contraction); storage proteins (e.g. milk casein and egg ovalbumin); and structural proteins (e.g. collagen).

2.3 Enzymes and ligand-binding proteins

a. Chemical equilibria

Enzymes are proteins having a catalytic function. Catalysts in general speed up reactions but remain unchanged by the reaction. Enzymes do not change the overall thermodynamics of a reaction (i.e. the “free energy difference” between the initial and equilibrium conditions) but speed up the reactions, that is, enzymes increase the rate at which equilibrium is achieved.

Let us consider a reaction:



This can be described by an equilibrium constant (K_{equ}):

$$K_{\text{equ}} = [C][D]/[A][B]$$

where $[A]$, $[B]$, $[C]$ and $[D]$ are the concentrations of the reagents and products at equilibrium (i.e. when there is no further net reaction). K_{equ} can also be defined in terms of the rate constants, k_f and k_b , for the forward and backward reactions, respectively:

$$K_{\text{equ}} = k_f/k_b$$

where the rate forward = $k_f[A][B]$ and the rate backward = $k_b[C][D]$.

The thermodynamic feasibility of a reaction is described by Gibbs free energy change (or simply “free energy change”) (ΔG): when $\Delta G < 0$, the reaction is “exergonic”, thermodynamically favoured and can proceed spontaneously (subject, however, to kinetic constraints determined by a so-called “activation energy barrier” (ΔG_{act}) that must be overcome before the reaction can proceed “downhill” to equilibrium). When $\Delta G > 0$, the reaction is “endergonic” and requires a free energy input to “drive” the unfavourable reaction “uphill”. When $\Delta G = 0$ the process is at equilibrium.

At this point it is useful to specify G more precisely in a cell biological context, that is, in conditions of essentially constant temperature, volume and pressure. For a reaction at constant pressure the energy change (ΔE) is the difference between heat produced (q) and work done by the system (w) (e.g. pressure \times volume change ($P\Delta V$) work):

$$\Delta E = q - w = \Delta H - P\Delta V$$

where ΔH is the “enthalpy change” or the heat evolved in a reaction at constant pressure. However in a cell biological context volume is also essentially constant and hence ΔH approximates to the energy change ΔE .

The directionality of a cellular reaction at constant pressure and at a particular temperature (T) (i.e. whether ΔG is positive or negative) is determined by both the enthalpy change (ΔH) and the change in “disorder” of the system described by the change in entropy (ΔS):

$$\Delta G = \Delta H - T\Delta S$$

The First Law of Thermodynamics states that the energy of a system is constant and the Second Law states that the entropy (or disorder) of a system tends to increase. A simple example of these relations is given by the melting of ice in a “closed system”. At temperatures below 0°C (the freezing point of H_2O) the values of ΔH and ΔS for the solid to liquid transition are such that $\Delta H > T\Delta S$, that is, the energy input required to break the hydrogen bonds holding the ice crystal lattice together is greater than the value of $T\Delta S$ (deriving from the increased disorder or randomness associated with the dissociation of H_2O molecules from each other). Accordingly, at temperatures below 0°C (i.e. below the freezing point) $\Delta G > 0$ for the ice to water transition and melting does not occur. However at temperatures greater than 0°C the values of ΔH and ΔS for the solid to liquid transition are such that $T\Delta S > \Delta H$ and accordingly $\Delta G (= \Delta H - T\Delta S)$ is negative, indicative of the thermodynamically favoured, spontaneous melting of ice at temperatures above the melting point of ice.

Returning to our biochemical reaction, we can define a free energy change (ΔG):

$$\Delta G = \Delta G^0 + RT \ln[C][D]/[A][B] = \Delta G^0 + 2.303RT \log_{10}[C][D]/[A][B]$$

where R is the gas constant ($8.315 \text{ J mol}^{-1} \text{ K}^{-1}$), T is the absolute temperature (K) and ΔG^0 is the “standard free energy change” (with all reagents at 1M).

At equilibrium, $\Delta G = 0$ and accordingly:

$$\Delta G^0 = -RT \ln[C][D]/[A][B] = -RT \ln K_{\text{equ}} = -2.303 \log_{10} K_{\text{equ}}$$

b. Enzymes overcome an activation energy barrier

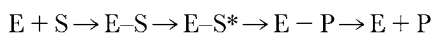
Enzymes do not change the free energy change (ΔG) for a reaction, that is, do not change the overall thermodynamics of a reaction. However enzymes do greatly decrease the activation energy barrier (ΔG_{act}) for a reaction. Thus $\Delta G < 0$ for a thermodynamically favoured reaction $A \rightarrow B$, but the reaction will not proceed unless A is first “excited” to a state at a higher energy level (A^*) by an input of free energy (ΔG_{act}) (noting that $\Delta G_{\text{act}} > 0$). (Imagine driving a Chevy to the levee in the words of the song but before rolling it into the Mississippi you first have to push it to the top of the levee bank.) In the laboratory the reaction could be pushed to proceed by applying heat but in the cell biological context the temperature range is confined to 0 – 100°C (and indeed the normal core temperature for man is $37 \pm 0.7^\circ\text{C}$). An enzyme (E) catalyses this reaction in physiological conditions by binding A to form an enzyme–substrate complex (E–A) and thence forming an “excited” transition state complex E– A^* which has the propensity to react and form the product B. By this means the enzyme overcomes the barrier in physiological conditions (i.e. greatly reduces ΔG_{act}).

c. Mechanisms of enzyme catalysis

An enzyme (E) will have an active site that can bind the reagent or substrate (S) to form an enzyme–substrate complex (E–S). The active site is highly specific for S (and structurally

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closely related compounds). This binding is determined by stereochemistry (S has to fit in the active site) and by molecular interactions (e.g. hydrogen bonding, electrostatic, Van der Waals, dipole–dipole and hydrophobic interactions). This E–S formation has been described by a “lock and key” model that has been extended by the notion of “induced fit”, that is, S binding causes a subtle change of active site conformation resulting in even better binding. Through electronic redistribution promoted by R groups at the active site, the E–S complex can now form a transition state complex (E–S*) which is highly reactive and ultimately yields the product (P). The active site reaction may involve R groups of particular amino acids (e.g. Ser, Asp, Glu and His) that may donate or abstract a proton (H^+) and may involve a covalent intermediate complex with the enzyme. Ultimately the product (P) is released leaving the enzyme unchanged and ready for another round of catalysis. This process can be summarized thus:



d. Enzyme cofactors and enzyme classification

Many enzymes require cofactors. When such cofactors are metal ions (e.g. Cu^{2+} , Zn^{2+} , Ni^{2+} , Fe^{2+}/Fe^{3+}) the enzymes are called metalloenzymes. When organic cofactors (coenzymes) are required the coenzyme may be free or tightly bound to the enzyme (as a so-called “prosthetic group”). The enzyme–cofactor complex is termed the “holoenzyme” and the enzyme free of cofactor or coenzyme is called the “apoenzyme”.

Some vitamins (trace compounds required to be ingested in our diet) give rise to coenzymes. Thus niacin (nicotinic acid) gives rise to nicotinamide which becomes part of the oxidoreductase coenzymes reduced/oxidized nicotinamide adenine dinucleotide ($NADH/NAD^+$) and reduced/oxidized nicotinamide adenine dinucleotide phosphate ($NADPH/NADP^+$). Riboflavin (vitamin B_2) becomes part of the oxidoreductase coenzymes reduced/oxidized flavin mononucleotide ($FMNH_2/FMN$) and reduced/oxidized flavin adenine dinucleotide ($FADH_2/FAD$). Thiamine (vitamin B_1) becomes part of thiamine pyrophosphate (TPP) (critically involved in catabolism as a cofactor for pyruvate dehydrogenase and α -ketoglutarate dehydrogenase). Pyridoxine (vitamin B_6 , the deficiency of which causes pellagra) becomes the coenzyme pyridoxal phosphate (involved in transaminase reactions). Folic acid (pteroylglutamic acid) is abundant in leafy vegetables and deficiency of this vitamin causes megaloblastic anaemia and is correlated with the neural tube defect condition of spina bifida. Folic acid is reduced to 7,8-dihydrofolate (DHF) by the NADPH-specific oxidoreductase dihydrofolate reductase, DHF being involved as a coenzyme in methyl transfer reactions.

Enzymes have been classified by an international Enzyme Commission (EC) and assigned EC numbers. Thus the enzyme creatine kinase (the muscle enzyme that catalyses the “energy storage” reaction $ATP + \text{creatine} \rightarrow ADP + \text{phosphocreatine}$) has the EC number 2.7.3.2, these numbers successively referring to a transferase function (2), a phosphotransferase function (7), phosphotransfer with a nitrogen (N) acceptor (3) and creatine kinase *per se* (2).

Enzymes are placed in various major categories indicated by the first number of the EC number, namely (reaction catalysed in parentheses): (a) oxidoreductases (oxidation–reduction reactions); (b) transferases (transfer of chemical groups e.g. phosphoryl transfer); (c) hydrolases (hydrolysis or cleavage of bonds involving reaction with H_2O); (d) lyases (cleavage of C–C, C–O and C–N bonds and often yielding a double bond); (e) isomerases

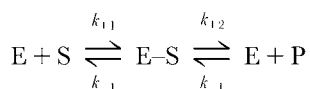
(isomerization or interconversion of isomers); and (f) ligases (formation of bonds coupled to ATP hydrolysis).

e. Enzyme kinetics

The amount of a purified enzyme can be measured either from the amount of protein present or the rate of the enzyme-catalysed reaction in specified standard conditions. If an amount x of an enzyme (E) is added to a reaction mixture containing substrate (S) (plus cofactors and a buffer solution to keep the pH constant at a defined value) we will observe a constant initial rate or initial velocity (v_0) of production of product (P) (or disappearance of the substrate S). However as the substrate is progressively consumed the rate of the reaction will eventually decline and the rate will be zero when the substrate is exhausted. If we add amount $2x$ of the enzyme to the identical reaction mixture we will observe an initial rate that is twice that observed with amount x of enzyme.

If we set up the same “enzyme assay” with a fixed amount of enzyme but vary the substrate concentration we will observe that initial velocity (v_0) will steadily increase as we increase substrate concentration ($[S]$) but at very high $[S]$ the v_0 will asymptote towards a maximal value referred to as the V_{\max} (or maximal velocity). A plot of v_0 versus $[S]$ will yield a hyperbola, that is, v_0 will increase until it approaches a maximal value. The initial velocity v_0 is directly proportional to the amount of enzyme–substrate complex (E–S) and accordingly when all the available enzyme (total enzyme or E_T) has substrate bound (i.e. $E-S = E_T-S$ and the enzyme is completely “saturated”) we will observe a maximal initial velocity (V_{\max}). The substrate concentration for half-maximal velocity (i.e. the $[S]$ when $v_0 = V_{\max}/2$) is termed the K_m (or the Michaelis–Menten constant). However because v_0 merely asymptotes towards V_{\max} as we increase $[S]$ it is difficult to accurately determine V_{\max} or K_m by this graphical method. However such accurate determinations can be made based on the Michaelis–Menten equation that describes the relationship between v_0 and $[S]$.

The Michaelis–Menten equation was derived based on an assumption that $[E-S]$ is constant (i.e. is always being replenished) during the v_0 measurement period (during which negligible S is being used up because we are measuring an initial rate). We further assume the following model for what is happening during the enzyme-catalysed reaction:



The dissociation constant of E–S (K_d) can be defined in two ways:

- 1 $K_d = [E][S]/[E-S]$
- 2 $K_d = k_{-1}/k_{+1}$

However the Michaelis–Menten constant (K_m) is defined in terms of E–S association, dissociation and generation of the reaction product P (noting that since we are concerned with initial rates the product concentration ($[P]$) is essentially zero):

$$K_m = \frac{k_{-1} + k_{+2}}{k_{+1}}$$

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The rate constant k_{+2} is also known as k_{cat} , the rate constant for E–S breakdown to yield P. If k_{+2} is very low in relation to the other rate constants then K_m approximates to K_i , that is, K_m gives a loose estimate of K_i .

The Michaelis–Menten equation relates initial velocity (v_0) to substrate concentration ($[S]$) thus:

$$v_0 = \frac{V_{\text{max}}[S]}{K_m + [S]}$$

When $v_0 = V_{\text{max}}/2$ (i.e. at half-maximal initial velocity), this equation reduces to $K_m = [S]$, that is, as defined in the initial graphical description, K_m is the substrate concentration giving half-maximal reaction velocity.

Enzyme kinetic data of v_0 at different substrate concentrations is typically presented as either of two linear plots:

- 1 Lineweaver–Burk (or “double-reciprocal”) plots of $1/v_0$ versus $1/[S]$ (intercepts on these axes respectively providing values of $1/V_{\text{max}}$ and $-1/K_m$);
- 2 Eadie–Hofstee plots of v_0 versus $v_0/[S]$ (the intercept on the v_0 axis and the negative of the slope yielding values of V_{max} and K_m , respectively).

f. Enzyme assays

Enzyme activity is measured in defined conditions from the rate of disappearance of S or the rate of formation of P. S and P concentration changes can be quantitated directly from specific changes in absorbance or fluorescence characteristic of these molecules using spectrophotometers or fluorimeters, respectively. Alternatively “linked” or “coupled” assays can couple formation of a product to the formation of a further characteristically absorbing (e.g. coloured) or fluorescent product. Thus the enzyme glucose oxidase can be measured as follows: glucose + O_2 + H_2O [via glucose oxidase] \rightarrow gluconic acid + H_2O_2 ; H_2O_2 + X [via peroxidase] \rightarrow H_2O + XO (coloured). Further types of assays can be based on reaction-dependent changes in pH (measured using a pH electrode). It may be necessary to separate S and P and this can be achieved by a variety of techniques, for example, thin layer chromatography (TLC), paper chromatography, ion exchange chromatography, high voltage electrophoresis and high performance liquid chromatography (HPLC). Use of radioactively or fluorescently labelled synthetic substrates can provide great sensitivity, for example, in assays of protein kinases (Chapter 8). Automated enzyme analysis can be achieved using autoanalysers and automated microtitre plate fluorescence and absorbance readers.

In contrast to small, disulphide-rich, stable ectoproteins, enzymes functioning in the intracellular reducing environment are typically relatively large and thermolabile proteins. Accordingly enzymes are typically isolated at just above 0°C . Conditions that destroy the enzyme tertiary structure (e.g. elevated temperature, nonpolar organic solvents, hydrogen bond-breaking compounds such as urea, ionic detergents and extremes of pH) are avoided in enzyme isolation. Enzymes are stored as solutions at just above 0°C or stored as crystals or as a lyophilized (freeze-dried) powder at -70°C . As the enzyme assay temperature is increased the reaction rate increases (a typical Q_{10} , or increase in rate for a 10°C rise, is about 2). However at high temperatures the rate may fall off due to increasing denaturation of the enzyme.

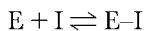
Enzyme activity will typically involve protonatable amino acid R groups that bind substrates or are otherwise involved in the catalytic mechanism (e.g. through abstracting or accepting protons in acid–base catalysis). Enzymes typically have a pH optimum (the pH for optimum activity) due to the existence of ionizable (protonatable) groups both on the substrates and at the enzyme active site. In some cases the pH optimum may reflect physiological circumstances – thus the pH optimum of intestinally operating trypsin is about 7 (the pH of the small intestine) whereas that of the gastric protease pepsin is about 2 (close to the pH of the stomach). Enzyme assays are routinely conducted in solutions that are buffered so that there is a defined pH that is kept constant even if protons are produced or consumed during the enzyme-catalysed reaction.

The routine unit of enzyme activity has been the international unit (I.U.), namely μ moles P formed (or S consumed) per minute. The specific activity of an enzyme preparation is the number of μ moles P formed (or S consumed) per minute per milligram of protein (clearly this will be very low in a crude cell extract and have a maximal value for a pure preparation of the enzyme). If the molecular mass is known, the specific activity of a pure enzyme measured in “saturating” (V_{\max} conditions) can be used to calculate the “turnover number” (or “molecular activity”) of an enzyme, namely the number of P molecules formed (or S molecules transformed) per molecule of enzyme per second (units: sec^{-1}). If we recall that the maximal velocity (V_{\max}) equals $k_{+2}(\text{sec}^{-1})[\text{ET}]$, we can see that the molecular activity equals $k_{+2}(\text{sec}^{-1})$, that is, $k_{\text{cat}}(\text{sec}^{-1})$. The katal is the S.I. unit of enzyme activity (moles substrate transformed sec^{-1}) from whence come the corresponding units for specific activity (katal kilogram $^{-1}$) and molar activity (katal per mole of enzyme).

g. Enzyme inhibition

Many of the targets of plant-derived defensive compounds are enzymes. It is accordingly useful to outline key features of enzyme inhibition and its analysis. Initially one can distinguish between irreversible and reversible inhibition of an enzyme. Irreversible inhibition occurs in conditions that denature (unfold) the enzyme (e.g. acid, ionic detergents, nonpolar solvents and elevated temperature). However some specific compounds can cause irreversible inhibition of particular enzymes by reacting with critical active site R groups. Thus diisopropylfluorophosphate (DIFP) is representative of organophosphate insecticides and nerve gases that react with the active site Ser of acetylcholinesterase (AChE), inactivating the enzyme and (lethally) preventing requisite hydrolysis of the neuromuscular neurotransmitter acetylcholine (ACh).

Most of the enzyme-inhibitory compounds described in this book act by reversibly binding to the target enzyme to form an inactive enzyme–inhibitor (E–I) complex:



The affinity of the inhibitor (I) for the enzyme (E) can be described by the dissociation constant of the E–I complex (K_i):

$$K_i = [\text{E}][\text{I}]/[\text{E-I}]$$

where the concentration terms are those obtained at equilibrium. Note that the unit for K_i , K_d and K_m is molar (M), that is, moles per litre. If one translates from *in vitro* determinations of these parameters (in the test tube) to the *in vivo* situation (in the living cell), they provide

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a useful indicator of the *in vivo*, cellular concentration of an enzyme inhibitor, ligand or substrate, respectively, for half-maximal binding to the enzyme (in the absence of competition from other compounds).

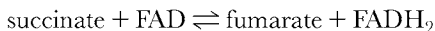
Reversible inhibition can be competitive or non-competitive. Competitive inhibitors bind to the active site and compete with the substrate for binding to the enzyme. However this means that increasing the S concentration will progressively outcompete the inhibitor. Accordingly a Lineweaver–Burk analysis of enzyme kinetic data obtained in the presence or absence of a competitive inhibitor will yield the same V_{\max} (at infinite S concentration) but the K_m in the presence of the inhibitor (K'_m) will be higher (poorer binding) than the K_m measured in the absence of competitive inhibitor. Knowing the inhibitor concentration [I] one can calculate the K_i from the relation:

$$K'_m = K_m(1 + [I]/K_i)$$

Non-competitive inhibitors bind to the enzyme at a site other than the active site and accordingly do not compete with the substrate. Accordingly a Lineweaver–Burk analysis of enzyme kinetic data obtained in the presence or absence of a non-competitive inhibitor will yield the same K_m but the V_{\max} in the presence of the inhibitor (V'_{\max}) will be lower than the V_{\max} measured in the absence of competitive inhibitor. Knowing the inhibitor concentration [I] one can calculate the K_i from the relation:

$$V_{\max} = V'_{\max} (1 + [I]/K_i)$$

A competitive inhibitor of an enzyme will typically structurally resemble a substrate of the enzyme. Thus malonate (methanedicarboxylate; $^-OOC-CH_2-COO^-$) is structurally similar to succinate (ethanedicarboxylate; $^-OOC-CH_2-CH_2-COO^-$) and is a competitive inhibitor of the oxidoreductase succinate dehydrogenase that catalyses the reaction:

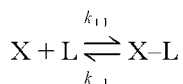


Many studies of inhibition of animal or fungal enzymes by plant-derived compounds or related synthetic compounds have involved assaying the enzyme in standard reaction conditions in the presence of increasing concentrations of the test compounds. From such analyses one can determine IC_{50} values (concentrations for 50% inhibition) for the test compounds. However such IC_{50} values can be markedly affected by the assay conditions used. Thus if the compound is a competitive inhibitor then the IC_{50} value will be much lower when determined at much lower concentrations of substrate. As indicated above, K_i values can be determined from kinetic analysis as outlined above. However such *in vitro* determinations have to be qualified in relation to different *in vivo* conditions including possible competing ligands and compound-sequestering entities *in vivo*.

h. Non-enzyme ligand-binding proteins

A variety of proteins not having a catalytic activity can nevertheless bind low molecular weight metabolites, other proteins, polynucleotides, polysaccharides, membrane components or metal ions. In some cases (such as the receptor tyrosine kinases (RTKs)) there is a catalytic domain at one part of the molecule and non-catalytic ligand binding domains elsewhere. In general, for all ligand-binding entities X (including enzymes, non-enzyme

ligand-binding proteins, polynucleotides, polysaccharides and membrane components) the association and dissociation of a ligand (L) can be represented thus:



where the rate of association (Msec^{-1}) = $k_{+1}[\text{X}][\text{L}]$ and the rate of dissociation (Msec^{-1}) = $k_{-1}[\text{X-L}]$.

The dissociation constant of the X-L complex (K_{d}) can be defined in various ways:

- 1 $K_{\text{d}} = [\text{X}][\text{L}]/[\text{X-L}]$
where the concentration terms are the equilibrium concentrations of the indicated components
- 2 $K_{\text{d}} = k_{-1}/k_{+1}$
- 3 We can derive an equation relating tightness of binding of the ligand, the free ligand and total binding entity as follows. If we represent the total concentration of X as $[\text{X}_{\text{T}}]$ then the concentration of X-L complex ($[\text{X-L}]$) is given by:

$$[\text{X-L}] = \frac{[\text{X}_{\text{T}}][\text{L}]}{[K_{\text{d}}] + [\text{L}]}$$

When half of the ligand-binding entity has ligand bound to it, $[\text{X-L}] = [\text{X}_{\text{T}}]/2$ and the equation reduces to $K_{\text{d}} = [\text{L}]$, that is, the K_{d} corresponds to the ligand concentration for 50% binding. The value of K_{d} is typically expressed in units of moles per litre (M). The association constant ($K_{\text{a}} = 1/K_{\text{d}}$ (units: M^{-1}). Ligand affinities are expressed as K_{d} values in this text because (subject to obvious qualifications in relation to *in vitro* measurement versus *in vivo* conditions) they provide a useful estimate of the *in vivo* ligand concentration required for ligand occupation of half the available sites.

K_{d} values can be experimentally determined by measuring the bound ligand concentration ($[\text{X-L}]$) and free ligand concentration ($[\text{L}]$) at equilibrium at various ligand concentrations. When X is a macromolecule, bound and free ligand can be separated for analysis (e.g. spectrophotometric, fluorimetric or radiochemical analysis) by high-speed centrifugation and equilibrium dialysis. Alternatively, the amount of bound ligand can be directly measured (e.g. if the fluorescence of the ligand is quenched on binding to X). Plasmon resonance analysis now provides a powerful means for determining K_{d} s of ligands for macromolecules (immobilized on electronics-linked gold leaflets) from measurements of k_{+1} and k_{-1} from analysis of association and dissociation kinetics.

Equilibrium bound ligand (L_{B}) and free ligand (L_{F}) concentrations can be plotted in several ways to determine K_{d} values and binding stoichiometries:

- i Klotz (or “double-reciprocal”) plots of $1/[L_{\text{B}}]$ versus $1/[L_{\text{F}}]$ (intercepts on these axes respectively providing values of $1/[\text{maximal } L_{\text{B}}]$ and $-1/K_{\text{d}}$);
- ii Scatchard plots of $[L_{\text{B}}]/[L_{\text{F}}]$ versus $[L_{\text{F}}]$ (the intercept on the $[L_{\text{F}}]$ axis and the negative reciprocal of the slope yielding values of maximal mol L bound per mol X and K_{d} , respectively). The Scatchard plot is particularly useful for picking up more than one type of binding site.

Ligand binding stoichiometries and K_{d} s having been determined by the methods sketched above, displacement of fluorescent or radioactively labelled ligands from macromolecules is a powerful method for detecting and analysing the effectiveness of novel ligands. Such methods have been very useful for screening for potentially pharmaceutically useful ligands binding to hormone or neurotransmitter receptors (see Chapters 3–6).

2.4 Metabolic strategies

A number of excellent, recent biochemistry texts provide detailed descriptions and explanations of biochemical systems (see Bibliography). The essential biochemistry involved in particular biochemical targets for plant defensive compounds is outlined in the relevant chapters following this section. However it is useful at this point to provide a framework, summary and rationale for key biochemical “strategies” involved, notably in “mice and men” and related higher organisms that are the major mammalian targets of biochemical pharmacological research.

a. Photosynthesis – the primary energy source

Plant chloroplasts absorb light energy (photons) through light harvesting pigments (carotenes and chlorophylls) to photolyse H_2O yielding O_2 (a strong oxidant) and a strong reductant (XH_2). Electrons flow “downhill” to an ultimate acceptor NADP^+ (to yield the reduced form NADPH) through the photosynthetic electron transport chain (ETC) composed of electron transfer components such as cytochromes, plastocyanin and plastoquinone. In this process energy is conserved through the “coupled” formation of ATP by the process of photophosphorylation. The downhill flow of electrons through the photosynthetic ETC is exergonic ($\Delta G < 0$) and is mechanistically coupled to the endergonic formation of ATP from adenosine 5'-diphosphate (ADP) and inorganic phosphate (P_i) ($\Delta G > 0$).

Oxidation–reduction potential (or redox potential, E) is the potential of compounds to accept electrons and is by convention measured relative to that of hydrogen. Thus E is very negative for NADPH (a strong reductant) but positive for O_2 (a strong oxidant). Standard redox potentials (E_o' values in volts) refer to standard conditions (1M redox components) at neutral pH (pH 7). The standard free energy change at pH 7 for a particular redox reaction ($\Delta G_o'$) is given by:

$$\Delta G_o' = -nF\Delta E_o'$$

where n is the number of electrons transferred, $\Delta G_o'$ is in units of kilocalories per mole (kcal mol^{-1}), $\Delta E_o'$ (oxidant minus reductant E_o' value) is in volts (V) and F is the Faraday constant ($23.06 \text{ kcal V}^{-1} \text{ mol}^{-1}$). [Note that actual ΔG and ΔE values in physiological conditions are related to the reactant concentrations and the $\Delta G_o'$ and $\Delta E_o'$ values, respectively].

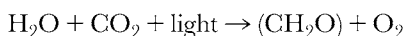
In the so-called “light reactions” of photosynthesis electrons (e^-) are donated to the chain from H_2O and ultimately accepted by NADP^+ to yield NADPH . The difference between the E_o' values of the $\text{NADPH}/\text{NADP}^+$ (-0.32 V) and $\text{H}_2\text{O}/\frac{1}{2} \text{O}_2$ ($+0.82 \text{ V}$) “half reactions” (electron acceptor minus electron donor) is $-0.32 - 0.82 \text{ V} = -1.14 \text{ V}$ and accordingly $\Delta G_o' = -nF\Delta E_o' = +52.6 \text{ kcal mol}^{-1}$ for the overall reaction:



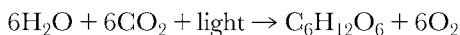
This overall endergonic reaction is “driven” by absorbed solar energy in an extraordinarily efficient process (efficiency *c.* 40%). [In *Disturbing the Universe*, eminent physicist Freeman

Dyson speculated on the properties of a highly efficient, self-repairing, self-replicating, photosynthetic “machine” for space colonization – and could not get past plants]. The photosynthetic ETC involves two ETC-linked light absorbing photosystems (photosystems I and II) and is described by the so-called Z scheme. Electron flow in “downhill” “noncyclic” and “cyclic” sections of the chain is coupled to ATP synthesis by noncyclic and cyclic photophosphorylation, respectively.

The ATP and NADPH synthesized by the light-dependent reactions of photosynthesis are used to reduce carbon dioxide (CO₂) to yield carbohydrates in the so-called “dark reactions” of photosynthesis (otherwise known as the Calvin cycle). This reduction of CO₂ initially yields phosphoglycerate (C₃) and thence glucose-1-phosphate (C₆). Glucose-1-phosphate yields the storage and transport sugar sucrose (C₁₂, 1-α-glucosido-2-β-fructofuranose) and the storage carbohydrate starch (α-(1 → 4)glucopyranose). The Calvin CO₂ fixation cycle involves a variety of C₃, C₄, C₅, C₆ and C₇ carbohydrates not detailed here. The essential overall reaction can be represented thus:



where (CH₂O) represents carbohydrate. With glucose (C₆, C₆H₁₂O₆) as an end product:



Carbohydrate is then oxidized back to CO₂ and H₂O by plant cells and by plant-consuming eukaryotes (animals and fungi) and prokaryotes (bacteria), this exergonic process being mechanistically “coupled” to the endergonic formation of ATP, the so-called “energy currency” of living cells.

b. Oxidation of carbohydrate coupled to ATP synthesis

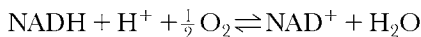
As a result of over 3 billion years of photosynthesis the earth’s atmosphere contains 21% O₂, that is, most above-ground organisms live in a highly oxidizing environment. Ingested carbohydrate (glucose, related sugars and glucose polymers) are metabolized in an aqueous environment at roughly ambient temperature. However this process can also be anaerobic (e.g. in the anaerobic glycolysis of yeast fermentation or of high activity skeletal muscle). In anaerobic yeast fermentation glucose (C₆) is phosphorylated (by ATP) to glucose-6-phosphate which is subsequently oxidized by the process of glycolysis through a succession of C₆ and C₃ intermediates to yield pyruvate (C₃). Pyruvate is then reduced to ethanol (in yeast fermentation) or to lactate (lactic acid) (in high activity skeletal muscle), the yield of ATP in either case being 2 ATP per glucose metabolized. Anaerobic glycolysis occurs in the cytosol.

Aerobic oxidation of glucose is a much more efficient process in which the glycolytic end product pyruvate (C₃) is decarboxylated and oxidized by pyruvate dehydrogenase in the inner matrix compartment of organelles called mitochondria. The product of this oxidation reaction is acetyl-coenzyme A (the acetyl group being C₂) and reduced coenzyme (NADH). Acetyl-coenzyme A reacts with oxaloacetate (C₄) to yield the tricarboxylic acid citrate (C₆) and thence a series of reactions successively decarboxylate or oxidize C₆ and C₄ intermediates to ultimately regenerate oxaloacetate (C₄). Associated with these reactions of the so-called mitochondrial tricarboxylic acid cycle (TCA, citric acid or Krebs cycle) is the production of reduced coenzymes (FADH₂ and 4 NADH) and GTP (which can readily generate ATP). The reduced coenzymes are re-oxidized via the mitochondrial inner membrane

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ETC, which conveys electrons from reduced coenzymes to the terminal electron acceptor O_2 . The exergonic “downhill” flow of electrons to O_2 is “coupled” to the endergonic synthesis of ATP from ADP and P_i , a process analogous to photophosphorylation and called “oxidative phosphorylation”. The overall yield of ATP from this process of glycolysis, the mitochondrial TCA cycle and mitochondrial oxidative phosphorylation is about 38 ATP per glucose oxidized.

It is now useful to consider the overall reaction in which, for example, NADH is oxidized via the mitochondrial ETC, the electrons finally going to the terminal electron acceptor, O_2 :



The difference between the E_o' values of the $\text{H}_2\text{O}/\frac{1}{2} \text{O}_2$ (0.82 V) and NADH/NAD^+ (0.32 V) “half reactions” (oxidant minus reductant) is $+0.82 \text{ V} - (-0.32 \text{ V}) = +1.14 \text{ V}$ and accordingly $\Delta G_o' = -nF\Delta E_o' = -52.6 \text{ kcal mol}^{-1}$.

This exergonic process is coupled to the endergonic process of ATP synthesis catalysed by the ATP synthase (or F_0 - F_1 complex) of the mitochondrial inner membrane:

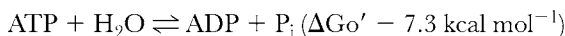


In the event, 3 ATP molecules are synthesized per NADH oxidized by the mitochondrial ETC (and 2 ATP per FADH_2 oxidized).

The actual mechanism involved in oxidative phosphorylation critically involves the relative proton (H^+) impermeability of the mitochondrial inner membrane surrounding the inner matrix. (Note that a further mitochondrial membrane, the outer membrane that is relatively permeable to many solutes, encloses an intermembrane space between the inner and outer membranes.) Electron transfer down the ETC (respiratory chain) results in H^+ (proton) extrusion to the cytosolic side of the inner membrane, creating a pH and charge difference across the membrane. The F_0F_1 complex is a transmembrane protein complex located on the inner membrane and oriented towards the matrix. The F_0 part is buried in the membrane and the knob-like F_1 part (which has the catalytic activity) is oriented away from the cytosol. Protons move back across the membrane through the F_0 complex and in so doing cause a rotation of the F_1 complex in which the catalytic β subunits successively exist in three conformational states in which ADP and P_i are loosely bound, subsequently synthesised ATP is very tightly bound and a state having a low affinity for ATP. The downhill movement of electrons to O_2 is thus “coupled” to the formation of a proton gradient which in turn drives successive conformational changes of the β subunits of the ATP synthase (F_0 - F_1) resulting in ATP synthesis.

c. ATP as the energy currency of cells

ATP is regarded as a “high energy” compound, hydrolysis of ATP being exergonic:



ATP is directly (or indirectly) used to “drive” all kinds of biosynthetic reactions that are endergonic and would normally not occur, for example, synthesis of proteins, RNA, DNA, phospholipids and polysaccharides and other biosynthetic reactions. Mechanistically, this can involve ATP hydrolysis-dependent generation of a reactive intermediate.

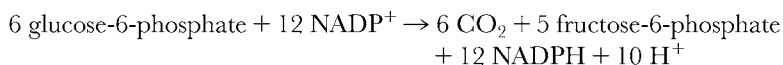
ATP hydrolysis is also used to drive motility (e.g. muscle contraction) and active solute translocation across membranes. Thus 70% of the ATP utilization in the brain is for operation of the $\text{Na}^+ \text{K}^+$ -ATPase responsible for ATP-driven pumping of Na^+ out of cells and K^+ into cells, thereby generating the Na^+ and K^+ gradients critical for action potentials and cell signalling. The mechanism involves phosphorylation of an aspartyl residue in the plasma membrane-located $\text{Na}^+ \text{K}^+$ -ATPase causing a conformational change resulting in Na^+ release to the outside of the cell and binding of external K^+ ; dephosphorylation of the $\text{Na}^+ \text{K}^+$ -ATPase causes a reversion to the original conformational state and release of bound K^+ on the inside of the cell.

d. NADH for catabolism and NADPH for reductive biosynthesis

NADP^+ is the 2'-phospho derivative of NAD^+ . In plants the light reactions of photosynthesis generate ATP and NADPH, which are then used in the Calvin cycle for the reduction of CO_2 and the synthesis of glucose and glucose polymers. ATP and NADPH are also used in the “anabolic” (building up) synthesis of fatty acids. NADH (and its oxidized form NAD^+) are used in the “catabolic” (breaking down) “energy metabolism” of plant cells, for example, in glycolysis, the TCA cycle and in fatty acid oxidation.

In animals and fungi there is a similar dichotomy. NADPH can be generated by cytosolic malic enzyme which catalyses the reaction: $\text{malate} + \text{NADP}^+ \rightarrow \text{pyruvate} + \text{CO}_2 + \text{NADPH}$. Cytosolic malate derives from the following successive reactions: the pyruvate/citrate shuttle on the mitochondrial inner membrane takes pyruvate to the mitochondrion in exchange for citrate; cytosolic ATP citrate lyase catalyses: $\text{ATP} + \text{citrate} + \text{CoA-SH} \rightarrow \text{acetylCoA} (\text{CH}_3\text{CO-S-CoA}) + \text{oxaloacetate}$; and cytosolic malate dehydrogenase, which catalyses: $\text{NADH} + \text{oxaloacetate} \rightleftharpoons \text{NAD}^+ + \text{malate}$. This scheme provides both acetylCoA and NADPH for subsequent long chain fatty acid synthesis (see section on “Fatty acid synthesis”).

NADPH is also generated by the cytosolic “pentose phosphate pathway” that achieves the following:



The NADPH generated can thence be used for reductive biosynthesis (e.g. of long chain fatty acids). The specialized use of NADPH and NADH for reductive biosynthesis and energy metabolism, respectively, means that NADPH and NADH can be used simultaneously in the cytosol for fatty acid synthesis and glycolysis, respectively. The pentose phosphate pathway involves the following key reactions [key responsible enzymes are indicated in square brackets]: $\text{glucose-6-phosphate} (\text{C}_6) + \text{NADP}^+ \text{ [via glucose-6-phosphate dehydrogenase]} \rightarrow \text{6-phosphoglucono-}\delta\text{-lactone} (\text{C}_6) + \text{NADPH}$; $\text{6-phosphoglucono-}\delta\text{-lactone} (\text{C}_6) + \text{H}_2\text{O} \text{ [via 6-phosphogluconolactonase]} \rightarrow \text{6-phosphogluconate} (\text{C}_6)$; $\text{6-phosphogluconate} (\text{C}_6) + \text{NADP}^+ \text{ [via 6-phosphogluconate dehydrogenase]} \rightarrow \text{3-keto-6-phosphogluconate} (\text{C}_6) \rightarrow \text{CO}_2 (\text{C}_1) + \text{D-ribulose-5-phosphate} (\text{C}_5)$. D-ribulose-5-phosphate (C_5) is then converted into D-ribose-5-phosphate (C_5) [via ribose-5-phosphate isomerase] and xylulose-5-phosphate (C_5) [via ribose-5-phosphate-3-epimerase] which are then involved in a series of C_3 , C_4 , C_5 , C_6 and C_7 sugar phosphate interconversions [involving the enzymes transketolase and transaldolase] yielding fructose-6-phosphate and thence glucose-6-phosphate.

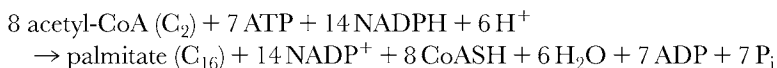
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e. Monomer polymerization to yield polymers

A relatively small set of monomeric precursors can generate a wide range of polymers. This is most evident in the case of polypeptides and polynucleotides but the same principle applies to fatty acids, lipids and polysaccharides. The synthesis of these polymers is briefly sketched below [the enzymes catalysing key steps are indicated in square brackets for clarity].

i. Fatty acid synthesis. The anabolic (building up) process of fatty acid synthesis occurs in the cytosol whereas the converse catabolic (breaking down) process of fatty acid oxidation (β -oxidation) is confined to the mitochondrial matrix. Nevertheless there is an interplay of both compartments in both processes. The thioester acetylCoA ($\text{CH}_3\text{-CO-S-CoA}$) is generated in mitochondria as a result of pyruvate oxidation [catalysed by pyruvate dehydrogenase] but cannot cross the inner membrane. AcetylCoA (C_2) condenses with oxaloacetate (C_4) to form citrate (C_6) [via citrate synthase] and is transported into the cytosol in exchange for pyruvate (C_3) which can regenerate oxaloacetate (C_4) in the mitochondrial matrix [via ATP and pyruvate carboxylase]. In the cytosol citrate (C_6) plus CoASH [via ATP and ATP-citrate lyase] yields acetylCoA (C_2) and oxaloacetate (C_4). Oxaloacetate (C_4) is reduced to malate (C_4) [via NADH and malate dehydrogenase] which is thence decarboxylated [via NADP^+ and malic enzyme] to yield CO_2 (C_1), pyruvate (C_3) (which can return to the mitochondrial matrix) and NADPH. The first committed step of fatty acid synthesis is synthesis of malonylCoA (C_3) from acetylCoA (C_2) and CO_2 (C_1) [via ATP and the biotin-containing acetylCoA carboxylase].

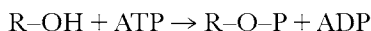
Subsequent reactions are catalysed by enzymes of the dimeric eukaryote fatty acid synthase complex together with a small acyl carrier protein (ACP). ACP (like coenzyme A) has a phosphopantotheine (a thiol) as a prosthetic group and can form malonyl-S-ACP (C_3) [via malonylCoA and malonylCoA-ACP transacetylase]. Similarly an acetyl transferase catalyses the reaction of acetyl-S-CoA (C_2) with a thiol (-SH) on an acyl-malonyl-ACP condensing enzyme (CE) to form acetyl-S-CE (C_2). In an irreversible reaction [catalysed by β -ketoacyl-ACP synthase (= acyl-malonyl-ACP CE)] acetyl-S-CE (C_2) and malonyl-S-ACP (C_3) react with loss of CO_2 (C_1) to form acetoacetyl-S-ACP (C_4). Acetoacetyl-S-ACP is reduced [via NADPH and β -ketoacyl-ACP reductase] to yield D-3-hydroxy-butyryl-ACP, which is then dehydrated [via 3-hydroxyacyl-ACP dehydratase] to yield a *trans*- Δ^2 -enoyl-ACP, which is thence finally reduced [via NADPH and enoyl-ACP reductase] to yield butyryl-ACP (C_4). Butyryl-ACP generates a butyryl-S-CE (C_4) which reacts with further malonyl-ACP (C_3) (with CO_2 (C_1) release) and the cycle can then be repeated (with a C_2 addition in each cycle) until a palmitoyl-ACP (C_{16}) is generated. At this chain length free palmitate ($\text{CH}_3(\text{CH}_2)_{14}\text{COO}^-$) is formed [via a thioesterase]. The overall stoichiometry is:



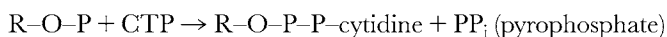
ii. Lipid complexity – triacylglycerol, phospholipid, sterols and membrane bilayers. Long chain fatty acids represent high energy density catabolite sources and are stored as triacylglycerols. The synthetic route can be summarized as follows: glycerol-3-phosphate (an intermediate in glycolysis derived from glycerol, that is, 1,2,3-trihydroxy-propane) \rightarrow [via fatty acyl transferase + 2 fatty acylCoA (R-CO-S-CoA)] 1,2-diacyl-glycerol-3-phosphate (phosphatidate) \rightarrow [via phosphatidate phosphatase + H_2O] 1,2-diacylglycerol (DAG) \rightarrow [via fatty acyl transferase] triacylglycerol. One can appreciate the potential complexity of phosphatidates, monoacylglycerols, diacylglycerols and

triacylglycerols (the variables being fatty acid chain length and location and number of double bonds in the unsaturated fatty acyl chains).

3-Phosphodiacylglycerol derivatives are phospholipids and are major constituents of cell membranes. Phosphatidate (1,2-diacylglycerol-3-phosphate) is a phosphomonoester. We can simply represent phosphatidate as DAG–P (P denoting a phosphoryl or PO_3 substituent). However diacylglycerols can form phosphodiester with a variety of alcohols (ROH). These so-called phospholipids are major components of biological membranes. Major phospholipids include phosphatidylcholine (DAG–P–O– $\text{CH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$), phosphatidylethanolamine (DAG–P–O– $\text{CH}_2\text{CH}_2\text{NH}_2$), phosphatidylserine and phosphatidylinositol (where inositol is hexahydroxycyclohexane). The enzyme-catalysed synthesis of these phospholipids involves a prior activation through phosphorylation of the alcohol (ROH) (such as choline) by reaction with ATP [catalysed by choline kinase]:



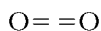
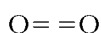
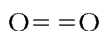
R–O–P can react with the related “high energy” nucleoside triphosphate CTP (cytidine 5'-triphosphate):



R–O–P–P–cytidine can react with DAG to form a phospholipid:



Phospholipids are amphipathic molecules, that is, they have parts of different polarity. The fatty acyl chains are nonpolar and hydrophobic whereas the phosphoryl alcohol “head group” is polar and can be solvated by H_2O . Phospholipids form bimolecular membranes in which the hydrophobic fatty acyl chains are located in the interior of the membrane (away from H_2O) and the head groups are on the surface (on either side of the membrane) and exposed to H_2O . Representing phospholipids as =O (where = represents the fatty acyl chain and O the head group), we can represent such a “phospholipid bilayer” thus:



The “phospholipid bilayer” is the basic structure of all biological membranes. In addition to the phospholipids noted above a variety of others exist. Thus cardiolipin (in which a glycerol diester links two phosphatidates) is present in mitochondrial and bacterial membranes. Sphingosine is an amphipathic lipid having the structure:



Long chain fatty acid amides involving the 2-amino of sphingosine (RCONHX) are called ceramides and are structurally similar to diacylglycerols in having a glycerol-like head and two long hydrocarbon chains. Ceramide 1-*O*-phosphorylcholine is a phospholipid called sphingomyelin. Related, amphipathic, membrane-associated lipids that are related to sphingomyelin include the cerebrosides (ceramide 1-*O*-glucose and ceramide 1-*O*-galactose) and the gangliosides (ceramide 1-*O*-oligosaccharides).

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Cholesterol ((3 β)-cholest-5-en-3-ol) is a major non-phospholipid component of animal membranes and is the principal sterol of animals. Cholesterol is also amphipathic, the 3-hydroxy being polar and the rest of the molecule hydrophobic. Cholesterol can insert into phospholipid bilayers, lowering membrane permeability and lowering the “melting point” of membranes (i.e. making the membranes less ordered and more fluid).

The phospholipids and sphingolipids of biological membranes can have considerable structural diversity through having different “head groups” and different fatty acids chains (that can vary in terms of chain length and the number and disposition of double bonds). Unsaturated fatty acids have lower melting points than saturated fatty acids and a higher proportion of unsaturated fatty acids in membranes makes for higher membrane fluidity (i.e. for lower transition temperatures at which the viscosity of the membrane sharply increases as the membrane “solidifies”).

iii. Monosaccharides and polysaccharides. Monosaccharides (or sugars) are carbohydrates with the general formula $(\text{CH}_2\text{O})_n$ and contain either a ketone group ($\text{C}-\text{C}(=\text{O})-\text{C}$) (ketose sugars) or are aldehydes ($\text{X}-\text{CHO}$) (aldose sugars). Sugars with 3, 4, 5, 6 and 7 carbons are called trioses, tetroses, pentoses, hexoses and heptoses, respectively. These polyalcohols have asymmetric carbon centres and hence have stereoisomers that differ in optical activity in relation to rotation of the plane of polarization of plane polarized light. Thus the triose glyceraldehyde has an asymmetric C (C*) ($\text{CHO}-\text{C}^*\text{H}(\text{OH})-\text{CH}_2\text{OH}$) and can exist as 2 mirror image forms, namely D- and L-glyceraldehyde. Larger sugars have accordingly more asymmetric centres and by convention D and L refer to the asymmetric C configuration furthest from the aldehyde or ketone group.

A sugar aldehyde group (CHO) can react with a hydroxyl to form a hemiacetal, that is, $\text{R}-\text{OH} + \text{R}'-\text{CHO} \rightarrow \text{R}-\text{O}-\text{C}(\text{OH}, \text{R}', \text{H})$. Similarly, a sugar ketone can react with a hydroxyl to form a hemiketal, that is, $\text{R}-\text{OH} + \text{R}'-\text{CO}-\text{R}'' \rightarrow \text{R}-\text{O}-\text{C}(\text{OH}, \text{R}', \text{R}'')$. Through such reactions sugars such as the aldose hexose D-glucose and the ketose hexose D-fructose can exist in open chain forms or can cyclize. It should be noted that both the ketone and aldehyde groups of monosaccharides can reduce the cupric ion (Cu^{2+}) to cuprous (Cu^+) and hence they are referred to as “reducing sugars”.

D-glucose ($\text{CHO}-\text{CH}(\text{OH})_4-\text{CH}_2\text{OH}$, with the aldehyde carbon being numbered carbon 1 or C-1) cyclizes to form a 6-membered ring (called a pyranose ring after the 6-membered cyclic ether ring compound tetrahydropyran), the reaction involving the CHO (C-1) and the hydroxy on carbon-5 (C-5). The substituents of C-1 are accordingly the hemiacetal O, C-2, an H and an OH. Two anomers are possible in relation to the orientation of the 1-OH of cyclized D-glucose and thus we have α -D-glucose and β -D-glucose that interconvert in solution via the open chain form (mutarotation) (Section 4, Appendix). These forms can be represented by Haworth projection formulae in which the plane of the ring is approximately perpendicular to the plane of the paper, the C-2–C-3 bond is closest to the reader (and indicated thus by a very thick line), the hemiacetal O is furthest away from the reader and the CH_2OH (C-6) and the C-1 OH are both oriented upwards (in the β -anomer). In this arrangement the OH is oriented downwards from the anomeric carbon 1 (C-1) in the α -anomer.

Similarly, open-chain D-fructose ($\text{CH}_2\text{OH}-\text{CO}-(\text{CH}_2\text{OH})_4-\text{CH}_2\text{OH}$), a ketose hexose, can cyclize via the keto ($\text{C}=\text{O}$) of C-2 reacting to form a hemiketal with the hydroxy (OH) of C-5 to generate a 5-membered ring (called a furanose ring after the 5-membered cyclic ether ring compound tetrahydrofuran). Again anomers are possible in relation to the OH on the anomeric C-2 and thus D-fructose can exist as α -D-fructose and β -D-fructose that interconvert in solution by mutarotation via the open chain form (Section 4, Appendix).

Monosaccharides can form disaccharides through reaction of the anomeric carbon OH with an OH of another sugar to eliminate H_2O and form a C–O–C linkage called a “glycosidic link”. Thus formation of a glycosidic link between the anomeric carbon (C-1) of β -D-galactose (Gal) and C-4 of β -D-glucose (Glc) yields the disaccharide lactose (β -D-galactopyranosyl(1 \rightarrow 4)- β -D-glucopyranoside; β -D-Gal(1 \rightarrow 4)- β -D-Glc) involving a “ β (1 \rightarrow 4) bond”. Note that lactose has a “reducing end” (C-1 of the glucose part). Similarly a glycosidic link between the anomeric C-1 of α -D-glucose and C-4 of α -D-glucose yields maltose (α -D-glucopyranosyl(1 \rightarrow 4)- α -D-glucopyranoside; α -D-Glc(1 \rightarrow 4)- α -D-Glc), this glycosidic link being an “ α -(1 \rightarrow 4) bond” and maltose having a “reducing end”.

Sucrose (cane sugar) is a disaccharide in which the glycosidic link involves the anomer C-1 of α -D-glucose and the anomeric C-2 of fructose. Sucrose (α -D-glucopyranosyl(1 \rightarrow 2) β -D-fructofuranoside; α -D-Glc(1 \rightarrow 2) β -D-Fru) does not have a reducing end because the reducing ends of both the constituent monosaccharides are involved in glycosidic bond formation (Section 4, Appendix).

Other monosaccharide derivatives are of importance. Thus phosphorylated monosaccharides are important intermediates in metabolism (e.g. in the Calvin cycle, the pentose phosphate pathway, glycolysis and gluconeogenesis). The monosaccharides β -D-glucosamine (GlcN) and β -D-galactosamine (GalN) are analogues of β -D-Glc and β -D-Gal, respectively, in which there is a 2-amino (NH_2) instead of a 2-hydroxy (OH); β -D-N-Acetylglucosamine (GlcNAc) and β -D-N-acetylgalactosamine (GalNAc) are the corresponding acetylated sugars that are often components of glycoproteins (glycosylated proteins) that can be decorated by complex oligosaccharide structures involving various sugars including Glc, Gal, GlcNAc, GalNAc, fucose (Fuc), mannose (Man) and sialic acid (N-acetylneuraminic acid, NeuNAc). O-linked oligosaccharides are attached via O-glycosidic bonds to the OH groups of Ser or Thr. N-linked oligosaccharides are attached via the amide NH_2 of the R group of Asn, Asn typically occurring within the sequence Asn-X-Ser. Complex oligosaccharides are synthesized on the cytosolic side of the ER membrane attached to a lipid carrier (dolichol phosphate). After synthesis of a $(Man)_3(GlcNAc)_2$ -pyrophosphate-dolichol the molecule “flips” across the membrane and inside the lumen of the ER the oligosaccharide part (G-oligosaccharide) is transferred to a protein acceptor [catalysed by membrane-bound oligosaccharide transferase] after which it is subject to processing or “trimming”.

Nucleosides are N-glycosides in which an N-glycosidic bond is formed between the anomeric carbon of a sugar and a nitrogen (N) of a base. Thus formation of an N-glycosidic link between the anomeric carbon (C-1) of the pentose furanose sugar ribose and the N9 of adenine (6-aminopurine) yields the nucleoside adenosine. Phosphorylation of the 5'-hydroxyl of the ribose moiety of adenosine yields the “nucleotide” adenosine 5'-monophosphate (5'-AMP or AMP) and further phosphorylation successively yields ADP and thence ATP, the “energy currency” of living cells.

Other related ribonucleotides with different purine or pyrimidine bases include uridine 5'-triphosphate (UTP) (pyrimidine base, uracil), cytidine 5'-triphosphate (CTP) (pyrimidine base, cytosine) and guanosine 5'-triphosphate (GTP) (purine base, guanine). In deoxynucleotides ribose is replaced by 2'-deoxyribose and we have the analogous deoxynucleosides deoxyadenosine, deoxyguanosine, deoxycytidine and deoxythymidine (for which thymine (5-methyluracil) is the corresponding base) and the corresponding deoxynucleoside 5'-monophosphates (dNMPs), 5'-diphosphates (dNDPs) and 5'-triphosphates (dNTPs). The polynucleotide RNA is composed of nucleoside monophosphate monomers (AMP, GMP, UMP and CMP) linked by 3',5'-phosphodiester linkages. The polynucleotide DNA is

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composed of deoxynucleoside monophosphate monomers (dAMP, dGMP, dTMP and dCMP) linked by 3',5'-phosphodiester linkages.

Polysaccharides have major structural and storage functions in cells. Plant cell walls have as a major component the $\beta(1 \rightarrow 4)$ glucan polymer cellulose in which the β -D-glucopyranosyl units are linked by $\beta(1 \rightarrow 4)$ linkages. Cellulose forms linear fibrils which in the plant cell wall are associated with other polysaccharides and with phenolic lignin cross-links that provide further strength. Callose is a wounding-induced plant cell wall $\beta(1 \rightarrow 3)$ glucan polysaccharide in which β -D-glucopyranosyl units are linked by $\beta(1 \rightarrow 3)$ linkages. Cellulose and callose are produced by PM-located enzyme complexes that use UDP-glucose (uridine 5'-diphosphate α -D-glucopyranosyl ester; UDP-Glc; UDPG) as a biosynthetic precursor.

After glucose synthesis in photosynthesis, the disaccharide sucrose (α -D-Glc(1 \rightarrow 2) β -D-Fru) is used as a readily transportable sugar. Sucrose synthesis successively involves the following: UDP-glucose + fructose-6-phosphate \rightarrow sucrose-6-phosphate + UDP [via sucrose phosphate synthase]; sucrose-6-phosphate + H₂O \rightarrow sucrose + P_i [via sucrose-6-phosphatase].

The major form of stored, readily metabolizable sugar in plants is the polysaccharide starch, a polymer in which α -D-glucopyranosyl units are linked by $\alpha(1 \rightarrow 4)$ linkages. Starch is synthesized in the inter-thylakoid space (stroma) of chloroplasts and stored there as starch grains. Starch synthesis uses ADP-glucose, CDP-glucose and GDP-glucose as precursors (UDP-glucose being used for cellulose and callose synthesis).

In animal cells the glucose polymer glycogen is an important carbohydrate energy reserve, principally in the liver and skeletal muscle. Glycogen involves glucose residues linearly linked by $\alpha(1 \rightarrow 4)$ linkages but with periodic branches every *c.* 10 residues due to $\alpha(1 \rightarrow 6)$ linkages. Glycogen is formed by the following reactions: (a) UTP + glucose-1-phosphate \rightarrow UDP-glucose + PP_i [via UDP-glucose pyrophosphorylase]; (b) PP_i + H₂O \rightarrow 2P_i [via pyrophosphatase, this reaction making reactions (a) and (b) combined exergonic overall]; (c) glycogenin (a protein) autocatalytically transfers 8 glucosyl residues to a tyrosine OH on itself and this then acts as a “primer” at the core of the glycogen molecule that is subsequently formed [via glycogen synthase + UDP-glucose] by addition of glucosyl residues to the non-reducing end by $\alpha(1 \rightarrow 4)$ linkages (the requirement of glycogen synthase to be in contact with glycogenin limiting the ultimate size of the glycogen granule): UDP-Glc + (Glc)_{*n*}-X \rightarrow Glc $\alpha(1 \rightarrow 4)$ (Glc)_{*n*}-X + UDP; (d) $\alpha(1 \rightarrow 6)$ branches are added (thereby creating many new ends for subsequent synthesis and degradation) by cutting $\alpha(1 \rightarrow 4)$ links and re-joining blocks of about 7 Glc residues by $\alpha(1 \rightarrow 6)$ links [catalysed by branching enzyme (amylo(1-4 \rightarrow 1-6) transglycosylase)].

iv. DNA structure and synthesis. DNA chains are polymers of dNMPs (dAMP, dGMP, dCMP and dTTP) that are linked by 3',5'-phosphodiester linkages (deoxyribose_{*n*}-C-3'-O-P(-O)₂-O-C-5'-deoxyribose_{*n+1*}) between successive deoxyribose residues, the purine (A, G) and pyrimidine (C, T) bases being linked by N-glycosidic linkages to the anomeric carbon (C-1') of each deoxyribose. DNA sequences are conventionally written as base sequences from the 5'-end to the 3'-end of the sugar-phosphate-sugar backbone.

DNA can be single stranded (ssDNA) or double stranded (dsDNA). In dsDNA the two strands are antiparallel and are complementary based on the hydrogen bonding between bases (base pairing). Thus adenine (a purine) hydrogen bonds to thymine (a pyrimidine), this involving 2 hydrogen bonds between keto and amino groups (that we can denote as A=T). Hydrogen bonding between guanine (a purine) and cytosine (a pyrimidine) is much stronger since it involves 2 hydrogen bonds between keto and amino groups and a further hydrogen bond between a purine N and a pyrimidine N (i.e. G≡C). A notional dsDNA sequence could be:

5'-AATTGGCC-3'

3'-TTAACCGG-5'

The 2 antiparallel strands are “plectonemically” coiled (intertwined as in 2-stranded plaits) as a right-handed “double helix” with the paired bases located within the structure, these planar heterocyclic molecules being roughly stacked parallel to each other and perpendicular to the long axis of the dsDNA. Base-pairing between the bulkier purines and the smaller pyrimidines ensures efficient packing within the hydrophobic core of the DNA. The outer part of the dsDNA in contact with H₂O is composed of the negatively charged, polar sugar–phosphate backbone. The intertwining of the two strands creates “minor grooves” (in which the strands are closer together) and “major grooves” (in which the strands are further apart), these grooves alternating in a “minor groove”–“major groove” pattern along the molecule.

Because hydrophobic interactions and hydrogen bonding are favoured at higher ionic strength and lower temperatures, respectively, such conditions promote dsDNA formation. Conversely, increasing temperature can overcome hydrogen bonding and cause denaturation of dsDNA to give single strands. Single strands can be “renatured” or “hybridized” at lower temperatures, with the exact fidelity of re-association being determined by the complementary base sequences. It is this fidelity of hybridization that underpins the revolution in molecular biology.

Genes are composed of dsDNA that is organized in a specific organelle (the nucleus) in eukaryotes (plants, fungi and animals) but is merely packaged into a region of the cell called the nucleoid in prokaryotes (bacteria). Because of the length of a typical bacterial chromosome (that of *Escherichia coli* being a circular, dsDNA molecule containing 4.6 million base pairs), the DNA is “negatively supercoiled” and twisted into some 50 loops associated with some DNA-binding, histone-like proteins that in turn enable association with the cell membrane.

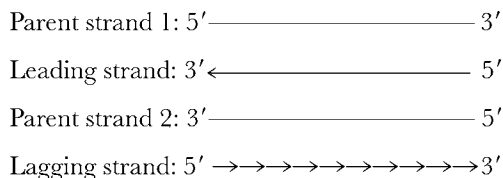
In eukaryotes (such as man), DNA includes the encoding genes (exons), intervening sequences (introns) and regulatory elements. In man DNA is organized into chromosomes – 2 sets of 23 per cell in diploid somatic cells (including an X and a Y chromosome in male cells and two X chromosomes in female cells) and 1 set per cell in haploid germ cells. The length of dsDNA in these chromosomes ranges from 1.6 to 8.4 cm and accordingly has to be very compactly packaged at various levels. (a) So-called core DNA is wound about basic histone protein octamers (containing 2 copies each of histones H2A, H2B, H3 and H4) with a histone H1 molecule binding to the surface of this 11 nanometer (nm) diameter “nucleosome”; individual nucleosomes are connected by 55 base pair linear “linker DNA”. (b) Nucleosomes are helically packaged into 30-nm diameter solenoid-like fibres. (c) The 30-nm fibres are organized into radial looped structures perpendicular to a protein “scaffold” at the centre of each chromosome.

DNA synthesis is catalysed by DNA polymerases and requires the precursor dNTPs (dATP, dGTP, dCTP and dTTP, each of these existing as Mg²⁺ complexes), a template (i.e. the dsDNA being copied) and a primer (an initial deoxyribose 3'-OH to enable the reaction to insert the first new nucleotide). The reaction proceeds in a 5' to 3' direction, that is, at the end of the synthesis there is a “vacant” deoxyribose 3'-OH. The fidelity of the replication process is based on the incoming nucleotides “base pairing” with the correct base on the antiparallel template. DNA synthesis is semi-conservative (i.e. the newly synthesized strand partners its antiparallel complementary strand) and is bidirectional (because both original strands are replicated).

In prokaryotes DNA polymerase I has a 5' → 3' DNA polymerase activity as well as a “proof reading” capacity to “chop out” nucleotides in either direction through a 5' → 3' and a 3' → 5' direction exonuclease activity; DNA polymerases II and III have 5' → 3'

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DNA polymerase activity and $3' \rightarrow 5'$ direction exonuclease activity. Because there are 2 strands to be replicated the 2 strands of the dsDNA have to unwind and in a circular dsDNA bidirectional replication results in a “replication bubble” bounded by two Y-shaped “replication forks” that move around the circle. The continuous or leading strand is made unbroken around its ssDNA template. However the other (antiparallel) strand (the lagging strand), proceeding from the same starting point as the dsDNA opens up, is made with the same $5' \rightarrow 3'$ polarity but in the opposite direction to that for the leading strand. Further, the lagging strand is made as short bits (called Okazaki fragments) which are subsequently joined up by an ATP-dependent enzyme DNA ligase:



DNA replication requires a primer as well as a template and the primer is a piece of RNA made by a primase. DNA polymerase I eventually excises the RNA primer and fills in the gap which is then closed by DNA ligase. Without detailing the topological problem, unwinding of circular DNA requires an ATP-dependent helicase (to unwind the strands), an ssDNA-binding protein (to stop the strands winding back again), topoisomerase I (to make a single-strand break on one strand just ahead of the fork to permit it to rotate about the unbroken strand with subsequent rejoining of the break) and topoisomerase II (to make a double-strand break for one of the interlocked daughter dsDNA circles to pass through and then re-join the break).

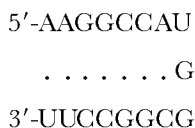
A similar semiconservative, bidirectional DNA replication process takes place in eukaryote cells but there are many DNA replication origins (replicons) that can occur in clusters called “replication units”. Eventually all the regions of replication are joined up to form 2 continuous semi-conservative dsDNAs. Specialized DNA polymerases are required, namely: DNA polymerase α (which synthesises the lagging strand and has primase activity to make the RNA primer but does not have $3' \rightarrow 5'$ exonuclease activity); DNA polymerase δ (which makes the leading strand and has $3' \rightarrow 5'$ exonuclease activity that excises nucleotides in that direction); DNA polymerases β and ϵ (involved in DNA repair); and DNA polymerase γ (which replicates mitochondrial DNA). Finally, the replication of linear DNA (as opposed to that of bacterial circular DNA) has a problem of potential failure to replicate the $3'$ -ends by the lagging strand. This arises because when the RNA primers are removed there is then no $3'$ -OH end template to permit requisite DNA synthesis. This has been overcome by having telomeres at the ends of chromosomes having short repeated sequences and a telomerase containing a complementary RNA sequence that can extend the parent strand $3'$ -end by reverse transcription (RNA-dependent DNA synthesis) to be followed by DNA-dependent DNA polymerase α filling in the gap.

v. RNA structure and synthesis. RNA chains are polymers of NMPs (AMP, GMP, CMP and UMP) that are linked by $3',5'$ -phosphodiester linkages (ribose_nC- $3'-O-P(-O)_2-O-C-5'$ ribose_{n+1}) between successive ribose residues, the purine (A, G) and pyrimidine (U, C) bases being linked by N-glycosidic linkages to the anomeric carbon (C-1') of each ribose. RNA sequences are conventionally written as base sequences from the $5'$ -end to the $3'$ -end of the sugar–phosphate–sugar backbone.

RNA is single stranded but can have “secondary structure” by forming double stranded regions where it is “self-complementary”. Thus the linear RNA sequence:

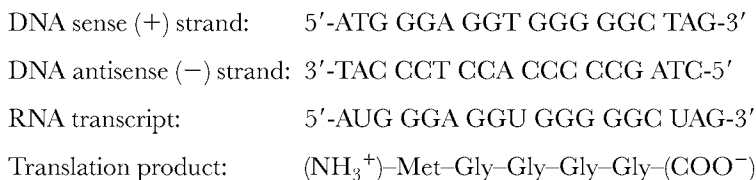


can form a looped structure involving 2 hydrogen bonds between A and U pair (A=U) and 3 hydrogen bonds between each G and C pair (G≡C) (these links being indicated as dots below):



“Transcription” of the gene encoding a protein yields a messenger RNA (mRNA) which can be subsequently “translated” on ribosomes to yield the encoded protein. The Genetic Code involves combinations of three bases (triplet codons), there being a total of $4 \times 4 \times 4 = 64$ possible triplet combinations of four bases. Three of the codons (UAG, UGA and UAA) do not encode amino acids but are “stop codons” or “termination codons” that specify termination of translation of the mRNA to yield a polypeptide. Accordingly there remain 61 codons for coding 20 amino acids. Two amino acids have only one codon, namely Met (AUG) and Trp (UGG). The other amino acids have variously 2 to 6 codons and the Genetic Code is accordingly described as being “degenerate”. Thus Gly has the codons GGA, GGG, GGU and GGC (the less stringent third position being referred to as the “wobble” position). AUG is the universal “start codon” and thus initial polypeptide translation products start with Met (in eukaryotes) or *N*-formylMet (in prokaryotes). The Genetic Code is universal (except for some changes in some mitochondrial codons).

The DNA of a gene has a sense (+) strand and a complementary antisense (–) strand. The antisense strand acts as a template for transcription yielding a complementary RNA that is made in a $5' \rightarrow 3'$ direction. The RNA sequence is complementary to the DNA sequence, fidelity of transcription being established through base pairing of the incoming ATP, GTP, UTP or CTP RNA precursors with the bases T, C, A and G, respectively, of the DNA antisense strand. The notional example below (with spacing introduced between codons for clarity) illustrates this “information flow” in “gene expression”:



The mRNA transcript is a linear molecule but can have secondary structure through “auto-complementarity” as indicated above. In addition to mRNA there are other types of RNA, notably ribosomal RNA (rRNA) and transfer RNA (tRNA). The rRNAs in eukaryotes include 18S, 5.8S, 28S and 5S rRNAs (S, the Svedberg, being a measure of rate of sedimentation in ultracentrifugation and hence of relative size). The rRNAs have extensive secondary structure. The rRNAs and a number of proteins make up the ribosome upon which translation occurs.

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tRNAs are clover leaf-shaped RNAs with extensive secondary structure that determine fidelity of translation through an “anticodon sequence” that can base pair with an mRNA codon. Thus a Met-specific tRNA (tRNA_{Met}) (that becomes aminoacylated with Met in protein synthesis) will have an anticodon sequence 3'-UAC-5' to enable it to base pair exactly with the Met codon (5'-AUG-3') of the mRNA and hence introduce the right amino acid (in this instance Met) into the growing peptide chain on the ribosome:

mRNA codon: 5'-AUG-3'

...

tRNA_{Met} anticodon: 3'-UAC-5'

The process of DNA-dependent RNA synthesis is catalysed by RNA polymerases and requires the precursor nucleoside 5'-triphosphates (ATP, GTP, CTP and UTP, each as Mg^{2+} complexes) and a template (i.e. the DNA being “transcribed”). The reaction proceeds in a 5' to 3' direction, that is, at the end of the synthesis there is a “vacant” ribose 3'-OH. The fidelity of the replication process is based on the incoming nucleotides base-pairing with the correct base on the antiparallel “antisense” ssDNA template that has to “unwind” from its complementary “sense” strand during the process.

Further details of the nature and regulation of transcription in prokaryotes and eukaryotes and the post-transcriptional “processing” of mRNA transcripts are given in Chapter 9.

vi. Protein synthesis and processing. Translation of mRNA to yield the encoded polypeptide occurs on ribosomes. As indicated in the section on “RNA structure and synthesis”, the mRNA is “read” in a 5' → 3' direction, the polypeptide is synthesized in an amino terminal (N-terminal) to carboxy terminal (C-terminal) direction and the exact fidelity of translation is determined by the hydrogen bonding interaction of the anticodon of each amino acid-specific tRNA with the complementary mRNA codon. The ribosomes are huge rRNA-ribosomal protein complexes involving a multiplicity of rRNAs and ribosomal proteins. The ribosomes are composed of two subunits, namely the large (L) and small (S) subunits. The ribosomes have 2 tRNA binding sites located near the interface of the L and S subunits, namely the A (or aminoacyl-tRNA site) and the P (or peptidyl-tRNA site). The prokaryote ribosome (70S) is composed of 50S (L) and 30S (S) subunits whereas the eukaryote ribosome (80S) is composed of 60S (L) and 40S (S) subunits. The following summary is based on the prokaryotic system.

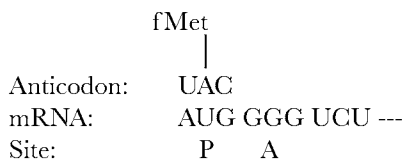
Amino acid-specific aminoacyl tRNA synthetases couple amino acids ($^+\text{H}_3\text{N}-\text{CH}(\text{R})-\text{COO}^-$) to the 3'-OH of amino acid-specific tRNAs ($\text{tRNA}-\text{CCA}-3'-\text{OH}$) in the following reactions:

- 1 $^+\text{H}_3\text{N}-\text{CH}(\text{R})-\text{COO}^- + \text{ATP} \rightarrow ^+\text{H}_3\text{N}-\text{CH}(\text{R})-\text{CO}-(\text{PO}_3)-\text{O}-\text{ribose}-\text{adenine}$ (aminoacyl-adenylate, aminoacyl-AMP) + PP_i (which is thence hydrolysed to 2P_i , thus driving the reaction to the right)
- 2 aminoacyl-AMP + tRNA → aminoacyl-tRNA + AMP

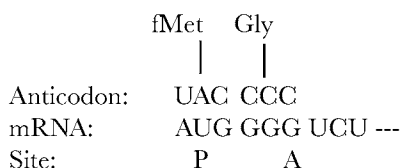
The first amino acid for reaction is *N*-formylmethionine (fMet) which has a specific tRNA ($\text{tRNA}_f^{\text{Met}}$) (as opposed to the Met-specific tRNA $\text{tRNA}_m^{\text{Met}}$). Using GTP hydrolysis as an energy source, the 30S subunit complexes with initiation factors IF1, IF2 and IF3. This complex binds the mRNA with the anticodon (3'-UAC-5') of the *N*-formylmethionyl-tRNA $_f^{\text{Met}}$ (fMet-tRNA $_f^{\text{Met}}$) hydrogen bonding to the start codon (5'-AUG --- 3') of the mRNA, the fMet-tRNA $_f^{\text{Met}}$ binding at the so-called “P site” with release of IF3.

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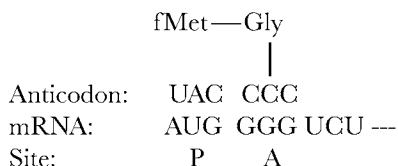
The 50S subunit now binds with release of IF1, IF2, GDP and P_i to yield the following P site–A site arrangement (the vertical line represents the specific aminoacyl-tRNA):



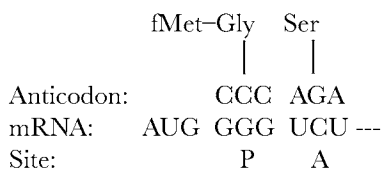
An elongation factor EF-T catalyses a further GTP hydrolysis-dependent binding of the next aminoacyl-tRNA to the adjoining “A site”:



A 50S subunit peptidyl transferase (PT) catalyses the formation of a peptide bond between fMet and Gly (i.e. yielding fMet–CO–NH–Gly–):



Now an elongation factor EF-G catalyses a GTP hydrolysis-dependent translocation of the mRNA by three nucleotides so that codon 2 (bearing an fMet–Gly–tRNA) is now in the P site, the first tRNA is released and codon 3 is in the A site, ready to accept the next aminoacyl-tRNA, in this instance Ser-tRNA^{Ser} (anticodon AGA):



The process continues until a stop codon ends up in the A site at which point a protein release factor binds to the stop codon, the peptide (H₃N⁺–fMet–Gly–Ser–HN–CH(R_n)COO[–])–tRNA bond is hydrolysed, the completed polypeptide is released and the ribosomal subunits separate.

However the synthesis of the polypeptide (typically a precursor pro-protein) is followed by various processes that can include targeting of polypeptides to specific organelles (e.g. mitochondria, ER, nucleus, vacuole or indeed for extracellular export), assistance with protein folding to form the proper tertiary structure, proteolytic processing (removing parts of the pro-protein) and further covalent modification (notably by glycosylation). Protein

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synthesis, protein targeting, folding and glycosylation will be considered in greater detail in Chapter 9.

f. Regulation of metabolism and development

A recurrent need in complex metabolic pathways is to avoid “futile cycles” in which an intermediate is simultaneously being synthesized (with energy expenditure) and broken down (with energy conservation). Thus anabolic reactions are endergonic ($\Delta G > 0$), require an energy input (e.g. from coupled hydrolysis of ATP or related compounds) and make complex molecules from simple precursors (e.g. proteins from amino acids, triacylglycerols from fatty acids and glycerol, glycogen from glucose and polynucleotides from nucleotide monomers). Conversely, catabolic reactions break down more complex molecules to their monomers and thence oxidize the monomers, the free energy change from these exergonic reactions ($\Delta G < 0$) ultimately being conserved through the coupled formation of ATP.

The differential rates of anabolic and catabolic reactions, in particular, conditions, derive from differential compartmentation within the cell, distinct biosynthetic and degradative pathways, the actual amounts of the relevant enzymes and the activity of these enzymes having access to the metabolic intermediates (as regulated by regulatory metabolites such as allosteric effectors and by hormonal signalling-induced covalent modification of the enzymes). Thus rates of metabolic processes are determined by the activities of the key enzymes (notably those catalysing irreversible or “committed” steps of particular metabolic pathways as opposed to simple mass action effects due to precursor or end-product build up). Ultimately the end result is “homeostasis” (“equilibrium” or “balance”). Non-dividing cells extract energy from outside, repair their existing orderly structures and maintain metabolic homeostasis.

Nevertheless in an overall cell developmental context there is a dichotomy of repair of existing structures versus cell replication. In a mature organism developmental homeostasis means that there has to be a balance between cell division (creation of new cells) and apoptosis (or programmed cell death). An imbalance of cell division over apoptosis gives a cancerous state of excessive expansion of cell number. Accordingly these two radical processes of cell division and apoptosis must be tightly regulated. Further, in a developing organism (e.g. an embryo) in addition to cell division (new cells) and apoptosis (cell death to make way for new cellular structures) there is differentiation of cells into specific cell types, this arising from differential gene expression that has to be switched on and off with the correct chronology. Finally, metazoan (multicellular) organisms are composed of cells operating as a coherent whole; variously have motility and perceptive capacities; and must be able to respond to emergencies (e.g. pathogen invasion) – all of these being achieved by specific regulatory machineries and hormonal and other signalling mechanisms.

The major metabolic, developmental and signal responsive pathways are determined by the functionality of proteins (notably enzymes) and the amounts of particular proteins. The turnover of proteins is determined by the dichotomy of gene expression (protein synthesis) and protein degradation. The nature and regulation of these various pathways are sketched below.

g. Metabolic compartmentation in cells

Animal cells are bounded by a cell membrane or PM and within the interior cytosol are various membrane-bound organelles, namely: the nucleus (containing the genome and surrounded by a double membrane having elaborate pore structures); the ER network; the *cis*- and *trans*-Golgi network of membranes (involved in processing, folding and glycosylation of

newly synthesized proteins destined for export or a vacuolar localization); lysosomes (acidic vacuoles involved in hydrolytic degradation including the protease-catalysed degradation of proteins such as those engulfed or internalized by endocytosis and the fusing of PM vesicles); mitochondria (containing the machinery for ATP-providing oxidative phosphorylation and having an inner membrane enclosing an inner matrix and a high permeability outer membrane enclosing an intermembrane space); and peroxisomes (involved in elimination of hydrogen peroxide).

i. The cytosol includes the enzymic machinery for **glycolysis** (glucose (C₆) metabolism to yield pyruvate (C₃) with concomitant ATP synthesis and thence lactate (C₃) or ethanol (C₂) formation from pyruvate (C₃) in anaerobic conditions); the **pentose phosphate pathway** (glucose (C₆) decarboxylation and oxidation with concomitant C₃–C₅ sugar phosphate inter-conversions and production of NADPH for biosynthetic purposes); **fatty acid synthesis** (synthesis of palmitic acid (C₁₆) using NADPH and acetylCoA (C₂) deriving from metabolite translocation from mitochondria); **protein synthesis on ribosomes** (with ribosomes producing proteins for insertion into the ER being located on the ER membrane); **protein degradation via proteasomes** (involving ATP-dependent protein attachment via a peptide link to the protein ubiquitin (via ubiquitinating and polyubiquitinating enzymes), this permitting such specifically “marked” proteins to be subject to ATP-dependent proteolysis by the proteasome complex).

ii. The mitochondrial matrix contains the enzymic machinery for the **TCA cycle** (pyruvate (C₃) decarboxylation and oxidation via acetylCoA (C₂) and C₄ and C₆ di- and tri-carboxylic acid intermediates with generation of GTP (and hence ATP), CO₂ and NADH and FADH₂ for coupled ATP formation by oxidative phosphorylation); **oxidative phosphorylation** (the coupling of NADH and FADH₂ oxidation via the ETC complex to ATP synthesis via the F₀F₁ ATP synthase complex, both of these complexes being located on the mitochondrial inner membrane); **β-oxidation of fatty acids** (yielding acetylCoA that can feed into the TCA cycle and NADH and FADH₂ for ATP formation by oxidative phosphorylation); **ketone body formation** (in which 2 acetylCoA (C₂) yields acetoacetate (C₄), which thence by reduction yields 3-hydroxybutyrate (C₄), these C₄ entities being highly mobile energy sources for further oxidation).

iii. The cytosol and mitochondrial matrix compartments cooperate in gluconeogenesis (in which, e.g. lactate- or Ala-derived pyruvate is carboxylated (via CO₂ (C₁), ATP and pyruvate carboxylase in the matrix) to yield oxaloacetate (C₄), which in the cytosol yields phosphoenolpyruvate (PEP) (C₃) and CO₂ (C₁) (via GTP and PEP carboxykinase), this permitting glycolysis to reverse in the cytosol to ultimately yield glucose); and the **urea cycle** (in which in the mitochondrial matrix carbamoylphosphate (H₂N–CO–OPO₃²⁻) (C₁, N₁) is synthesized from HCO₃⁻ (C₁) and NH₃ (N₁) (via ATP and carbamoylphosphate synthetase) and is thence transferred to ornithine (–OOC–CH(NH₃⁺)–(CH₂)₃–NH₃⁺ = X–NH₃⁺) (C₅, N₂) to yield citrulline (X–NH–CO–NH₂) (C₆, N₃) (via ornithine transcarbamoylase); in the cytosol, citrulline (C₆, N₃) and aspartate (NH₃⁺–CH(COO⁻, CH₂COO⁻) (C₄, N₁) yield arginosuccinate (X–NH–C(=NH₂⁺)–NH–CH(COO⁻, CH₂COO⁻) (C₁₀, N₄) plus H₂O (via ATP and arginosuccinate synthetase), which then yields fumarate (–OOC–CH=CH–COO⁻) (C₄) and arginine (X–NH–C(NH₂, =NH₂⁺) (C₆, N₄) (via arginosuccinase); finally arginine (C₆, N₄) plus H₂O (via arginase) yields urea (H₂N–CO–NH₂); C₁, N₂) for excretion via the kidneys and ornithine (X–NH₃⁺) (C₅, N₂) for re-entry into the mitochondria for reaction with carbamoyl-phosphate).

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iv. The nucleus contains the genome (histone-decorated dsDNA involving encoding genes (exons), intervening sequences (introns) and regulatory elements) and the enzymic machinery for transcription and DNA replication. The nucleolus is a specific section of the nucleus involved in rRNA synthesis.

v. The endoplasmic reticulum (ER) network consists of the rough ER (RER, having ribosomes on the outside responsible for membrane protein and secretory protein (ectoprotein) synthesis and involving folding-, proteolysis- and glycosylation-based processing of such proteins) and the smooth ER (not having associated ribosomes and involved in phospholipid biosynthesis and detoxification and steroid modification processes involving the NADPH-coupled monooxygenases linked to heme-containing cytochrome P450 and catalysing overall reactions of the kind: $\text{NADPH} + \text{O}_2 + \text{RH} + \text{H}^+ \rightarrow \text{ROH} + \text{H}_2\text{O} + \text{NADP}^+$).

vi. The Golgi apparatus is a network of membranes enclosing an internal lumen. Vesicles from the RER (the ER with associated ribosomes) fuse with the Golgi network in which proteins are processed, glycosylated and sorted into vesicles for final vacuolar or extracellular disposition.

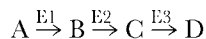
vii. Lysosomes have a pH of about 4–5 and contain various hydrolytic enzymes, namely (functions in parentheses): proteases (proteolysis of endocytosed proteins), lipases (lipid hydrolysis), phosphatases (hydrolysis of nucleotide, protein and phospholipid phosphate esters) and nucleases (RNA and DNA degradation).

viii. Peroxisomes are involved in removal of hydrogen peroxide (H_2O_2) catalysed by catalase: $2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2$. H_2O_2 in turn arises from reactive (and hence potentially damaging) oxygen radicals such as superoxide (O_2^-) produced as a by-product of aerobic metabolism and detoxified via the metalloenzyme superoxide dismutase (SOD): $2\text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$. We will see in Chapter 14 that many plant phenolics found in leafy vegetables are good scavengers of such ageing-promoting reactive oxygen species (ROSs).

h. Regulation of enzyme activity and protein function

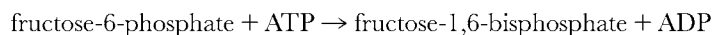
The activity of enzymes (and indeed of the functionality of proteins in general) can be regulated by reversibly binding ligands (allosteric effectors) and by covalent modification (that can be either reversible or irreversible).

1. Allosteric regulation involves a ligand binding at a site on an enzyme other than the active site in such a way that enzyme activity is affected. Allosteric regulation often involves the enzyme catalysing the first reaction of a sequence of interconversions, for example:

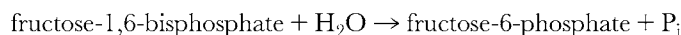


and the end product D inhibits the enzyme E1 catalysing the first reaction of the pathway (this being termed “feedback regulation”, “negative feedback” and “end-product inhibition”). Irreversible reactions (e.g. reactions driven by coupled ATP hydrolysis) are often key sites for such regulation because they represent “committed” steps in the pathway.

Good examples are the regulation of phosphofructokinase (PFK) that catalyses the reaction



and fructose-1,6-bisphosphatase (FBPase) that catalyses the reaction:



These reactions are effectively irreversible and represent key control sites in the process of glycolysis (glucose catabolism ultimately yielding TCA cycle intermediates such as citrate, decreased pH (i.e. increased acidity), increased ATP, decreased ADP and operating in conditions of plenty, that is, of high blood glucose) and of gluconeogenesis (glucose synthesis by reversal of glycolysis after conversion of Ala and lactate through pyruvate to PEP and occurring at times of “fasting”, i.e. of lower blood glucose). However a further consequence of elevated blood glucose is elevation of a “plenty signal” fructose-2,6-bisphosphate (F26BP) in the liver (see section on “Reversible covalent modification”).

PFK is activated by AMP (the precursor for ADP and ATP) and by F26BP (which also acts as a “positive allosteric effector”) but is inhibited by ATP, citrate and lowered pH (“end products” of the pathway), ATP and citrate acting as “negative allosteric effectors”. In contrast FBPase is activated by citrate (a “positive allosteric effector”) and inhibited by the “plenty signal” F26BP (a “negative allosteric effector”).

In these examples, precursors of the enzyme-catalysed reaction act as “feed-forward inhibitors” (AMP for PFK and citrate for FBPase). The “plenty signal” F26BP (elevated as a result of the precursor elevated blood glucose conditions) also activates PFK. Conversely, “down the track”, “end products” act as “feedback inhibitors” (ATP and citrate for PFK and F26BP – that can be loosely seen as an “end product” of blood glucose elevation by gluconeogenesis – for FBPase).

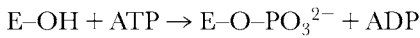
A “classical” enzyme exhibits a hyperbolic v_0 versus [S] kinetic plot (in which v_0 initially rises quasi-linearly as [S] increases before flattening out as V_{\max} is approached). However an “allosteric” enzyme exhibits “sigmoidal” kinetics (in which v_0 initially increases only a small amount as [S] increases but eventually “takes off” and flattens out as it asymptotes to V_{\max} , that is, a lop-sided “S-shaped” curve is obtained. Positive effectors tend to make v_0 rise more rapidly at low [S] (giving the plot a more “classical” appearance) whereas negative effectors exaggerate the sigmoidal kinetics, making v_0 even lower. The sigmoidal kinetics derive from having multisubunit allosteric enzymes in which S binding at the active site (or effector binding at the allosteric binding site) of one subunit affects the catalytic activity and ligand binding of other subunits in a “cooperative” way. This type of cooperativity can be observed with non-enzyme multisubunit proteins, a good example being O₂ binding to hemoglobin (which has a heterotetrameric subunit composition $\alpha_2\beta_2$ with O₂ binding to each subunit).

2. Reversible covalent modification of enzymes involves reversible chemical modification (typically of an R group of an enzyme amino acid residue) with consequent change in the catalytic activity of the modified enzyme. Examples include adenylation (E–Tyr–OH + ATP → E–Tyr–O–AMP + PP_i) and carboxymethylation (E–Glu–COO[−] + R–CH₃ (methyl donor) → E–Glu–CO–OCH₃ + R), such modifications being reversed hydrolytically by enzyme-catalysed de-adenylation and demethylation, respectively. Specific types of protein kinases (PKs) can catalyse the phosphorylation of particular amino acid R groups such as those of Ser (–OH), Thr (–OH), Tyr (phenolic –OH), His (an imidazole N), Asp (–COO[−]) and Glu (–COO[−]). Specific types of phosphoprotein phosphatases (PPs) catalyse the corresponding dephosphorylation reactions. The modifying enzymes may be switched on by particular signals (e.g. hormonal signals or changes in the concentrations of key signalling metabolites). Of course reversible covalent modification can also modify the function of proteins other than enzymes.

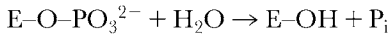
A good example of reversible covalent modification is provided by PKs that catalyse the phosphorylation of specific R groups of residues of specific proteins. Thus a

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Ser-/Thr-specific PK will catalyse the phosphorylation of particular Ser or Thr –OH groups on specific substrate proteins. In the case of an enzyme (E) this reaction can be written as



The corresponding de-phosphorylation reaction is catalysed by PPs:



A key Ser-/Thr-specific PK is the 3',5'-cyclic AMP (cyclic AMP, cAMP)-dependent PK (PKA) (the properties of which are described in much greater detail in Chapters 7 and 8). The cyclic nucleotide cAMP is a so-called “second messenger” that signals “hunger” in non-plant eukaryotes and in prokaryotes. The levels of cAMP rise in liver cells (hepatocytes) in response to fasting and a decrease in blood glucose. Conversely the levels of F26BP (a “plenty” signal) rise in liver in response to the postprandial increase in blood glucose (see section on “Allosteric regulation”). The sequence of events (described in more detail in Chapter 5) can be sketched as follows (noting that the primary stimulus is a decrease in blood glucose and the desired, ultimate “homeostatic” response an increase in blood glucose concentration):

Fasting \rightarrow \downarrow blood glucose \rightarrow \uparrow glucagon (gluconeogenesis promoting hormone secreted from α -cells of the pancreas) \rightarrow glucagon binds to glucagon-specific “G-protein coupled receptors” on the hepatocyte PM \rightarrow generation of a $G_{\alpha s}$ -GTP transducing protein-GTP complex \rightarrow activation of adenylyl cyclase \rightarrow catalysis of the reaction: $\text{ATP} \rightarrow$ 3',5'-cyclic AMP (cAMP) \rightarrow \uparrow cAMP \rightarrow activation of PKA \rightarrow phosphorylation of the hepatocyte F26BP-synthesizing (fructose-6-phosphate-2-kinase)/hydrolysing (fructose-2,6-bisphosphate-2-phosphohydrolyase) dual activity enzyme (E-OH) \rightarrow E-O- PO_3^{2-} (F26BP synthesizing activity thence being inhibited and F26BP hydrolysing activity increased with the phosphorylated form of E) \rightarrow \downarrow F26BP \rightarrow PFK less active (\downarrow allosteric activator F26BP) and FBPase more active (\downarrow allosteric inhibitor F26BP) \rightarrow fructose-1,6-bisphosphate is hydrolysed to fructose-6-phosphate (gluconeogenic direction) \rightarrow \uparrow gluconeogenesis and \downarrow glycolysis \rightarrow increased blood glucose (the desired result, the signalling pathway having been initiated by a fall in blood glucose).

3. Irreversible covalent modification of enzymes typically involves specific proteolysis of an inactive, autoinhibited (self-inhibited) enzyme resulting in activation of the enzyme. Good examples of this are provided by digestive proteases (such as trypsin, chymotrypsin and pepsin) that necessarily have to be inactive when synthesized to prevent digestion of the secreting cell. These proteases are secreted as inactive “zymogens” but are subsequently activated by specific proteolytic cleavage to remove the inhibitory part of the protein. Similarly, blood clotting is mediated by a “cascade” of “factors” that are proteases. The blood clotting cascade proteases are activated by specific proteolysis and then proteolytically activate the next protease in the cascade. The cascade ultimately results in blood clotting and dangerous adventitious blood clotting is prevented by this exquisite control of proteolysis.

i. Regulation of protein expression

The levels of particular enzymes (and indeed of specific proteins in general) is determined by the balance of protein degradation versus the specific expression of the protein (through the process of specific gene transcription, translation and post-translational processing of the protein). Genes can either be constitutively expressed (in which case they are normally always being transcribed) or are inducible, that is, specific transcription factors are activated

to enable transcription of specific genes to occur with resultant ultimate formation of the properly folded and processed fully functional protein. Gene expression will be considered in greater detail in Chapter 9 but the following example is provided here as an introduction.

Sustained stress (involving cortisol) and short-term stress (involving epinephrine) can affect metabolism by switching on the expression of genes encoding proteins involved in gluconeogenesis, notably PEP carboxykinase (PEPCK). The end result is increased gluconeogenesis and an increase in glucose entering the blood. The pathways involved can be summarized as shown below:

Stress → central nervous system (CNS) → nervous signalling to adrenal medulla → ↑ epinephrine secretion → epinephrine binds to specific hepatocyte β-adrenergic receptors → generation of G_{αs}-GTP → activation of adenylyl cyclase → ↑ cAMP → activation of PKA → phosphorylation of cAMP response element binding protein (CREB) → CREB-P (phosphorylated and activated transcription factor) → binds to the cAMP response element (CRE, the regulatory or “promoter” DNA regulating specific gene transcription) → transcription of specific genes including that for PEPCK → ↑ PEPCK → ↑ gluconeogenesis → ↑ blood glucose → useful stress response.

The glucocorticoid cortisol is secreted from the adrenal cortex as a stress response under the control of adrenocorticotrophic hormone (ACTH, corticotropin) produced by the anterior pituitary. Cortisol promotes catabolism by inducing synthesis of specific proteins. Cortisol binds to a cytosolic cortisol receptor which then translocates to the nucleus and switches on the expression of specific genes, notably that for PEP carboxykinase (PEPCK). Cortisol-induced expression of the key gluconeogenesis enzyme PEPCK increases levels of the enzyme and hence increases gluconeogenesis and available blood glucose. The cAMP- and cortisol-mediated pathways for induction of PEPCK expression are further linked by CREB-dependent expression of a coactivator protein PGC-1 that promotes cortisol-dependent expression of PEPCK.

2.5 Inhibition of biochemical processes by plant defensive compounds

The overview of animal biochemistry provided above indicates that there are many potential sites for interference by plant defensive compounds directed against animal herbivores and microbial plant pathogens. However, as is documented in the following chapters, most of the biochemical targets for plant defensive compounds are proteins involved in cellular regulation. Interference with fundamental processes common to both plants and plant-consuming organisms would necessarily damage the plant cells producing such agents. In the case of cyanogenic glycosides the product cyanide blocks the fundamental process of oxidative phosphorylation by inhibition of the last electron transfer step in the mitochondrial respiratory chain. However the inactive precursor is benign in the producing plant and the toxic agent is only liberated after ingestion of the plant material by microbial pathogens or animal herbivores. Further, the cyanogenic glycosides are bitter tastants and hence also act at a cognitive (i.e. signalling) level as feeding deterrents for animal herbivores. The remainder of this book deals systematically with the targets of plant defensive compounds with each chapter amplifying the nature, physiological role and special features of the particular susceptible biochemical systems.

3 Neurotransmitter- and hormone-gated ion channels

3.1 Introduction – electrical signalling in excitable cells

Animal cells (notably neurons, sensory cells and muscle cells) are made excitable in part through the operation of ion pumps that variously keep cytosolic concentrations of Na^+ , Cl^- and Ca^{2+} low and cytosolic K^+ concentration high. It should be noted that the cytosolic free concentration of Ca^{2+} is extremely low ($0.1 \mu\text{M}$ in resting cells and about $10 \mu\text{M}$ in excited cells) as compared to cytosolic concentrations of Na^+ , Cl^- and K^+ of about 10, 10 and 100 mM, respectively. The transmembrane potential (ψ_m) of animal cells is typically about -0.1 volt (V) (potential difference inside with respect to the outside), this being substantially due to internal constituents, selective membrane permeability and the operation of electrogenic ion pumps. Changes in the permeability of the cell membrane (plasma membrane, PM) to particular ions causes a change in ψ_m as described below.

The transmembrane potential difference can be described by the Goldman equation that relates ψ_m to the permeabilities of the membrane to specific ions and the concentrations of such major ions on either side of the PM:

$$\begin{aligned} \psi_m & \text{ (potential difference of the inside with respect to the outside)} \\ & = (2.303 RT/F) \log_{10} \frac{P_{\text{K}^+} [\text{K}^+]_o + P_{\text{Na}^+} [\text{Na}^+]_o + P_{\text{Cl}^-} [\text{Cl}^-]_i}{P_{\text{K}^+} [\text{K}^+]_i + P_{\text{Na}^+} [\text{Na}^+]_i + P_{\text{Cl}^-} [\text{Cl}^-]_o} \end{aligned}$$

[where R =the gas constant, T =absolute temperature, F =the Faraday constant; P_{K^+} , P_{Na^+} and P_{Cl^-} are the permeabilities of the membrane for K^+ , Na^+ and Cl^- respectively, and $[\text{K}^+]$, $[\text{Na}^+]$ and $[\text{Cl}^-]$ are the concentrations of K^+ , Na^+ and Cl^- , respectively, inside (i) or outside (o) the cell]:

$$\psi_m = 0.06 \log_{10} \frac{P_{\text{K}^+} [\text{K}^+]_o + P_{\text{Na}^+} [\text{Na}^+]_o + P_{\text{Cl}^-} [\text{Cl}^-]_i}{P_{\text{K}^+} [\text{K}^+]_i + P_{\text{Na}^+} [\text{Na}^+]_i + P_{\text{Cl}^-} [\text{Cl}^-]_o} \text{ V (at } 37^\circ\text{C)}$$

Let us suppose in the following illustrative example that the concentrations of Na^+ , Cl^- and K^+ inside the cell are 10, 10 and 100 mM, respectively and that the concentrations of Na^+ , Cl^- and K^+ outside the cell are 100, 100 and 10 mM, respectively. Let us further suppose that in the “resting state” ψ_m is -0.05 V.

An increase in the permeability of the PM to sodium ions (Na^+) permits Na^+ to enter the cell down a concentration gradient with a consequent increase in the positive charge within the cell that opposes Na^+ entry. At equilibrium there is no further net entry and ψ_m approximates to the Nernst equilibrium potential (ψ_N) for Na^+ given by the following equation (noting that z =the charge on the ion (+1)):

$$\psi_N = (2.303 RT/zF) \log_{10} (P_{\text{Na}^+} [\text{Na}^+]_o) / (P_{\text{Na}^+} [\text{Na}^+]_i)$$

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(noting, further, that the Goldman equation reduces to the above Nernst equation for Na^+ when $P_{\text{Na}^+} \gg P_{\text{K}^+}$ and P_{Cl^-})

$$\begin{aligned}\psi_N &= 0.06 \log_{10} ([\text{Na}^+]_o / [\text{Na}^+]_i) \text{ at } 37^\circ\text{C} \\ &= 0.06 \log_{10} (100/10) \\ &= 0.06 \text{ V}\end{aligned}$$

Thus an increase in the permeability of the plasma membrane to Na^+ (P_{Na^+}) can be seen to have depolarized the cell ψ_m (i.e. made it more positive).

Similarly, increasing the permeability of the membrane to K^+ (P_{K^+}) will permit K^+ to flow out of the cell down a concentration gradient, this efflux of positively charged K^+ causing the inside of the cell to be more negative with respect to the outside and hence increasingly opposing further efflux. At equilibrium, when there is no further net efflux of K^+ , the ψ_m approximates to the Nernst equilibrium potential (ψ_N) for K^+ :

$$\begin{aligned}\psi_N &= 0.06 \log_{10} ([\text{K}^+]_o / [\text{K}^+]_i) \text{ at } 37^\circ\text{C} \\ &= 0.06 \log_{10} (10/100) \\ &= -0.06 \text{ V}\end{aligned}$$

Thus an increase in the permeability of the PM to K^+ (P_{K^+}) can be seen to have hyperpolarized the cell ψ_m (i.e. made it more negative).

Finally, an increase in the permeability of the PM to Cl^- (P_{Cl^-}) permits Cl^- to enter the cell down a concentration gradient with a consequent increase in the negative charge within the cell that opposes further Cl^- entry. At equilibrium there is no further net Cl^- entry and ψ_m approximates to the Nernst equilibrium potential (ψ_N) for Cl^- given by the equation:

$$\psi_N = 0.06 \log_{10} ([\text{Cl}^-]_i / [\text{Cl}^-]_o) \text{ at } 37^\circ\text{C}$$

(noting that the charge z on the chloride ion is -1)

$$\begin{aligned}&= 0.06 \log_{10} (10/100) \\ &= -0.06 \text{ V}\end{aligned}$$

Thus an increase in the permeability of the PM to Cl^- (P_{Cl^-}) can be seen to have hyperpolarized the cell ψ_m .

Some kinds of membrane receptor proteins are ligand-gated ion channels that “open” in response to the binding of specific neurotransmitters. Thus the neurotransmitter binds to the specific receptor protein with a consequent subtle change in receptor conformation, an opening of a specific ion channel and an effective increase in the permeability of the membrane to an ion. When the permeability of the PM to Na^+ (P_{Na^+}) increases, the cell ψ_m depolarizes and the cell is “excited”. When there is an increase in the permeability of the PM to K^+ (P_{K^+}) or to Cl^- (P_{Cl^-}) as a result of neurotransmitter-gated receptor ion channels opening, the cell ψ_m hyperpolarizes and the cell is “inhibited”, that is, is more refractory to excitation by depolarizing signals.

Depolarization has various consequences involving voltage-gated Na^+ , K^+ and Ca^{2+} channels, that is, specific ion channels that will “open” or “close” depending upon the ψ_m . Transient cycles of depolarization and hyperpolarization involving voltage-gated ion channels are involved in the passage of “action potentials” along nerve axons in neurotransmission. Further, depolarization-induced opening of voltage-gated Ca^{2+} channels increases the concentration of Ca^{2+} in the cytosol. Ca^{2+} acts as a “second messenger” through the activation

of Ca^{2+} - or Ca^{2+} -calmodulin-dependent enzymes (notably protein kinases, PKs) and processes such as muscle contraction. Voltage-gated ion channels and Ca^{2+} -dependent signalling will be dealt with in Chapters 4 and 7, respectively.

3.2 Iontropic neurotransmitter receptors – neurotransmitter-gated ion channels

The major neurotransmitters (NTs) activating neurotransmitter-gated ion channels (“ionotropic neurotransmitter receptors”) can have either a depolarizing (excitatory) or hyperpolarizing (inhibitory) effect depending upon the ionotropic receptor ion channel specificity. Compounds that elicit the effect of a hormone (H) or NT at a receptor are termed “agonists”. Compounds that simply block H or NT action by competing with them for binding to specific receptors are called “antagonists”.

The depolarizing (excitatory) NTs include (ionotropic receptor subtype and ion specificity in parentheses): acetylcholine (ACh) (nicotinic receptors, Na^+), ATP (P2X receptors, Na^+), glutamate (Glu) (non-N-methyl-D-aspartate (NMDA) receptors, Na^+), glutamate (NMDA receptors, Na^+ and Ca^{2+}), serotonin (HT3 receptors, Na^+ and Ca^{2+}) and sigma receptor ligands (sigma receptors (σ -Rs) giving ligand-activated K^+ channel blockade). The hyperpolarizing (inhibitory) NTs include (ionotropic receptor subtype and ion specificity in parentheses): γ -aminobutyric acid (GABA) (GABA(A) and GABA(C) receptors, Cl^-) and glycine (Gly) (Cl^-). However it must be noted that ACh, ATP, GABA, Glu, serotonin and sigma receptor ligands can also act through so-called “metabotropic receptors”, which act via heterotrimeric G protein transducers as detailed in Chapter 5.

3.3 Structure and function of ionotropic receptors

Acetylcholine receptors (nicotinic) (nACh-Rs) are multisubunit ionotropic receptors (Rs) that are oligomers of α -type and β -type subunits (e.g. $\alpha 7$, $\alpha 2\beta 2$, $\alpha 3\beta 2$, $\alpha 3\beta 4$ and $\alpha 4\beta 2$). A ligand-gated Na^+ channel opens after ACh binds, the subsequent depolarization causing cytosolic Ca^{2+} elevation. Excitatory neurotransmission via nACh-Rs at skeletal neuromuscular (NM) junctions causes depolarization, activation of PM voltage-gated Ca^{2+} channels and activation of associated sarcoplasmic reticulum ryanodine receptors (that are also Ca^{2+} channels). The resultant increase in cytosolic Ca^{2+} concentration results in Ca^{2+} binding to troponin C, this ultimately permitting actin–myosin interaction and muscle contraction. Excitatory neurotransmission via nACh-Rs also occurs at particular neuron–neuron synapses.

The nACh-Rs are the targets of a variety of plant and other toxins that can variously act as nACh-R agonists (e.g. blue-green algal (+)-anatoxin-a, hemlock (+)-coniine and tobacco nicotine) and antagonists (e.g. snake α -bungarotoxin and the curare principal component (+)-tubocurarine) (Table 3.1). However transmission at nicotinic synapses can also be interfered with by inhibitors of acetylcholinesterase (AChE), the enzyme that catalyses the hydrolysis of ACh to allow for muscle relaxation and further signalling. The inhibition of NT converting enzymes and NT transporters by plant compounds is described in Chapter 6.

Iontropic ATP receptors ATP is an excitatory NT in the central nervous system (CNS) and the peripheral nervous system (PNS). ATP acts via ionotropic, oligomeric P2X receptors that form ATP-gated Na^+ and K^+ channels which also have a significant permeability for Ca^{2+} . ATP also acts via excitatory, metabotropic, G protein-linked P2Y receptors (see Chapter 5).

Iontropic GABA receptors (GABA(A)-Rs and GABA(C)-Rs) are inhibitory (hyperpolarizing) GABA-gated Cl^- channels that have sequence homology with nACh-Rs

and glycine receptors (Gly-Rs). GABA is the main inhibitory neurotransmitter of the mammalian CNS and GABA agonists have potential as anticonvulsants and anxiolytics.

The GABA(A)-Rs are hetero-oligomeric, pentameric complexes involving $\alpha 1-6$, $\beta 1-4$, $\gamma 1-4$, δ , ϵ and π subunits (e.g. $\alpha 1\beta 2\gamma 2$ GABA(A)-R is abundant in the brain). GABA(A)-Rs are modulated by steroids, barbiturates, benzodiazepines (via $\alpha 1$ subunits) and ethanol and are blocked by the phthalideisoquinoline alkaloids (+)-bicuculline and *N*-methylbicuculline. GABA(A)-R agonists include GABA itself, the *Amanita* mushroom oxazole alkaloids muscimol and dihydromuscimol and the piperidine alkaloid isoguvacine (Table 3.2).

GABA(C)-Rs are pentameric complexes involving $\rho 1-3$ subunits. Unlike the GABA(A)-Rs, the homo-oligomeric GABA(C) receptors are insensitive to bicuculline, steroids, baclofen, barbiturates and benzodiazepines. GABA(C)-Rs are activated by GABA and muscimol and bind isoguvacine (Table 3.2).

It should be noted that in addition to the GABA(A)-R benzodiazepine-binding sites or central benzodiazepine Rs (CBZ-Rs) there are peripheral benzodiazepine Rs (PBZ-Rs) associated with the outer membrane of mitochondria in glial cells and cells of peripheral tissue and which are involved in cholesterol transport and hence in regulation of steroid hormone synthesis. The GABA(B)-Rs are metabotropic and coupled via heterotrimeric G proteins to Ca^{2+} and K^+ channels (Chapter 5). The psychotropic GABA breakdown product γ -hydroxybutyrate (GHB) also acts via heterodimeric G protein-linked receptors (see Chapter 5).

Ionotropic glutamate receptors (Glu-Rs) are excitatory receptors of two general kinds, the non-NMDA-binding Glu-Rs (non-NMDA-Glu-Rs) and the NMDA-binding Glu-Rs (NMDA-Glu-R) that are distinguished by their ability to bind the excitotoxic amino acid NMDA. The NMDA-Glu-R ligand-gated cation pore is inactive at rest due to a voltage-dependent pore block by Mg^{2+} . Depolarization via activation of non-NMDA-Glu-Rs removes Mg^{2+} and unblocks a channel in the NMDA-Glu-R, allowing for ligand-induced increases in permeability to Na^+ , further depolarization and opening of the Ca^{2+} channel.

Non-NMDA-Glu-Rs include the quisqualate- and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-binding Glu-Rs (AMPA-binding Glu-Rs 1-4) and kainate-binding Glu-Rs (kainate-binding Glu-Rs 5-7 and kainate-binding receptors 1 and 2). The non-NMDA-Glu-Rs are ligand-gated Na^+ pores that open on binding Glu, the resultant increased permeability to Na^+ causing depolarization, deblocking of the NMDA-Glu-R Ca^{2+} channel and ultimately increased cytosolic Ca^{2+} .

NMDA-Glu-Rs are 4 to 5 subunit complexes of NR1, NR2 (A-D) and NR3 subunits with sites for various modulatory ligands including NMDA, Gly (at a strychnine-insensitive site) and ion channel blocking entities such as polyamines, Zn^{2+} and Mg^{2+} (Table 3.3).

It should be noted that glutamate can also act via excitatory metabotropic, G protein-activating glutamate receptors (mGlu-Rs) namely those of Class I (mGlu-Rs 1 and 5), Class II (mGlu-Rs 2 and 3), Class III (mGlu-Rs 4, 6, 7 and 8) and phospholipase D (PLD)-coupled mGlu-Rs. The mGlu-Rs couple through G proteins to increase phospholipase C (PLC) (class I), decrease adenyl cyclase (classes II and III) and increase PLD (PLD-coupled mGlu-R) (Chapter 5).

Glycine receptors (Gly-Rs) are inhibitory, strychnine-sensitive, Gly-gated chloride (Cl^-) channels with homology to other NT-gated ion channel receptors such as the nACh-Rs. On Gly binding, the Gly-gated chloride (Cl^-) channel opens with consequent inhibitory hyperpolarization (i.e. the transmembrane potential (ψ_m) becomes more negative inside with respect to the outside) (Table 3.3).

Inhibitory glutamate receptors (iGlu-Rs) are inhibitory, Glu-gated ion channels related to the ionotropic GABA receptors and glycine receptors, the open channel being permeable to Cl^- and sometimes to K^+ . The isoxazole alkaloid ibotenic acid activates iGlu-Rs (Table 3.3).

Ionotropic 5-hydroxytryptamine (5HT or serotonin) receptors (5HT3-Rs) are excitatory 5HT-gated, pentameric cation channel receptors that become selectively permeable to Na^+ and Ca^{2+} on binding 5HT with consequent excitatory depolarization. These receptors are involved in excitatory neurotransmission and in processes such as cardiac stimulation, vasodilation, pain, nociceptive neuron sensitization, nausea and vomiting.

It should be noted that 5HT-Rs 1, 2, 4, 5, 6 and 7 are metabotropic, G protein-linked receptors. Thus 5HT-Rs 1 and 5 inhibit adenylyl cyclase (i.e. decrease 3'-5'-cyclic adenosine monophosphate (cAMP) concentration), 5HT-R 2 increases cytosolic Ca^{2+} concentration and 5HT-Rs 6 and 7 stimulate adenylyl cyclase (i.e. increase cAMP concentration) as detailed in Chapter 5.

Sigma receptors (σ -Rs) (such as $\sigma 1$ and $\sigma 2$ σ -Rs) are excitatory, ionotropic receptors involved in an indirect ligand-activated K^+ channel blockade causing depolarization of the transmembrane potential. Endogenous ligands for σ -Rs include some opiates and such σ -R ligands can have protectant effects against ischaemia-induced retinal disease involving neuronal cell death (e.g. retinal artery occlusion, glaucoma and diabetic retinopathy). σ -R activation can have antitussive, anxiolytic and ulceroprotective effects (Table 3.4). It should be noted that there is evidence for G-linked metabotropic σ -Rs as well as non-metabotropic σ -Rs (Chapter 5).

Vanilloid receptors (capsaicin receptors) (VAN-Rs) such as the VAN-R V1 are excitatory ligand-gated Ca^{2+} channels. An endogenous ligand is the lipid-derived agonist anandamide and exogenous plant-derived agonists include resiniferatoxin, piperine (from pepper) and capsaicin (from capsicum). Vanilloid receptors are involved in pain perception (nociception) (Table 3.4).

Table 3.1 Nicotinic acetylcholine receptor agonists and antagonists

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Protein target/process inhibited (other targets) in vivo effects </i>
Acetylcholine receptor (nicotinic) (nACh-R) Sir Charles Sherrington ("neuron", "synapse", integrated nervous system) & Lord Edgar Adrian (electrical p.d.-based neurotransmission) (UK, Nobel Prize, Medicine, 1932)	Sir Henry Dale (UK) & Otto Loewi (Germany) (Nobel Prize, Medicine, 1936, chemical neurotransmission, acetylcholine); Sir John Eccles (Australia), Sir Alan Hodgkin (UK) & Sir Andrew Huxley (UK) (Nobel prize, Medicine, 1963, neurotransmission, hyper- & de-polarization)	3.1 Julius Axelrod (USA), Ulf Von Euler (Sweden), Sir Bernard Katz (UK) (Nobel Prize, Medicine, 1979, synaptic neurotransmission, neurotransmitters); Erwin Neher & Bert Sakmann (Germany, Nobel Prize, Physiology/Medicine, 1991, patch-clamping & ion channels)

(continued)

Table 3.1 (Continued)

Compound (class)	Plant (family) part	Protein target/process inhibited (other targets) in vivo effects
Acetylcholine receptor (nicotinic) (nACh-R) agonist		3.1A
Alkaloid		3.1Aa
Adenosine 5'-triphosphate (= ATP) (purine nucleoside triphosphate)	Universal	nACh-R agonist (β polypeptide, site distinct from site for ACh), Physostigmine (P-R)
Anabasine (= 3-(2- Piperidiny)pyridine; Neonicotine) (pyridine piperidine)	<i>Alangium</i> (Alangiaceae), <i>Zinnia</i> , <i>Zollikoferia</i> (Asteraceae), <i>Anabasis</i> (Chenopodiaceae), <i>Sophora</i> (Fabaceae), <i>Nicotiana</i> (Solanaceae) spp.	nACh-R agonist [76 nM] ($\alpha 4\beta 2$)
Choline (= 2-Hydroxy- N,N,N-trimethyl- ethan ammonium) (tetraalkyl ammonium)	Universal; in choline phospholipids	$\alpha 7$ nACh-R agonist [antinociceptive]
Codeine (= 3-O- Methylmorphine) (isoquinoline)	<i>Papaver somniferum</i> (opium poppy), <i>Argemone</i> , <i>Eschscholzia</i> , <i>Papaver</i> spp. (Papaveraceae) [latex]	nACh-R non-competitive agonist i.e. allosterically potentiating ligand (APL) (opiate R) [analgesic, antitussive, narcotic, spasmolytic]
γ -Coniceine (= 2,3,4,5- Tetrahydro-6- propylpyridine) (piperidine)	<i>Conium maculatum</i> (hemlock) (Apiaceae) [seed], <i>Aloe gililandii</i> , <i>A. ballyi</i> , <i>A. ruspoliana</i> , <i>A. sabaea</i> (Liliaceae)	nACh-R agonist (cf. Coniine) [paralytic, teratogenic, toxic]
(+)-Coniine (= (S)-2- Propylpiperidine (piperidine)	<i>Sambucus nigra</i> (Aloxaceae), <i>Conium maculatum</i> (hemlock) (Apiaceae) [leaf, seed], <i>Sarracenia flava</i> (pitcher plant) (Sarraceniaceae); agent in judicial murder of Socrates, compelled to drink hemlock in Athens, 399 BC	nACh-R agonist – α BgTX displacement (70) [paralytic, teratogenic, toxic]; Roman poisoners Apollodorus & Canidia used hemlock in honey
(S)(-)-Cotinine (= <i>N</i> - Methyl-2-(3-pyridyl)- 5-pyrrolidone) (pyridine pyrrolidinone)	<i>Carica papaya</i> (Caricaceae), <i>Nicotiana tabacum</i> (Solanaceae) [leaf]; major brain metabolite of Nicotine	nACh-R agonist (30), human $\alpha 7$ (weak agonist, desensitizes (175)) [antidepressant, stimulates nAChR to evoke D release]
Cytisine (= Baptitoxine; Citisine; Sophorine; Ulexine) (quinolizidine)	<i>Laburnum anagyroides</i> (laburnum) [seed], <i>Lupinus alba</i> , <i>Baptisia</i> , <i>Cytisus</i> , <i>Genista</i> , <i>Sophora</i> , <i>Thermopsis</i> , <i>Spartium</i> , <i>Ulex</i> spp. (Fabaceae)	nACh-R agonist – $\alpha 4\beta 2$ [1 nM], [$\alpha 7$ (6)], α BgTX displacement (1) [cf. nicotine]; hallucinogenic, respiratory stimulant, teratogenic, toxic]
Galanthamine (= Galantamine; Lycorimine) (galanthaman)	<i>Crinum</i> , <i>Galanthus</i> , <i>Hippeastrum</i> , <i>Hymenocallis</i> , <i>Leucojum</i> , <i>Lycoris</i> , <i>Narcissus</i> , <i>Pancreatum</i> , <i>Ungernia</i> spp. (Amaryllidaceae)	nACh-R non-competitive agonist i.e. APL (AChE) [analgesic (\approx morphine), insecticidal]

(continued)

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Table 3.1 (Continued)

Compound (class)	Plant (family) / part/	Protein target/process inhibited (other targets) / in vivo effects/
5-Hydroxytryptamine (= 5-HT; Serotonin) (indole)	<i>Phoenix dactylifera</i> (Arecaceae), <i>Ananas comosus</i> (Bromeliaceae), <i>Hippophae rhamnoides</i> (Elacagnaceae), <i>Mucuna pruriens</i> (Fabaceae), <i>Juglans regia</i> (Juglandaceae), <i>Musa sapientum</i> (Musaceae), <i>Lycopersicon esculentum</i> (Solanaceae), <i>Urtica dioica</i> (Urticaceae) [stinging hairs]	nACh-R non-competitive agonist i.e. APL [CNS NT]
(-)-Lobeline (piperidine)	<i>Lobelia hassleri</i> , <i>L. inflata</i> , <i>L. nocitianaefolia</i> , <i>L. tupa</i> (S. Am. "Indian tobacco"), <i>Campanula medium</i> [seed] (Campanulaceae)	nACh-R agonist – $\alpha 4\beta 2$ [4 nM] ($\alpha 7$ antagonist) [anti-smoking use; racemate (Lobelidine) analeptic]
(+)-N-Methylconiine (= 1-Methyl-2-propylpiperidine) (piperidine)	<i>Conium maculatum</i> (hemlock) (Apiaceae) [seed]	nACh-R (cf. Coniine) [toxic]
N-Methylcytisine (= Caulophylline) (quinolizidine)	<i>Caulophyllum thalictroides</i> (Berberidaceae), <i>Baptisia perfoliata</i> , <i>Cytisus laburnum</i> , <i>Lupinus albus</i> , <i>Ormosia stipitata</i> , <i>Spartium junceum</i> , <i>Thermopsis rhombifolia</i> (Fabaceae)	nACh-R ligand (agonist) [toxic, snail repellent]
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (pyridine)	In cigarette smoke from Nicotine <i>ex Nicotiana tabacum</i> (Solanaceae) [leaf]	nACh-R agonist – $\alpha B\gamma$ TX – sensitive, $\alpha 7$ [cell proliferative, carcinogen]
(-)-Nicotine (pyridine pyrrolidine); global annual smoking-related death 6 million per year & fire-related cost US\$90 billion; Gamel Abdul Nasser excessive smoker and diabetic (inevitable complications & premature death 1970)	<i>Nicotiana tabacum</i> (tobacco), <i>N. spp.</i> (Solanaceae); also in <i>Asclepias syriaca</i> (Asclepiadaceae), <i>Sedum acre</i> (Crassulaceae), <i>Lycopodium spp.</i> , <i>Equisetum arvense</i> (Equisetaceae); tobacco smoking introduced to England from America by Sir Walter Raleigh (subsequently beheaded)	nACh-R agonist – $\alpha 4\beta 2$ [1 nM; 7 nM], [$\alpha 7$ (24); inhibits by R desensitization], $\alpha B\gamma$ TX displacement [9] ($\alpha 9$ nACh-R blocker) [addictive, antinociceptive, bitter, insecticide, respiratory paralytic, toxic, tranquillizer]
(+)-Nicotine (pyridine pyrrolidine)	<i>Nicotiana tabacum</i> (tobacco), <i>N. spp.</i> (Solanaceae); also in <i>Asclepias syriaca</i> (Asclepiadaceae), <i>Sedum acre</i> (Crassulaceae), <i>Lycopodium spp.</i> , <i>Equisetum arvense</i> (Equisetaceae)	nACh-R agonist – [$\alpha 7$ (45); $\alpha B\gamma$ TX displacement [52] ($\alpha 9$ nACh-R blocker) [addictive, insecticide, respiratory paralytic, toxic, tranquillizer]
[N'-Nitroso]nicotine (pyridine pyrrolidine)	In cigarette smoke from Nicotine (<i>ex Nicotiana tabacum</i> (Solanaceae) [leaf]	nACh-R agonist – Epibatidine-sensitive [carcinogen]
(+)-(R)-Nornicotine (pyridine pyrrolidine)	<i>Nicotiana tabacum</i> (tobacco), <i>N. spp.</i> , <i>Duboisia hopwoodii</i> (Solanaceae); metabolite of Nicotine	nACh-R agonist [1 nM] ($\alpha 4\beta 2$) [addictive, insecticide, toxic (0.3 \times nicotine)]

(continued)

Table 3.1 (Continued)

Compound (class)	Plant (family) part	Protein target/process inhibited (other targets) in vivo effects
(-)-(<i>S</i>)-Nornicotine (pyridine pyrrolidine)	<i>Duboisia hopwoodii</i> , <i>D. myoporoides</i> , <i>Nicotiana tabacum</i> (tobacco), <i>N. spp.</i> , (Solanaceae); metabolite of Nicotine	nACh-R agonist [1 nM] ($\alpha 4\beta 2$) [addictive, insecticide, toxic (0.3× nicotine)]
Physostigmine (= Eserine; Physosterine; Physostol) (indole)	<i>Hippomane mancinella</i> (Euphorbiaceae), <i>Physostigma</i> <i>venenosum</i> (calabar bean) (Fabaceae) [seed]	nACh-R agonist (at 1) ($\alpha 4\beta 2$), non-competitive agonist i.e. APL (AChE) [miotic, parasympathomimetic, toxic]
Pseudoconhydrine (= ψ - Conhydrine; 5-Hydroxy-2- propylpiperidine) (piperidine)	<i>Conium maculatum</i> (hemlock) (Apiaceae) [seed]	nACh-R (cf. Coniine) [toxic]
(-)-Sparteine (= Lupinidine) (quinolizidine)	<i>Anagyris foetida</i> , <i>Baptisia tinctoria</i> , <i>Cytisus scoparius</i> , <i>Lupinus spp.</i> , <i>Piptanthus nanus</i> , <i>Sarothammus</i> , <i>Sophora</i> , <i>Spartium spp.</i> (Fabaceae), <i>Peumus boldus</i> (Monimiaceae), <i>Aconitum napellus</i> (Ranunculaceae)	nACh-R agonist (V-gated Na ⁺ channel) [diuretic, insect feeding stimulant, hypoglycaemic, oxytocic, toxic]
(+)-Tubocurarine (= curare active principle) (bisbenzylisoquinoline); Heinrich Otto Wieland (Germany, Nobel Prize, 1927, bile acids)	<i>Chondrodendron tomentosum</i> (curare, pareira), <i>C. spp.</i> (Menispermaceae) [bark]; S. Am. Indian arrow poison curare component	Foetal nACh-R partial agonist (nACh-R potent antagonist) [toxic, skeletal muscle relaxant]
Phenolic		3.1Ap
Coryneine (= 3,4- Dihydroxyphenethyl- trimethylammonium) (catecholamine quaternary ammonium)	<i>Aconitum sp.</i> (Ranunculaceae)	nACh-R agonist (& mixed competitive & non-competitive antagonist)
Terpene		3.1At
Glaudelsine (diterpene)	<i>Delphinium sp.</i> (larkspur) (Ranunculaceae)	nACh-R ligand (42 pM)
Other		3.1Ao
Acetylcholine (basic non-heterocyclic); cholinergic agonist; myasthenia gravis (muscle weakness) from nACh-R destruction	<i>Helianthus annuus</i> (sunflower) (Asteraceae), <i>Pisum sativum</i> (pea) (Fabaceae), <i>Urtica dioica</i> (stinging nettle) (Urticaceae); blue-green algae; choline acetyltransferase (the acetylcholine synthesizing enzyme) in <i>Spinacia oleracea</i> (spinach) (Chenopodiaceae)	nACh-R agonist – $\alpha 4\beta 2$ [34 nM], $\alpha 7$ (330); inhibits by R densensitization], α BgTX displacement [11] [natural nAChR agonist; water resorption & photosynthesis regulation in plants];
Non-plant reference		3.1An
[1-Acetyl-4- methylpiperazine methiodide (= AMPM)] (piperazine)	Synthetic	nACh-R agonist – [$\alpha 7$ (170)], α BgTX displacement [37]
[(+)-Anatoxin-a] (tropane amine)	<i>Anabaena flos-aquae</i> (blue-green alga) (Cyanophyceae)	nACh-R agonist – [$\alpha 7$ (0.6)], α BgTX displacement [91 nM] [very toxic]

(continued)

94 3. Neurotransmitter- and hormone-gated ion channels

Table 3.1 (Continued)

Compound (class)	Plant (family) / part	Protein target/process inhibited (other targets) / in vivo effects
[Benzoquinonium] (quaternary ammonium benzoquinone)	Synthetic	nACh-R agonist at non-ACh site (at ~1) [skeletal muscle relaxant]
[Carbamylcholine (= Carbachol)] (tertiary amine)	Synthetic	nACh-R agonist (non-specific, resistant to AChE)
[Dimethylphenyl-piperazinium (= DMPP)] (piperazine)	Synthetic	nACh-R agonist – [α7 (64); inhibits by R desensitization], αBgTX displacement [8]
[Epibatidine] (organochlorine pyridine)	[From skin of frog <i>Epipledobates tricolor</i> ; synthetic derivative ABT-594 is a CNS nAChR-specific non-paralytic antinociceptive]	nACh-R agonist – α4β2 [30 pM], α3β2α [8 pM] [non-opioid analgesic (CNS nACh-R), neuromuscular blocker, paralytic]
[(-)-Norferruginine] (tropane)	Synthetic	nACh-R agonist (potent)
[Succinylcholine (= Bis [2-dimethyl-aminoethyl]-succinate)] (aliphatic quaternary ammonium)	Synthetic	nACh-R agonist – ε (adult, junctional), γ (foetal, extrajunctional) [skeletal muscle relaxant]
[Tacrine (= Cognex; 1,2,3,4-Tetrahydro-5-aminoacridine)] (acridine)	Synthetic	nACh-R ligand (AAhE, BChE) [esp. AD amyloid plaque- & tangle-associated ChE; clinical cognition enhancer for AD]
Acetylcholine receptor (nicotinic) antagonist		3.1B
Alkaloid		3.1Ba
Aconitine (= Acetylbenzoylaconine) (diterpene alkaloid)	<i>Aconitum carmichaelii</i> , <i>A. napellus</i> , (Ranunculaceae) [root, other parts]	nACh-R antagonist (weak, αBgTX site) [19] (V-gated Na ⁺ channel activator) [antinociceptive, arrhythmic, hypotensive, slows heart rate, very toxic]
Afrocurarine (bisquaternary ammonium, indole)	<i>Strychnos usambarensis</i> (Loganiaceae) [root]; S. Am. Indian poison curare component	nACh-R antagonist (cf. <i>C</i> -Curarine) [competitive NM blocking]
[Apomorphine] (aporphine isoquinoline)	Derived synthetically from morphine, a morphinan isoquinoline alkaloid from <i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [aerial]	nACh-R antagonist (3) (rat α3β4) (CDPK, MLCK, PKA, PKC)
Atropine (= Hyoscamine racemate; Tropine tropate) (tropane)	<i>Atropa belladonna</i> (belladonna = deadly nightshade), <i>Datura stramonium</i> , <i>Hyoscyamus</i> , <i>Latua</i> , <i>Mandragora</i> , <i>Scopolia</i> spp. (Solanaceae); vegetarian Adolph Hitler suffered cumulative poisoning from anti-flatulence pills (Strychnine + belladonna) taken from 1936 onwards	α9nACh-R (mixed n–m properties R) ACh-competitive blocker (mACh-R antagonist) [anticholinergic, anti-spasmodic, antidote to organophosphorous insecticide poisoning, mydriatic, toxic, vasodilatory]

(continued)

Table 3.1 (Continued)

Compound (class)	Plant (family) part	Protein target/process inhibited (other targets) in vivo effects
Avadharine (norditerpene alkaloid)	<i>Delphinium cashmerianum</i> (Ranunculaceae) [root]	nACh-R antagonist
Barbinine (norditerpene alkaloid)	<i>Delphinium</i> spp. (Ranunculaceae) [root]	nACh-R antagonist [curare-like, NM blockade, toxic]
Berbamine (= Berbenine) (bisbenzylisoquinoline)	<i>Berberis aquifolium</i> , <i>B. thunbergii</i> , <i>B. vulgaris</i> , <i>Mahonia aquifolia</i> (Berberidaceae), <i>Atherosperma moschatum</i> (Monimiaceae)	nACh-R antagonist (V-Ca ²⁺ CH)
Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> (Annonaceae), <i>Berberis</i> , <i>Hydrastis</i> , <i>Mahonia</i> , <i>Nandina</i> (Berberidaceae), <i>Archangelica</i> (Menispermaceae), <i>Argemone</i> , <i>Chelidonium</i> , <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> , <i>Thalictrum</i> (Ranunculaceae), <i>Evodia</i> , <i>Phellodendron</i> , <i>Toddalia</i> , <i>Zanthoxylum</i> (Rutaceae) spp.	nACh-R ligand (36) (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, MLCK, PKA, PKC) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
(+)-Bicuculline (phthalide isoquinoline)	<i>Adlumia fungosa</i> , <i>Corydalis incisa</i> , <i>C. thalictrofolia</i> (Papaveraceae), <i>Hydrastis canadensis</i> (golden seal) (Ranunculaceae)	nACh-R antagonist (GABAA-R) [antiseptic, convulsant, haemostatic]
Calebassine (bisquaternary ammonium, indole)	<i>Strychnos divaricans</i> , <i>S. mitschlichii</i> , <i>S. solimoensana</i> , <i>S. trineris</i> , <i>S. usambarensis</i> (Loganiaceae) [root]	nACh-R antagonist [competitive NM blocking, toxic, calabash curare poison component]
Caracurine V (indole)	<i>Strychnos chrysophylla</i> , <i>S. dolichthyrsa</i> (Loganiaceae) [stem bark]	nACh-R antagonist [competitive NM blocking, toxic, calabash curare poison component]
Condorphine (= 14-Acetylisotalatizidine) (norditerpene alkaloid)	<i>Aconitum delphinifolium</i> , <i>Delphinium confusum</i> , <i>D. denudatum</i> (Ranunculaceae) [root]	nACh-R antagonist (2) (rat neuronal α 7 α BgTX site) [curare-like, hypotensive, NM blocker]
C-Curarine (bisquaternary ammonium, indole)	<i>Strychnos divaricans</i> , <i>S. froesii</i> , <i>S. mitschlichii</i> , <i>S. solimoensana</i> , <i>S. usambarensis</i> (Loganiaceae) [root]	nACh-R antagonist [competitive NM blocking, toxic, S. Am. Indian calabash curare poison component]
Cytisine (= Baptitoxine; Citisine; Sophorine; Ulexine) (quinolizidine)	<i>Laburnum anagyroides</i> (laburnum) [seed], <i>Lupinus alba</i> , <i>Baptisia</i> , <i>Cytisus</i> , <i>Genista</i> , <i>Sophora</i> , <i>Spartium</i> , <i>Thermopsis</i> , <i>Ulex</i> spp. (Fabaceae)	α 9nACh-R (mixed n-m properties R) ACh-competitive blocker (nAChR agonist) [cf. nicotine; hallucinogenic, respiratory stimulant, teratogenic, toxic]
Dauricine (bisbenzylisoquinoline)	<i>Menispermum dauricum</i> , <i>M. canadense</i> (Menispermaceae)	nACh-R antagonist (weak curare-like) (V- Ca ²⁺) [AI, anaesthetic, toxic]
N-Deacetylnudicauline (norditerpene alkaloid)	<i>Delphinium barbeyi</i> , <i>D. cashmerianum</i> , <i>D.</i> spp. (larkspur) (Ranunculaceae) [root]	nACh-R antagonist [curare-like, NM blockade, toxic]
Delcorine (norditerpene alkaloid)	<i>Delphinium corumbosum</i> (Ranunculaceae) [root]	nACh-R antagonist (53) (α 7 α BgTX site) [hypotensive, respiratory inhibition]

(continued)

Table 3.1 (Continued)

Compound (class)	Plant (family) part	Protein target/process inhibited (other targets) in vivo effects
Delsoline (= Aconomine; 14-O-Methyldecosine) (norditerpene alkaloid)	<i>Aconitum monticola</i> , <i>Consolida ajacis</i> , <i>Delphinium consolida</i> , (Ranunculaceae) [root]	nACh-R antagonist (19) ($\alpha 7$ α BgTX site) [hypotensive]
Deltaline (norditerpene alkaloid)	<i>Delphinium barbeyi</i> , <i>D. elatum</i> , <i>D. occidentale</i> (Ranunculaceae) [root]	nACh-R antagonist (110) ($\alpha 7$ α BgTX site) [curare-like, NM blockade, toxic]
[3-Deoxy-18-O-desmethyl(2-aminobenzoyl)aconitine] (diterpene alkaloid)	Semi-synthetic from Aconitine	nACh-R antagonist (α BgTX site) [0.3]
[3-Deoxy-18-O-desmethyl[2-(methylsuccinimido)-benzoyl]aconitine] (diterpene alkaloid)	Semi-synthetic from Aconitine	nACh-R antagonist (α BgTX site) [6 nM]
N-Desacetylappaconitine (norditerpene alkaloid)	<i>Aconitum</i> spp. (Ranunculaceae) [aerial, tuber]; metabolite of Lappaconitine	nACh-R antagonist (7) (rat neuronal $\alpha 7$ α BgTX site) [curare-like, NM blockade, toxic]
Dihydro- β -erythroidine (erythrina isoquinoline)	<i>Erythrina</i> spp. (Fabaceae) [seed]	nACh-R, $\alpha 4\beta 2$ nACh-R antagonist [nM] [NM blocking; effective orally (unlike curare)]
Dihydrotoxiferine (bisquaternary ammonium, indole)	<i>Strychnos usambarensis</i> (Loganiaceae) [root]	nACh-R antagonist (cf. Curarine) [competitive NM blocking]
Elatine (norditerpene alkaloid)	<i>Delphinium elatum</i> (Ranunculaceae) [root]	nACh-R antagonist (6 nM) (neuronal $\alpha 7$ α BgTX site) [curare-like, NM blockade, toxic]
Erysinine (erythrina isoquinoline)	<i>Erythrina caribea</i> , <i>E. melanacantha</i> (Fabaceae)	nACh-R antagonist [NM blocking]
Erysodine (tetracyclic dienoid alkaloid)	<i>Erythrina berteriana</i> , <i>E. crista-galli</i> , <i>E. fusca</i> , <i>E. latissima</i> , <i>E. suberosa</i> (Fabaceae) [seed]	nACh-R competitive antagonist [NM blocking]
Erysotrine (erythrina isoquinoline)	<i>Erythrina suberosa</i> , <i>Erythrina</i> spp. (Fabaceae)	nACh-R antagonist [NM blocking]
Erythratidine (erythrina isoquinoline)	<i>Erythrina caribea</i> , <i>E. melanacantha</i> (Fabaceae)	nACh-R antagonist [curare-like NM blocking]
α -Erythroidine (erythrina isoquinoline)	<i>Erythrina</i> spp. (Fabaceae)	nACh-R antagonist [curare-like NM blocking]
β -Erythroidine (erythrina isoquinoline)	<i>Erythrina</i> spp. (Fabaceae)	nACh-R antagonist [curare-like NM blocking]
Geyerline (norditerpenoid alkaloid)	<i>Delphinium glaucum</i> (larkspur) (Ranunculaceae) [root]	nACh-R antagonist
Grandiflorine (norditerpenoid alkaloid)	<i>Selenicereus grandiflorus</i> (Cactaceae), <i>Delphinium geyeri</i> (Ranunculaceae) [root]	nACh-R antagonist

(continued)

Table 3.1 (Continued)

Compound (class)	Plant (family) part	Protein target/process inhibited (other targets) in vivo effects
Isochondrodendrine (= Isobebeerine) (bisbenzylisoquinoline)	<i>Guatteria megalophylla</i> (Annonaceae), <i>Hevea</i> <i>wallichii</i> (Apiaceae), <i>Chondrodendron tomentosum</i> [bark], <i>Epinetrum cordifolium</i> , <i>E. mangenotii</i> , <i>Sciadotenia toxifera</i> (Menispermaceae), <i>Cocculus laurifolius</i> (Menispermaceae)	nACh-R antagonist; Chondrodendron tomentosum bark source of S. American curare arrow poison & medical curare
Isococculidine (= O-Methylisococculine) (erythrina isoquinoline)	<i>Cocculus laurifolius</i> (Menispermaceae)	nACh-R antagonist [NM blocker]
Karakoline (= Carmichaeline; Karacolone) (norditerpene alkaloid)	<i>Aconitum carmichaeli</i> , <i>A. karakolicum</i> , <i>Delphinium pentagynum</i> (Ranunculaceae) [tuber]	nACh-R antagonist (2) (neuronal $\alpha 7$ α BgTX site) [hypotensive, NM blocker; respiratory inhibition, toxic]
Lappaconitine (norditerpene alkaloid)	<i>Aconitum excelsum</i> , <i>A. orientale</i> , <i>A. ranunculaefolium</i> , <i>A. sinomontanum</i> , <i>A. spp.</i> (Ranunculaceae) [aerial, tuber]	nACh-R antagonist – rat neuronal $\alpha 7$ α BgTX site (96) [AI, analgesic, curare-like, NM blockade, respiratory paralysis, toxic, ventricular fibrillation]
(–)-Lobeline (piperidine)	<i>Lobelia hassleri</i> , <i>L. inflata</i> , <i>L. nocibianaefolia</i> , <i>L. tupa</i> , <i>Campanula medium</i> [seed] (Campanulaceae)	nACh-R antagonist – $\alpha 7$ [9] ($\alpha 4\beta 2$ agonist) [anti-smoking use; racemate (Lobelidine) analeptic]
Lycoctonine (= Delsine; Royline) (norditerpene alkaloid)	<i>Inula royleana</i> (Asteraceae), <i>Aconitum lycocotum</i> , <i>Consolida ajacis</i> , <i>Delphinium consolida</i> , <i>D. spp.</i> (larkspur) (Ranunculaceae) [root]	nACh-R antagonist – rat neuronal $\alpha 7$ α BgTX site, brain α BgTX site (10) [hypotensive]
Magnoflorine (= Corytuberine; Escholone; Thalictrine) (aporphine isoquinoline)	<i>Aristolochia</i> (Aristolochiaceae), <i>Mahonia</i> (Berberidaceae), <i>Croton</i> (Euphorbiaceae), <i>Chelidonium</i> , <i>Eschscholzia</i> , <i>Glaucium</i> , <i>Papaver</i> (Papaveraceae), <i>Magnolia</i> (Magnoliaceae), <i>Thalictrum</i> (Ranunculaceae), <i>Zanthoxylum</i> (Rutaceae) spp.	nACh-R antagonist
7,8-Methylenedioxy-lycoctanone (= Delartine; Delsemidine) (diterpene)	<i>Delphinium spp.</i> (larkspur) (Ranunculaceae) [root]	nACh-R antagonist
Methyllycaconitine (= Delartine; Delsemidine) (norditerpene alkaloid)	<i>Delphinium barbeyi</i> , <i>D. elatum</i> , <i>D. spp.</i> (larkspur) (Ranunculaceae) [root]	nACh-R competitive antagonist – $\alpha 7$ α BgTX site (8 nM), α BgTX site [4 nM], nicotine site [8], $\alpha 9$ nACh-R (mixed n-m properties R) ACh-competitive blocker [curare-like, NM blockade, toxic]
Nicotine (pyridine pyrrolidine)	<i>Asclepias syriaca</i> (Asclepiadaceae), <i>Sedum acre</i> (Crassulaceae), <i>Lycopodium spp.</i> , <i>Equisetum arvense</i> (Equisetaceae), <i>Nicotiana tabacum</i> (tobacco), <i>N. spp.</i> (Solanaceae)	$\alpha 9$ nACh-R (mixed n-m properties R) ACh-competitive blocker (nAChR agonist) [addictive, insecticide, respiratory paralytic, toxic, tranquilizer]

(continued)

Table 3.1 (Continued)

Compound (class)	Plant (family) part	Protein target/process inhibited (other targets) in vivo effects
Nudicauline (norditerpene alkaloid)	<i>Delphinium stapeliosum</i> , <i>D.</i> spp. (larkspur) (Ranunculaceae) [root]	nACh-R antagonist (2 nM) (rat neuronal $\alpha 7$ α BgTX site) [curare-like, NM blockade, toxic]
Pilocarpine (furanone imidazole)	<i>Pilocarpus jaborandi</i> , <i>P. microphyllus</i> , <i>P. pennatifolius</i> , <i>P. racemosus</i> (Rutaceae)	$\alpha 9$ nACh-R (mixed n-m properties R) blocker (mACh-R agonist) [anti-glaucoma, cholinergic, gastric, salivary & lachrymal secretory stimulant, miotic, parasympathomimetic]
Pteleprenine (quinoline)	<i>Orixa japonica</i> (Rutaceae)	nACh-R antagonist (at 0.1–10)
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Fumaria officinalis</i> (Fumariaceae), <i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> , <i>Sanguinaria canadensis</i> , <i>Argemone</i> , <i>Bocconia</i> , <i>Eschscholzia</i> , <i>Glaucium</i> , <i>Macleaya</i> spp. (Papaveraceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	nACh-R ligand (12) ($\alpha 1$ A-R, $\alpha 2$ A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, MLCK, PKA, PKC) [antibacterial, AI]
Strychnine (indole)	<i>Argyrea nervosa</i> (Convolvulaceae), <i>Strychnos nux-vomica</i> [seed] (nux-vomica), <i>S. ignatii</i> (ignatius bean), <i>S. icaja</i> , <i>S. tieute</i> , <i>S. triplinervia</i> (Loganiaceae)	$\alpha 7$ nACh-R antagonist (Gly-R) [CNS stimulant, toxic]
Toxiferine I (= C-Toxiferine I; Toxiferine V; Toxiferine XI) (bisquaternary ammonium, indole)	<i>Strychnos froesii</i> , <i>S. toxifera</i> (Loganiaceae)	nACh-R antagonist [NM blocking ($8\times >$ tubocurarine), calabash curare poison component , toxic]
(+)-Tubocurarine (= curare active principle) (bisbenzylisoquinoline)	<i>Chondrodendron tomentosum</i> (curare, pareira), <i>C.</i> spp (Menispermaceae) [bark]; S. Am. Indian arrow poison curare component	nACh-R antagonist [1 nM] (rat $\alpha 4\beta 2$, GABAA-R) [toxic, skeletal muscle relaxant]
(-)-Tubocurarine (bisbenzylisoquinoline)	<i>Chondrodendron tomentosum</i> (pareira), <i>C.</i> spp (Menispermaceae) [bark]	nACh-R antagonist but much weaker than (+)-Tubocurarine
Terpene		3.1Bt
1,9-Dideoxyforskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae)	nACh-R antagonist (Ca^{2+} CH, MDR, inactive as AC activator)
Forskolin (labdane diterpenoid)	<i>Coleus barbatus</i> , <i>C. forskohlii</i> (Lamiaceae)	nACh-R antagonist (AC activator, Ca^{2+} CH, MDR) [hypotensive per arterial SM relaxation, increases cAMP, increases heart rate]
Ginsenoside Rg2 (triterpene saponin)	<i>Panax ginseng</i> [ginseng root] (Araliaceae)	nACh-R block (at 1–100) [antitumour]

(continued)

Table 3.1 (Continued)

Compound (class)	Plant (family) part	Protein target/process inhibited (other targets) in vivo effects
Linalool (monoterpene)	<i>Coriandrum sativum</i> (Apiaceae), <i>Bursera delpechiana</i> (Burseraceae), <i>Aeolanthus suaveolens</i> , <i>Lavandula</i> , <i>Origanum</i> , <i>Thymus</i> spp. (Lamiaceae), <i>Citrus</i> spp. (Rutaceae)	nACh-R inhibitor (NM presynaptic ACh release & nACh-R channel) [antifungal, antiseptic, sedative, perfume smell]
Non-plant reference		3.1Bn
[β -Amyloid (1–42)] (peptide)	Human	nACh-R ligand [5 pM] [Amyloid plaque formation in AD]
[Bethanecol] (tetraalkyl ammonium carbamate)	Synthetic	α 9nACh-R (mixed n–m properties R) blocker (mACh-R agonist) [cholinergic]
[α -Bungarotoxin] (8 kDa protein)	[From Elapidae snake <i>Bungarus multicinctus</i>]	nACh-R antagonist [curare-like, NM blockade, paralysis]
[β -Bungarotoxin] (S–S-linked 13 kDa–7 kDa subunit heterodimeric protein)	[From Elapidae snake <i>Bungarus multicinctus</i>]	Presynaptic NM ACh release inhibitor
[Fluoxetine (= Prozac) (trifluorophenoxy phenyl tertiary amine)	Synthetic	nACh-R non-competitive blocker (5HT uptake, 5HT3-R) [antidepressant]
[Gallamine (= Tri(β -diethylaminoethoxy)-1,2,3-benzene)] (aryl tetraalkyl ammonium)	Synthetic	α 9nACh-R (mixed n–m properties R) blocker (mACh-R antagonist) [skeletal muscle relaxant]
[Homoanatoxin-a] (tropane amine)	<i>Oscillatoria formosa</i> (blue-green alga) (Cyanophyceae)	nACh-R blocker (respiratory muscle)
[Muscarine] (quaternary ammonium furan)	<i>Amanita muscaria</i> (fly agaric mushroom) (Amanitaceae), <i>Inocybe fastigiata</i> , <i>I. imbrina</i> , <i>I. napipes</i> , <i>I. obscuroides</i> , <i>I. patouillardii</i> , <i>I. rimosa</i> , <i>I. umbrina</i> (mushroom) (Cortinariaceae), <i>Clitocybe</i> spp. (mushroom) (Tricholomataceae)	α 9 nACh-R (mixed n–m properties R) antagonist (mAChR agonist) [muscarinic cholinergic, lachrimatory, hypotensive, visual, bowel, bronchial and heart disturbance, toxic]
[Pancuronium] (steroidal piperidinium quaternary amine)	Synthetic	nACh-R antagonist [skeletal muscle relaxant]

Table 3.2 Iontropic γ -aminobutyric acid and benzodiazepine receptors

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) / in vivo effects
Central GABAA-R Benzodiazepine Receptor (BZ-R) site (CBZ-R) & peripheral BZ-R (PBZ-R)		3.2A
Alkaloid		3.2Aa
Delorazepam (benzodiazepine)	Synthetic; also in <i>Artemisia dracuncululus</i> (Asteraceae)	BZ-R agonist [sedative, tranquillizer]
Diazepam (benzodiazepine)	Synthetic; also in <i>Triticum aestivum</i> (wheat) (Poaceae) [germinating seed], <i>Solanum tuberosum</i> (Solanaceae) [plant]	CBZ-R agonist (18 nM) [~10 nM] [amnesic anxiolytic, skeletal muscle relaxant, tranquillizer]
Harmaline (= 3,4- Dihydroharmine; Harmidine) (indole, carboline)	<i>Banisteria caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae)	CBZ-R agonist (α 2A-R, NMDA-Glu-R) (Flunitrazepam displacement) (~100) [ataxic, excitatory, hallucinogenic, tremorigenic]
Harmalol (β -carboline, indole)	<i>Apocynum cannabinum</i> (Apocynaceae), <i>Hippophae rhamnoides</i> (Eleagnaceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Passiflora</i> spp. (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae)	CBZ-R agonist (at 100)
Harman (= Aribine; Loturine; 1-Methyl- β -carboline; Passiflorin) (β -carboline, indole)	<i>Cichorium intybus</i> (Asteraceae), <i>Eleagnus angustifolia</i> (Eleagnaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Sickingia</i> (= <i>Avariba</i>) <i>rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> , <i>Zygophyllum fabago</i> (Zygophyllaceae); smoke of tobacco <i>Nicotiana tabacum</i> (Solanaceae)	CBZ-R agonist (~100) (DNA) (α 1-A R, L-type Ca ²⁺ CH, DNA, 5HT2-R) [co-mutagenic, convulsant, cytotoxic, genotoxic, motor depressant, DNA intercalator, sheep “ <i>Tribulus stagers</i> ”, vasorelaxant]; from pyrolysate of Tryptophan (cooked food)
Harmine (= Banisterine; Leucoharmine; Telepathine; Yageine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> (Malpighaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> (Zygophyllaceae)	CBZ-R agonist (α 1A-R, L- type Ca ²⁺ CH, MAO-A) [CNS stimulant, hallucinogenic; Gestapo use as “truth drug”]
Lormetazepam (benzodiazepine)	Synthetic; also in <i>Solanum tuberosum</i> (potato) (Solanaceae) [germinating tuber]	BZ-R agonist [hypnotic, sedative]
Norharman (= β - Carboline) (β -carboline, indole)	<i>Cichorium intybus</i> (Asteraceae), <i>Tribulus terrestris</i> (puncture vine), <i>Zygophyllum fabago</i> (Zygophyllaceae); tobacco smoke [<i>ex Nicotiana tabacum</i> [leaf] (Solanaceae)]; cooked food	CBZ-R (DNA, MAO-A) [co-mutagenic, agent in sheep “<i>Tribulus stagers</i>”]; from pyrolysate of Tryptophan (Trp)

(continued)

Table 3.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Ricinine (dihydropyridine)	<i>Ricinus communis</i> (castor bean) (Euphorbiaceae) [seed, leaf]	BZ-R ligand (Flunitrazepam displacement) [convulsant, hypotensive, respiratory depressant, toxic]
Tabernanthine (= 13-Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> , <i>Conopharyngia</i> (<i>Tabernaemontana</i>) sp., <i>Stemmadenia</i> sp. (Apocynaceae)	BZ-R agonist (Flunitrazepam displacement) (150) [CNS active, Flunitrazepam-abolished tremorigenic]
Temazepam (benzodiazepine)	Synthetic; also in <i>Artemisia dracunculus</i> (Asteraceae), <i>Solanum tuberosum</i> (potato) (Solanaceae)	BZ-R agonist [hypnotic, sedative]
Phenolic		
Amentoflavone (= 3',8''-Biapigenin) (biflavone)	<i>Viburnum prunifolium</i> (Caprifoliaceae), <i>Cycas revoluta</i> (cycad) (Cycadaceae), <i>Rhus succedanea</i> (Anacardiaceae), <i>Ginkgo biloba</i> (Ginkgoaceae), <i>Hypericum hirsutum</i> , <i>H. olympicum</i> , <i>H. patulum</i> , <i>H. perforatum</i> (Hypericaceae), <i>Podocarpus montanus</i> (Podocarpaceae)	3.2Ap CBZ-R partial agonist (brain, mixed) (6 nM) (15 nM) (cAMP PDE, cGMP PDE) [antifungal; antidepressant activity in St John's wort (<i>Hypericum</i>) ?]
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Widespread; Lamiaceae, ferns [leaf surface]; <i>Matricaria chamomilla</i> (camomile) (Asteraceae) [flower]; glycosides in Apiaceae, Asteraceae, Fabaceae	CBZ-R-like R ligand; CBZ-R agonist (4) (PK, RTK) [antibacterial, AI, diuretic, hypotensive, non-amnestic anxiolytic, sedative, spasmolytic]
Baicalein (= 5,6,7-Trihydroxyflavone) (flavone)	<i>Scutellaria baicalensis</i> , <i>S.</i> spp. (Lamiaceae), <i>Plantago major</i> (Plantaginaceae); glycosides in <i>Oroxylum indicum</i> (Bignoniaceae), <i>S. galericulata</i> (Lamiaceae),	CBZ-R ligand [13] (glyoxalase I, 12-LOX) [AI]
Byakangelicol (furanocoumarin)	<i>Angelica dahurica</i> , <i>Ferula</i> spp. (Apiaceae), <i>Citrus limon</i> (Rutaceae)	CBZ-R ligand (Diazepam displacement) (12)
2,5-Dihydroxy-7-methoxy-6,8-dimethylflavan-3-one (flavan-3-one)	<i>Leptospermum scoparium</i> (Myrtaceae)	GABAA-R CBZ-R ligand
5,7-Dimethoxyflavone (flavone)	<i>Leptospermum scoparium</i> (Myrtaceae)	CBZ-R ligand (Flunitrazepam displacement) (2)
5,7-Dimethoxy-6-methylflavone (flavone)	<i>Leptospermum scoparium</i> (Myrtaceae)	CBZ-R ligand (Flunitrazepam displacement) (45)
Dinatin (= Hispidulin; 6-Methoxy-5,7,4'-Trihydroxyflavone; Scutellarein 6-methyl ether) (flavone)	<i>Artemisia herba alba</i> (Asteraceae), <i>Citrus sudachii</i> (Rutaceae) [peel], <i>Digitalis orientalis</i> , <i>D. purpurea</i> (Scrophulariaceae) [leaf]; Asteraceae, Hydrophyllaceae, Lauraceae [leaf]	CBZ-R ligand (Diazepam displacement) (1 nM) [PAI, increases platelet cAMP]

(continued)

Table 3.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) / in vivo effects
5,7-Dihydroxyflavone (= Chrysin) (flavone)	Widespread; <i>Daucus</i> (Apiaceae), <i>Spartium</i> (Fabaceae), <i>Scutellaria</i> (Lamiaceae), <i>Passiflora</i> (Passifloraceae), <i>Pinus</i> (Pinaceae) [wood], <i>Prunus</i> (Rosaceae), <i>Populus</i> (Salicaceae), <i>Escallonia</i> (Saxifragaceae) spp.	CBZ-R agonist [3], PBZ-R [13] (CKII, MLCK, PKA) [non-amnestic anxiolytic]
5-Hydroxy-7-methoxy-6- methylflavone (flavone)	<i>Leptospermum scoparium</i> (Myrtaceae)	CBZ-R ligand (Flunitrazepam displacement) (3)
5-Hydroxy-7-methoxy-6,8- dimethylflavone (flavone)	<i>Leptospermum scoparium</i> (Myrtaceae)	CBZ-R ligand (Flunitrazepam displacement) (40)
1-Hydroxypinoresinol (lignan)	<i>Nothapodytes foetida</i> (Icacinaeae), <i>Valeriana officinalis</i> , <i>V.</i> spp. (valerian) (Valerianaceae) [root]	CBZ-R ligand
Imperatorin (furanocoumarin)	<i>Ammi majus</i> , <i>Pastinaca sativa</i> (Apiaceae), <i>Angelica dahurica</i> (Asteraceae) [root]	CBZ-R ligand (Diazepam displacement) (8)
Kaempferol 4'-O-methyl ether (=Kaempferide; 3,5,7,4'-Tetrahydroxy flavone 4'-O- methyl ether) (flavonol)	<i>Pityrogramma</i> (fern) (Adiantaceae), <i>Baccharis</i> (Asteraceae), <i>Prunus</i> (Rosaceae), <i>Linaria</i> (Scrophulariaceae), Betulaceae, Salicaceae, <i>Tilia</i> (Tiliaceae), <i>Alpinia</i> (Zygophyllaceae) spp.	BZ-R ligand [93] (CDPK, MLCK, PKA) [AI (TPA- induced)]
Oroxylin A (flavone)	<i>Scutellaria baicalensis</i> , <i>S. galericulata</i> (Lamiaceae) [root]	CBZ-R ligand [15] (CYP, 12-LOX)
Pellopterin (furanocoumarin)	<i>Angelica archangelica</i> , <i>A. dahurica</i> , <i>Ferula alliacea</i> (Apiaceae) [root], <i>Citrus limon</i> (Rutaceae)	CBZ-R ligand (Diazepam displacement) (0.4)
Skrofullein (= 4',5- Dihydroxy-6,7-dime- thoxyflavone) (flavone)	<i>Artemisia herba alba</i> (Asteraceae)	CBZ-R ligand (Diazepam displacement) (23 nM)
Skullcapflavone II (= 5,1'- Dihydroxy-6,7,8,5'- Tetramethoxyflavone) (flavone)	<i>Scutellaria baicalensis</i> (Lamiaceae) [root]	BZ-R ligand [0.4] [cytotoxic]
Terpene		3.2At
Cryptotanshinone (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (sage) (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (2) [tranquillizer]
1,2-Didehydromiltirone (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (1) [tranquillizer]
(-)-1,2-Dihydrotanshinone I (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (9) [tranquillizer]

(continued)

Table 3.2 (Continued)

Compound (class)	Plant (family) [part]	Enzyme/process inhibited (other targets) / in vivo effects/
Egb 761 (= Egb) (diterpenoid extract)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf] standardized extract	Contains Ginkgolide A & related Ginkgolides [↓ adrenocortical mitochondrial PBZ-R expression → ↓ corticosteroid synthesis; antistress, neuroprotective]
Ginkgolide A (diterpenoid)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	[↓ adrenocortical mitochondrial PBZ-R expression → ↓ corticosteroid; AI, anti-asthmatic, antistress, insect antifeedant, bitter, neuroprotective]
Ginkgolide B (diterpenoid)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	[↓ adrenocortical mitochondrial PBZ-R expression → ↓ corticosteroid; AI, anti-asthmatic]
Isocurcumenol (sesquiterpene)	<i>Cyperus rotundus</i> (sedge) (Cyperaceae) [rhizome]	GABAA-R CBZ agonist
Majonoside-R2 (triterpene saponin)	<i>Panax ginseng</i> (Vietnamese ginseng) (Araliaceae)	GABAA-R CBZ agonist [↓ opiate-induced antinociception]
Methylenecryptotanshinquinone (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (11) [tranquillizer]
Methylenetanshinquinone (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (11) [tranquillizer]
4-Methylenemiltirone (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (2) [tranquillizer]
Miltirone (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (0.3) [tranquillizer]
Ro 09-0680 (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (11) [tranquillizer]
Tanshinone I (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (36) [tranquillizer]
Tanshinone IIA (diterpene quinone, tanshinone)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [root]	CBZ-R partial agonist (Flunitrazepam competition) (3) [tranquillizer]
Non-plant reference		3.2An
[6,3'-Dinitroflavone] (flavone)	Semi-synthetic	CBZ-R agonist [non-amnestic anxiolytic]
[Flumazenil] (benzodiazepine)	Synthetic	CBZ-R agonist

(continued)

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Table 3.2 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Enzyme/process inhibited (other targets) in vivo effects </i>
[Flunitrazepam] (benzodiazepine)	Synthetic	CBZ-R agonist [4 nM; ~10 nM] [hypnotic, tranquilizer]
GABA (A) Receptor (GABAA-R)		3.2B
Alkaloid		3.2Ba
(+)-Bicuculline (phthalide isoquinoline)	<i>Adlumia fungosa</i> , <i>Corydalis incisa</i> , <i>C. thalictrifolia</i> (Papaveraceae), <i>Hydrastis canadensis</i> (golden seal) (Ranunculaceae)	GABAA-R antagonist (20) (nACh-R) [antiseptic, convulsant, haemostatic]
Chelerythrine (benzophenanthridine)	<i>Chelidonium majus</i> , <i>Argemone</i> , <i>Bocconia</i> , <i>Eschscholzia</i> , <i>Glaucium</i> , <i>Sanguinaria</i> (Papaveraceae), <i>Zanthoxylum</i> (Rutaceae) spp.	GABAA-R ligand (25) (CAMPK, PKA, PKC, TK)
Cocaine (= Benzoyl- methylecgonine) (tropane)	<i>Erythroxylum coca</i> [coca leaf], <i>E. spp.</i> (Erythroxylaceae); total global illegal plant-derived & synthetic drug industry possibly worth \$400 billion per annum	GABAA-R current block (130) (D-TR, NE-TR, 5HT- TR) [CNS stimulant, local anaesthetic, mydriatic, narcotic]
Colchicine (tricyclic)	<i>Colchicum autumnale</i> , <i>C. spp.</i> , <i>Gloriosa superba</i> (Liliaceae)	GABAA-R (<100) (α 1 Gly- R, microtubule tubulin) [irritant, carcinogen, teratogen, tubulin & cell division inhibitor; toxic]
Corymine (indole)	<i>Hunteria zeylanica</i> (Apocynaceae) [leaf]	[GABAA-R antagonist (weak; at 100)]
Deformylcorymine (indole)	<i>Hunteria zeylanica</i> (Apocynaceae) [leaf]	GABAA-R (current inhibition) (at 100) (Gly-R)
N-Demethyl-3-epi- dihydrocorymine (indole)	<i>Alstonia glaucescens</i> (Apocynaceae) [stem bark]	GABAA-R antagonist (<100) (Gly-R)
[Dihydrocorymine] (indole)	Semi-synthetic from Corymine	GABAA-R antagonist (>100) (Gly-R)
(+)-Hydrastine (phthalide isoquinoline)	<i>Berberis vulgaris</i> , <i>Mahonia aquifolium</i> (Berberidaceae), <i>Corydalis stricta</i> (Papaveraceae), <i>Hydrastis canadensis</i> (golden seal) (Ranunculaceae)	GABAA-R antagonist (2); GABA stimulated Diazepam binding (0.4) [antiseptic, convulsant, haemostatic]
Isocoryne (phthalide isoquinoline)	<i>Corydalis pseudoadunca</i> (Fumariaceae)	GABAA-R inhibitor (blocks GABA induced current) [1]
Laudanosine (= Laudanine methyl ether) (benzylisoquinoline)	<i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [opium exudate]; also metabolic product of synthetic skeletal muscle relaxant Atracurium	GABAA-R antagonist (100) (O-R) [analgesic, convulsive, hypotensive, tetanic, toxic, naloxonazine- antagonized (μ 1O-R) antinoiceptive]

(continued)

Table 3.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Protopine (= Biflorine; Corydalis C; Corydinine; Fumarine; Macleyine) (benzylisoquinoline)	<i>Chelidonium majus</i> , <i>Argemone</i> , <i>Bocconia</i> , <i>Corydalis</i> , <i>Eschscholzia</i> , <i>Glaucium</i> , <i>Macleaya</i> , <i>Papaver somniaferum</i> (opium poppy), <i>Sanguinaria</i> spp. (Papaveraceae), <i>Fumaria officinalis</i> (fumitory) (Fumariaceae)	GABAA-R ligand (Muscimol displacement) [antibacterial, sedative, SM relaxant]
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Chelidonium</i> , <i>Papaver</i> , <i>Argemone</i> , <i>Bocconia</i> , <i>Corydalis</i> , <i>Eschscholzia</i> , <i>Glaucium</i> , <i>Macleaya</i> , <i>Sanguinaria</i> (Papaveraceae), <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> (Rutaceae), <i>Pteridophyllum</i> (Sapindaceae) spp.	GABAA-R ligand (Muscimol displacement) (39) (ATPase, CDPK, Diamine oxidase, MLCK, PKA, PKC) [antibacterial, AI]
Securinene (piperidinepyrrolidine)	<i>Phyllanthus discoides</i> , <i>Securinega suffruticosa</i> (Euphorbiaceae), <i>Securidaca longepedunculata</i> (Fabaceae)	GABAA-R antagonist
(+)-Tubocurarine (= curare active principle) (bisbenzylisoquinoline)	<i>Chondrodendron tomentosum</i> (pareira), C. spp (Menispermaceae) [bark]; S. Am. Indian arrow poison curare component	GABAA-R antagonist (nACh-R) [toxic, skeletal muscle relaxant]
Phenolic		3.2Bp
Daidzein (= 4',7- Dihydroxyisoflavone) (isoflavone)	<i>Glycine max</i> , <i>Trifolium repens</i> (clover), <i>Phaseolus</i> , <i>Psoralea</i> , <i>Pueraria</i> , <i>Sophora</i> , <i>Ulex</i> , <i>Vigna</i> (Fabaceae) spp.	(GABAA-R) (inactive as TK inhibitor cf. Genistein)
Desmethoxyyangonin (phenolic-derived dienolide lactone, kavapyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]	Inactive as GABAA-R modulatory agonist (cf. Yangonin & Kawain)
(+)-Dihydrokavain (= Dihydrogonosan; Dihydrokawain) (phenolic-derived lactone, kavapyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]; traditional Fiji drink kava (yaqona = yangona)	GABAA-R modulatory agonist; increases Bicuculline-binding (at 10); no binding to BZ-R [anxiolytic]
(+)-Dihydromethysticin (phenolic-derived lactone, kavapyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]	GABAA-R modulatory agonist; increases Bicuculline-binding (at 0.1); no binding to BZ-R [anxiolytic]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7- Trihydroxyisoflavone) (isoflavone)	Widespread; <i>Genista</i> , <i>Glycine</i> , <i>Phaseolus</i> , <i>Trifolium</i> spp. (Fabaceae), <i>Prunus</i> spp. (Rosaceae) [wood]; glycosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Sophora japonica</i> , <i>Ulex nanus</i> (Fabaceae) [pod]	GABAA-R (non- competitive antagonist) (EGF-RTK, HSK, MLCK, PKA, pp60 ^{v-src} TK (RSV), pp110 ^{src-fcs} TK, EGF- RTK, lipase, peroxidase) [antifungal, oestrogenic]
Honokiol (lignan)	<i>Magnolia officinalis</i> , <i>M. obovata</i> (Magnoliaceae) [root, stem, bark]	GABAA-R APL (8) [anti- cariogenic antibacterial, anxiolytic, central depressant]

(continued)

Table 3.2 (Continued)

Compound (class)	Plant (family) / part/	Enzyme/process inhibited (other targets) / in vivo effects/
(+)-Kawain (= Gonosan; Kavain) (phenolic-derived lactone, kavapyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]; nearly 600 secondary metabolites isolated from <i>Piper</i> spp. (an indicator of natural product diversity within any one genus)	GABAA-R agonist; APL (at 0.1); no binding to BZ-R [anxiolytic, kava dermopathy, skeletal muscle relaxant]
Magnolol (lignan)	<i>Sassafras randaiense</i> (Lauraceae) [root], <i>Magnolia officinalis</i> , <i>M. obovata</i> (Magnoliaceae) [root, stem, bark]	GABAA-R APL (6) [anti- cariogenic antibacterial, anxiolytic, central depressant]
(+)-Methysticin (phenolic-derived lactone, kavapyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]	GABAA-R modulatory agonist (at 0.1); no binding to BZ-R [anxiolytic]
Yanгонin (phenolic-derived dienolide lactone, kavapyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]; traditional Fijian drink kava (yaqona=yangona)	GABAA-R modulatory agonist (at 1); no binding to BZ-R [anxiolytic]
Terpene		
Anisatin (sesquiterpene lactone)	<i>Illicium anisatum</i> (Japanese star anise) (Illiciaceae) [seed]	3.2Bt GABA-R non-competitive antagonist (0.4–1); binds to Picrotoxinin site [Picrotoxin-like, toxic]
Carnosic acid (diterpene)	<i>Salvia officinalis</i> (sage) (Lamiaceae) [leaf]	GABAA-R chloride channel blocker, TBPS binding (33)
Carnosol (abietane diterpene)	<i>Rosmarinus officinalis</i> , <i>Salvia officinalis</i> (sage) (Lamiaceae) [leaf]	GABAA-R chloride channel blocker, TBPS binding (57)
Coriamyrtin (tutinolide sesquiterpene lactone)	<i>Coriaria japonica</i> , <i>C. myrtifolia</i> (Coriariaceae)	GABAA-R antagonist (at 10–30)
Dihydrotutin (tutinolide sesquiterpene lactone)	<i>Picrodendron baccatum</i> (Euphorbiaceae)	GABAA-R noncompetitive antagonist [nematocide]
Ginsenoside Rb1 (triterpene saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	GABAA-R ligand (Muscimol displacement)
Ginsenoside Rb2 (triterpene saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	GABAA-R ligand (Muscimol displacement, high affinity site)
Ginsenoside Rc (triterpene saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	GABAA-R ligand (Muscimol displacement) (GABAB-R)
Ginsenoside Re (triterpene saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	GABAA-R ligand (Muscimol displacement, high affinity site); increased Flunitrazepam binding to CBZ-R [analgesic]
Ginsenoside Rf (triterpene saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	GABAA-R ligand (Muscimol displacement); high affinity site); CBZ-R APL [antitumour]
Ginsenoside Rg1 (triterpene saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	GABAA-R ligand (Muscimol displacement) [antitumour]

(continued)

Table 3.2 (Continued)

Compound (class)	Plant (family) [part]	Enzyme/process inhibited (other targets) / in vivo effects/
Ginsenoside Rg2 (triterpene saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	GABA-R antagonist [blocks GABA-induced adrenal catecholamine secretion]
Horminone (diterpene)	<i>Salvia deserta</i> , <i>Plectranthus hereroensis</i> (Lamiaceae) [root]	GABAA-R chloride current inhibition (10)
Isohyenanchine (tutinolide sesquiterpene lactone)	<i>Picrodendron baccatum</i> (Euphorbiaceae)	GABAA-R non-competitive antagonist [nematocide]
Picrodendrin A (tutinolide sesquiterpene lactone)	<i>Picrodendron baccatum</i> (Euphorbiaceae)	GABAA-R non-competitive antagonist (<1) [nematocide]
Picrodendrin B (tutinolide sesquiterpene lactone)	<i>Picrodendron baccatum</i> (Euphorbiaceae)	GABAA-R non-competitive antagonist (<1) [nematocide]
Picrodendrin O (tutinolide sesquiterpene lactone)	<i>Picrodendron baccatum</i> (Euphorbiaceae)	GABAA-R non-competitive antagonist (1)
Picrodendrin Q (tutinolide sesquiterpene lactone)	<i>Picrodendron baccatum</i> (Euphorbiaceae)	GABAA-R non-competitive antagonist (16–22 nM)
Picrodendrins (tutinolide sesquiterpene lactones)	<i>Picrodendron baccatum</i> (Euphorbiaceae)	GABAA-R non-competitive antagonists [nematocides]
Picrotin (tutinolide sesquiterpene lactone)	<i>Anamirta paniculata</i> (= <i>A. cocculus</i> ; <i>Menispermum oculus</i>), <i>Tinomiscium philippinense</i> (Menispermaceae) [drupe]	GABAA-R non-competitive antagonist (Gly-R) [CNS stimulant, barbiturate antidote, insecticide]
Picrotoxin (= mixture of Picrotin and Picrotoxinin) (tutinolide sesquiterpene lactone)	<i>Anamirta paniculata</i> (= <i>A. cocculus</i> ; <i>Menispermum oculus</i>), <i>Tinomiscium philippinense</i> (Menispermaceae) [drupe]	GABAA-R antagonist (0.2); GABAA-R chloride current inhibition (1) (Gly-R) [CNS stimulant, barbiturate antidote, insecticide]
Picrotoxinin (= Dehydropicrotin) (tutinolide sesquiterpene lactone)	<i>Salvia deserta</i> (Lamiaceae), <i>Anamirta paniculata</i> (= <i>A. cocculus</i> ; <i>Menispermum oculus</i>), <i>Tinomiscium philippinense</i> (Menispermaceae)	GABAA-R non-competitive antagonist (Gly-R) [CNS stimulant, barbiturate antidote, insecticide, nematocide]
Taxodione (abietane diterpenoid)	<i>Taxodium distichum</i> (Taxodiaceae)	GABAA-R chloride current inhibition (100) [antitumour]
α - & β -Thujone (= Thujan-3 one isomers) (monoterpenes); neurotoxic agent of liqueur absinthe; affected Charles Baudelaire, Arthur Rimbaud & his lover Paul Verlaine, Oscar Wilde & Emile Zola (absinthe eventually banned)	<i>Artemisia absinthium</i> (wormwood), <i>Tanacetum vulgare</i> (tansy) (Asteraceae) [leaf oil], <i>Thuja occidentalis</i> (white cedar) (Cupressaceae) [leaf oil], <i>Salvia</i> spp. (Lamiaceae); absinthe affected Paul Gaugin, Vincent van Gogh, Pablo Picasso & Henri de Toulouse-Lautrec	GABAA-R antagonist/negative modulator (Cl ⁻ channel block) [anthelmintic, convulsant, hallucinogenic, intoxicant, pro-psychotic]; absinthistes painted in L'Absinthe by Edgar Dégas

(continued)

108 3. Neurotransmitter- and hormone-gated ion channels

Table 3.2 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Enzyme/process inhibited (other targets) in vivo effects </i>
Tutin (tutinolide sesquiterpene lactone)	<i>Coriaria thymifolia</i> (Coriariaceae), <i>Picrodendron baccatum</i> (Euphorbiaceae)	GABAA-R noncompetitive antagonist [nematocide]
Other		3.2Bo
β-Alanine (= 3-Aminopropionic acid) (amino acid)	<i>Lunaria</i> spp. (Brassicaceae), <i>Ribes nigrum</i> (Grossulariaceae), <i>Iris tingitana</i> (Iridaceae), <i>Lycopersicon esculentum</i> (Solanaceae)	GABAA-R agonist (reversed by Bicuculline) (Gly-R) [neurotoxic]
γ-Aminobutyric acid (= 4-Aminobutyric acid; GABA) (amino acid)	Numerous; <i>Phoenix dactylifera</i> (Aracaceae), <i>Phaseolus</i> , <i>Pisum</i> , <i>Vicia</i> spp. (Fabaceae), <i>Rehmannia glutinosa</i> (Scrophulariaceae), <i>Lycopersicon esculentum</i> (Solanaceae), <i>Valeriana officinalis</i> (valerian) (Valerianaceae)	GABAA-R, GABAC-R agonist (metabotropic GABAB-R) [antihypertensive, neurotoxic]
Cicutoxin (C ₁₇ polyacetylene)	<i>Cicuta virosa</i> (water hemlock) (Apiaceae)	GABAA-R chloride channel blocker [acute toxicity]
Glycine (α-amino acid)	Universal	GABAA-R agonist
Palmitone (= 16-Hentriacontanone) (aliphatic ketone)	<i>Annona diversifolia</i> (Annonaceae) [leaf], <i>Santalum album</i> (sandalwood) (Santalaceae)	[GABAA-R agonist?] [anticonvulsant, antiepileptic]
Virol A & Virol B (trans-polyacetylenic alcohols)	<i>Cicuta virosa</i> (water hemlock) (Apiaceae)	GABAA-R chloride channel blocker [acute toxicity]
Non-plant reference		3.2Bn
[Atracurium] (bisbenzylisoquinoline)	Synthetic	Metabolic product of skeletal muscle relaxant Atracurium is GABAA-R antagonist Laudanosine
[Avermectin B2a-23-one] (pyrane)	<i>Streptomyces avermitilis</i> (actinomycete fungus)	GABAA-R agonist [antimematode action blocked by Bicuculline & Picrotoxin]
[Baclofen (= β-(Aminomethyl)-4-chlorobenzenepropanoic acid)] (aryl amine)	Synthetic	GABAB-R antagonist [skeletal muscle relaxant]
[tertiary-Butylbicyclo-phosphorothioate (= TBPS)] (phosphorothioate)	Synthetic	GABAA-R chloride channel blocker
[Carisprodol] (imidazole)	Synthetic	GABAA-R indirect agonist [analgesic, skeletal muscle relaxant]
[Dieldrin] (hexachloro pentacyclic alicyclic)	Synthetic insecticide	GABAB-R antagonist
[Dihydromuscimol (= Dihydro-5-aminomethyl-3-hydroxyisoxazole] (isoxazole)	<i>Amanita muscaria</i> (fly agaric); aphrodisiac, hallucinogenic & highly poisonous	GABAA-R agonist [hallucinogenic]

(continued)

Table 3.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
[Gabapentin (= Neurontin; 1-Aminomethyl cyclohexane- carboxylic acid)] (amino alicyclic carboxylic acid)	Synthetic	GABAB-R agonist
[Isoguvacine (= Piperidine-4- carboxylic acid)] (piperidine)	Synthetic	GABAA-R agonist
[Lidocaine] (aryl tertiary amine)	Synthetic	GABAA-R chloride channel blocker (10,000) [additive with Cocaine, local anaesthetic]
[Meprobamate] (imidazole)	Synthetic; metabolite of Carisoprodol	GABAA-R indirect agonist [hypnotic, sedative, skeletal muscle relaxant,
[Muscimol (= 5- Aminomethyl- 3-hydroxyisoxazole] (isoxazole)	<i>Amanita muscaria</i> (fly agaric), <i>A. pantherina</i> (panther cap) (Amanitaceae); highly poisonous, hallucinogenic mushrooms; reported Amanita size- perception effects inspired Lewis Carroll's Alice's Adventures in Wonderland)	GABAA-R agonist [hallucinogenic, spasmodic, toxic]; fly agaric reputed aphrodisiac
[Nicardipine] (arylamino pyridine)	Synthetic	GABAA-R Cl ⁻ channel (at 1–10) (V-gated Ca ²⁺ entry, Gly-R Cl ⁻ channel)
[Pentobarbital] (pyrimidine trione; barbiturate)	Synthetic	GABAA-R agonist [anaesthetic, anticonvulsant; used for euthanasia]
[Phenobarbital (= 5-Ethyl- 5-phenylbarbituric acid; Phenylbarbitone)] (pyrimidine; barbiturate)	Synthetic	GABAA-R agonist [anticonvulsant, hypnotic, sedative]
[Taurine (= 2-Amino- ethanesulphonic acid)] (β-amino acid)	Animals	GABAA-R agonist (Gly-R)
[Valproic acid (= 2- Propylpentanoic acid; 2- Propylvaleric acid)] (carboxylic acid)	Synthetic	GABA transaminase inhibitor (cf. 4- Hydroxybenzaldehyde) [anticonvulsant, antiepileptic]
[Waglerin-1 (= 22 amino acid peptide)] (polypeptide)	Wagler's pit viper venom	GABAA-R chloride current block (3)

Table 3.3 Ionotropic glutamate, glycine and serotonin receptors

Compound (class)	Plant (family) part	Enzyme / process inhibited (other targets) in vivo effects
Glutamate ionotropic receptor (Glu-R) – N-methyl-D-aspartate (NMDA)- binding Glu-R (NMDA-Glu-R)		3.3A
Alkaloid		3.3Aa
[<i>O</i> - <i>t</i> -Butyl- <i>O</i> -desmethylibogaine] (indole)	Synthetic metabolism-resistant derivative of Ibogaine	NMDA-Glu-R antagonist [179]
(±)-Coronaridine (= Carbomethoxyibogamine) (indole)	<i>Tabernanthe coronaria</i> , <i>T. iboga</i> , (Apocynaceae)	NMDA-Glu-R antagonist [6] [cytotoxic, diuretic, oestrogenic]
<i>O</i> -Desmethylibogaine (= 12-Hydroxyibogamine) (indole)	Primary metabolite of Ibogaine	NMDA-Glu-R antagonist [5; 6] (κO-R, V-D-TR, V-MA-TR)
Harmaline (= 3,4-Dihydroharmine; Harmidine) (indole, carboline)	<i>Banisteria caapi</i> (Malpighaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae)	NMDA-Glu-R inverse agonist (α2A-R, BZ-R, Na ⁺ , K ⁺ -ATPase, NMDA-Glu-R) [ataxic, excitatory, hallucinogenic, increases cGMP, tremorigenic]
Ibogaine (= 12-Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> , <i>Voacanga thouarsii</i> (Apocynaceae)	NMDA-Glu-R antagonist [1] (antagonist Dizocilpine displacement) [1] (AD-R, mACh-R, D-R, 5HT-R, 5HT-TR, NE-TR, κO-R, V-D-TR, V-MA-TR) [anticonvulsant, CNS activity, hallucinogen, inhibits morphine dependence]
Ibogamine (indole)	<i>Tabernanthe iboga</i> (iboga) (Apocynaceae); West African stimulant & aphrodisiac	NMDA-Glu-R antagonist [6] (antagonist Dizocilpine displacement) (BZ-R) [brachycardiac, cytotoxic, hypotensive]
Nuciferine (aporphine isoquinoline); principle of Egyptian and Mayan lotus narcotic (psycho-sleptic) for priestly ecstasies; & of Odysseus (Ulysses) & Land of the Lotus Eaters	<i>Nymphaea caerulea</i> (Egyptian blue lotus), <i>N. ampla</i> (Mayan water lily), <i>Nelumbo nucifera</i> (water lotus) (Nymphaeaceae) [flower], <i>Papaver bracteatum</i> (Papaveraceae); Egyptian blue lotus sacred, source of creation; in wine gives “tranquil euphoria”	Non-Kainate Glu-R antagonist (D-R) [antispasmodic, antiviral, neuroleptic]; Egyptian lotus depicted in social & sexual scenes, emblem of Nefertem, God of Perfumes
Tabernanthine (= 13-Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> , <i>Conopharyngia</i> (<i>Tabernaemontana</i>) sp., <i>Stemmadenia</i> sp. (Apocynaceae)	NMDA-Glu-R antagonist [11] (antagonist Dizocilpine displacement) (BZ-R)[CNS activity]
Terpene		3.3At
Bilobalide (sesquiterpene)	<i>Ginkgo biloba</i> (Ginkgoaceae)	Inhibits NMDA-Glu-R-mediated PLA ₂ activation (2)

(continued)

Table 3.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Other		
Agmatine (= (4-Aminobutyl)guanidine; 1-Amino-4-guanidinobutane) (guanidine polyamine)	<i>Ricinus communis</i> (Euphorbiaceae), <i>Glycine max</i> , <i>Lathyrus sativus</i> (Fabaceae), <i>Sesamum indicum</i> (Pedaliaceae), <i>Hordeum vulgare</i> (barley) (Poaceae)	3.3Aa NMDA-Glu-R antagonist (NOS) [antineurotoxic (196), reverses pain from inflammation & neuropathy]
1-β-Cyanoalanine (= 3-Cyanoalanine) (amino acid)	<i>Vicia sativa</i> (vetch), <i>V. spp.</i> (Fabaceae)	NMDA-Glu-R agonist [convulsions, excitotoxic, neurolethargy, neurotoxic]
[1-Cysteine (Cys) (= (R)-2-Amino 3-mercapto-propionic acid; β-Mercapto-1-alanine)] (amino acid)	Universal; thiol precursor (X-SH) of oxidation products Cysteine sulphinic acid (X-SO ₂ H), Cysteic acid (X-SO ₃ H) & Cystine (X-S-S-X)	[Oxidized to Cys sulphinic acid & Cysteic acid (Aspartic acid analogues), NMDA-Glu-R agonists & excitotoxins]
[1-Cys sulphinic acid (C-SO ₂ H)] (amino acid)	Oxidation product of Cys	NMDA-Glu-R agonist [excitotoxic, stimulates IP ₃ formation (~100)]
[1-Cysteic acid (C-SO ₃ H)] (amino acid)	Oxidation product of Cys (C-SH)	NMDA-Glu-R agonist [excitotoxic, stimulates IP ₃ formation (~100)]
1-Glu (= (+)-α-Amino-1-glutaric acid) (α-amino acid)	All organisms; numerous plant sources; <i>Brassica</i> (Brassicaceae), <i>Cerantonia</i> , <i>Glycine</i> , <i>Lupinus</i> (Fabaceae) spp.	NMDA-Glu-R agonist (Non-NMDA-Glu-R, mGlu-R agonist)
1-Gly (= Aminoacetic acid) (α-amino acid)	All organisms; numerous plant sources; <i>Arachis</i> , <i>Cerantonia</i> , <i>Glycine</i> , <i>Lupinus</i> , <i>Phaseolus</i> (Fabaceae)	NMDA-Glu-R co-agonist (Gly-R agonist)
[1-Homocysteine (= (R)-2-Amino-4-mercaptobutyric acid)] (amino acid)	<i>Spinacia oleracea</i> (Chenopodiaceae); animals; thiol precursor (HC-SH) of oxidation products Homocysteine sulphinic acid (HC-SO ₂ H) & Homocysteic acid (HC-SO ₃ H)	[Oxidized to Homocysteine sulphinic acid & Homocysteic acid (Glutamic acid analogues) NMDA-Glu-R agonists & excitotoxins]
[1-Homocysteine sulphinic acid (HC-SO ₂ H)] (amino acid)	Oxidation product of Homocysteine	NMDA-Glu-R agonist [excitotoxic, stimulates IP ₃ formation (~100)]
[1D-Homocysteine sulphinic acid (HC-SO ₂ H)] (amino acid)	Oxidation & alkaline racemization product of 1-Homocysteine	NMDA-Glu-R agonist [excitotoxic]
[1-Homocysteic acid (HC-SO ₃ H)] (amino acid)]	Oxidation product of Homocysteine	NMDA-Glu-R agonist [excitotoxic, stimulates IP ₃ formation (~100)]
β-ODAP (= 1-3-Oxalylamino-2-aminopropionic acid) (amino acid)	<i>Lathyrus sativus</i> (chickling pea) (Fabaceae)	NMDA-Glu-R (at 50) (Non-NMDA-Glu-R) [excitatory, excitotoxin, causal agent of human neurolethargy]
Putrescine (polyamine)	All plants	NMDA-Glu-R co-agonist at polyamine site [neurotoxic – potentiates excitotoxicity of NMDA & NMDA-R agonists]

(continued)

Table 3.3 (Continued)

Compound (class)	Plant (family) / part/	Enzyme / process inhibited (other targets) / in vivo effects/
Spermine (= Gerontine; Musculamine; Neuridine) (polyamine)	All plants	NMDA-Glu-R co-agonist, promotes NMDA-R deactivation (polyamine site) (at 1) [neurotoxic – potentiates excitotoxicity of NMDA & NMDA-R agonists]
Spermidine (polyamine)	All plants	NMDA-Glu-R co-agonist at polyamine site [neurotoxic – potentiates excitotoxicity of NMDA & NMDA-R agonists]
Thiocyanate (= S=C=N ⁻) (thioacyanate ion)	Generated (plus isothiocyanates & nitriles) from Glucosinolates; principal metabolite of CN ⁻ from cyanogenic glycosides e.g. Vicianin, Prunasin & β-Cyanoalanine from <i>Vicia</i> spp. (vetch) (Fabaceae) & Linamarin (Manihotoxine) from <i>Manihot esculentum</i> (cassava) (Euphorbiaceae)	↑ Glutamate-AMPA Glu-R binding [nucleophilic & reactive, toxic, neurotoxic]; SCN⁻ from cassava manihotoxine-derived CN⁻ causes neurotoxic konzo (“tired legs”) motor neuron disease
Zn ²⁺ (divalent metal ion)	Universal	NMDA-Glu-R binding site (modulatory ligand; inhibits binding of non-competitive antagonist Dizocilpine) [neurotoxic]
Non-plant reference		3.3An
[Acamprosate] (alkyl amide sulphonic acid)	Synthetic	NMDA-Glu-R (reverses potentiating effect of indirect agonist spermine) [reduces alcoholic craving]
[Amantadine] (amino cyclic aliphatic)	Synthetic	NMDA-Glu-R antagonist [analgesic, anti-parkinson, excitatory, memory storage impairment]
[N-Acetylaspartylglutamate (= NAAG)] (peptide)	Animals	NMDA-Glu-R agonist
[Arcaine] (guanidine)	Synthetic	NMDA-Glu-R ligand (displaces Dizocilpine)
[7-Chlorokynurenic acid] (quinoline)	Synthetic	Strychnine-insensitive Gly-R (NMDA-Glu-R) antagonist
[<i>Conus geographus</i> peptide] (peptide)	<i>Conus geographus</i> (sea gastropod) [venom]	NMDA-Glu-R antagonist
[Dextromethorphan] (isoquinoline)	Synthetic	NMDA-Glu-R antagonist (σ-R) [analgesic, antitussive]
[Dizocilpine] (dibenzocycloheptene imine)	Synthetic	NMDA-Glu-R non-competitive antagonist [anti-excitatory, attention deficit disorder application]
[Gacyclidine] (piperidine)	Synthetic; Phencyclidine derivative	NMDA-Glu-R antagonist [CNS protectant for treating organophosphorous poisoning]

(continued)

Table 3.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
[Haloperidol (= 1-(3- <i>p</i> -Fluorobenzoylpropyl)-4- <i>p</i> -chlorophenyl-4-hydroxypiperidine)] (aryl piperidine)	Synthetic	NMDA-Glu-R antagonist (σ -R) [antidyskinetic (in Tourette Syndrome), antipsychotic]
[Ibotenic acid (= α -Amino-3-hydroxy-5-isoxazoleacetic acid)] (isoxazole α -amino acid)	<i>Amanita muscaria</i> , <i>A. pantheria</i> (fly agaric mushroom) (Agaricaceae); highly poisonous, hallucinogenic mushrooms; reported Amanita size-perception effects inspired Lewis Carroll (Charles Dodgson) (<i>Alice's Adventures in Wonderland</i>)	NMDA-Glu-R (K-R) agonist (iGlu-R, non-NMDA-Glu-R) [insecticidal, narcosis-potentiating, neurotoxic]; highly toxic, hallucinogenic; fly agaric mushroom reputed aphrodisiac
[Ifenprodil (= 1-Methyl-2-hydroxy-2-(4-hydroxyphenyl)ethyl-1-(4-benzyl-piperidine)]- (aryl piperidine)	Synthetic	NMDA-Glu-R antagonist [25 nM; 34 nM] (σ -R) [cerebral & peripheral vasodilator]
[<i>endo</i> -3-(Indol-2-yl)-8-methyl-8-azabicyclo-[3.2.1]octane](indolotropane)	Synthetic	NMDA-Glu-R antagonist (antagonist Dizocilpine displacement)
[Kynurenic acid (= 4-Hydroxy-2-quinolinecarboxylic acid)] (quinoline carboxylic acid)	Metabolic product of Tryptophan via Kynurenine cyclization by Kynurenine Aminotransferases I & II (KATI & KATII)	Antagonist of NMDA-Glu-R (181) (non-NMDA-Glu-R) [anti-excitotoxic]
[Memantine (= 1-Amino-3,5 dimethyladamantane)] (amino adamantane, amino cyclic aliphatic)	Synthetic	NMDA-Glu-R antagonist [anti-parkinson, excitatory, memory storage impairment, skeletal muscle relaxant]
[Methadone (= 6-Dimethylamino-4,4-diphenyl-3-heptanone)] (aryl tertiary amine)	Synthetic	NMDA-Glu-R antagonist (O-R) [analgesic, narcotic]
[<i>endo</i> -3-(1-Methylindol-2-yl)-8-methyl-8-azabicyclo-[3.2.1]octane(indolotropane)	Synthetic	NMDA-Glu-R antagonist (antagonist Dizocilpine displacement)
[<i>exo</i> -3-(1-Methylindol-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (indolotropane)	Synthetic	NMDA-Glu-R antagonist (antagonist Dizocilpine displacement)
[NMDA] (amino acid)	Synthetic	NMDA-Glu-R agonist [excitatory, excitotoxic]
[Phencyclidine (= Angel dust; PCP; 1-(1-Phenylcyclohexyl)piperidine) (piperidine)	Synthetic; drug of abuse with dangerous, addictive, psychotic effects	NMDA-Glu-R antagonist [analgesic, anaesthetic, depressant, hallucinogen, induces schizophrenia-like state]
[Philanthotoxin] (arylalkylamine)	Spider toxin	NMDA-Glu-R non-competitive antagonist [non-amnesic, does not impair LTP]
[Quinolinic acid (= 2,3-Pyridinedicarboxylic acid)] (pyridine carboxylic acid)	Metabolic product of Tryptophan via Kynurenine-3-hydroxylase	NMDA-Glu-R agonist [excitatory, excitotoxic]

(continued)

Table 3.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) / in vivo effects
Glutamate ionotropic receptor (Glu-R) – Non-NMDA binding Glu-R (Non-NMDA-Glu-R) – AMPA-R, Kainate-R (K-R)		3.3B
Alkaloid		3.3Ba
Domoic acid (pyrrolidine)	<i>Chondria armata</i> (red alga) (Rhodamelaceae)	Non-NMDA-Glu-R (K-R) agonist [amnesic, excitotoxic]
Kainic acid (= 2-Carboxy-3-carboxymethyl-4-isoprenylpyrrolidine) (pyrrolidine)	<i>Digenea simplex</i> (red alga) (Rhodamelaceae)	Non-NMDA-Glu-R (K-R) agonist [anthelmintic, excitatory, excitotoxic (70)]
Quisqualic acid (= (S)- α -Amino-3,5-dioxo-1,2,4-oxadiazolidine-2-propionic acid) (oxadiazolidine amino acid)	<i>Quisqualis chinensis</i> , <i>Q. indica</i> (Combretaceae) [seed]	Non-NMDA-Glu-R (K-R) agonist (displaced by Kainate at 30) (KATII, mGlu1a-R, mGlu5a-R) [anthelmintic, excitatory]
Stizolobic acid (= 2-Amino-3-(6-carboxy-2-oxo-2H-pyran-4-yl) propanoic acid) (pyranyl propionic acid)	<i>Stizolobium hassjoo</i> (Fabaceae)	Non-NMDA-Glu-R (K-R) antagonist (at 500)
Stizolobinic acid (= 2-Amino-3-(6-carboxy-2-oxo-2H-pyran-4-yl) propanoic acid) (pyranyl propionic acid)	<i>Stizolobium hassjoo</i> (Fabaceae)	Non-NMDA-Glu-R (K-R) antagonist (at 500; <Stizolobic acid)
Phenolic		3.3Bp
Cyandione A (biacetophenone)	<i>Cynanchum wilfordii</i> (Asclepidaceae) [root]	Non-NMDA-Glu-R (K-R) interaction – alleviates neurotoxicity of Glutamate & kainate (but not of NMDA)
Other		3.3Bo
1-Glutamate (= (+)- α -Amino-1-glutaric acid) (α -amino acid)	All organisms; numerous plant sources; <i>Brassica</i> (Brassicaceae), <i>Cerantonia</i> , <i>Glycine</i> , <i>Lupinus</i> (Fabaceae) spp.	Non-NMDA-Glu-R agonist (NMDA-Glu-R agonist)
S-(4-Hydroxybenzyl)-glutathione (phenolic peptide)	<i>Gastrodia elata</i> (Orchidaceae)	Non-NMDA-Glu-R ligand
1- α -Amino- γ -oxalylaminobutyric acid (amino acid)	<i>Acacia</i> spp., <i>Lathyrus latifolius</i> (Fabaceae) [seed]	Non-NMDA Glu-R (AMPA-R) agonist [causes neurolathyrism]
1-3-Oxalylamino-2-aminopropionic acid (= 3-N-Oxalyl-2,3-diamino propionic acid; β -ODAP; β -N-Oxalylamino-1-alanine; 1-BOAA) (amino acid)	<i>Lathyrus sativus</i> (chickling pea) (Fabaceae); a so-called “famine plant” consumed in India in the absence of other sustenance but with potential neurotoxic effects	Non-NMDA-Glu-R (AMPA-R) agonist (NMDA-Glu-R, norepinephrine TR) [cytotoxicity (at 1 pM) prevented by quinoxalinedione non-NMDA antagonists, excitatory, lathyrism (neuronal damage disease) in humans]

(continued)

Table 3.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
3-Methylamino-1-alanine (= BMAA; β - Methylamino-1-alanine) (amino acid)	<i>Cycas circinalis</i> (Cycadaceae)	Non-NMDA-Glu-R agonist (weak, HCO_3^- -dependent) (norepinephrine transport) [excitotoxin, lathyrism (neuronal damage disease) in humans]
Isowillardine (uracil amino acid)	<i>Pisum sativum</i> (pea) (Fabaceae) [seed, seedling]	Non-NMDA-Glu-R agonist
1-2-Oxalylamino-2- aminopropionic acid (= α -ODAP) (amino acid)	<i>Lathyrus sativus</i> (chickling pea) (Fabaceae)	Non-NMDA-Glu-R agonist (cf. Kainic & Quisqualic acids) (NMDA-Glu-R) [excitatory, excitotoxin, causal agent of human neurolathyrism]
Non-plant reference		3.3Bn
[AMPA (= 2-Amino-3-(3- hydroxy-5-methyl-4- isoxazolyl)propionic acid)] (isoxazole carboxylic acid)	Synthetic	Non-NMDA-Glu-R agonist (AMPA-R) [excitatory, excitotoxic (11)]
[(S)-Homoibotenic acid (= 2-Amino-3-(3-hydroxy-5- isoxazolyl)propionic acid)] (isoxazole carboxylic acid)	Synthetic	Non-NMDA-Glu-R agonist (AMPA-R) (0.8) (mGlu1a-R, mGlu5a-R) [excitatory (330), excitotoxic]
[2-Amino-3-(3-hydroxy-4- methyl-5-isoxazolyl) propionic acid]] (isoxazole carboxylic acid)	Synthetic	Non-NMDA-Glu-R agonist (AMPA-R) (0.3) (mGlu1a-R, mGlu5a-R) [excitatory (18), excitotoxic]
[2-Amino-3-(3-hydroxy-4- butyl-5-isoxazolyl) propionic acid]] (isoxazole carboxylic acid)	Synthetic	Non-NMDA-Glu-R agonist (AMPA-R) (0.5) (mGlu1a-R, mGlu5a-R) [excitatory non- NMDA-Glu-R (17), excitotoxic]
[Ibotenic acid (= α -Amino-3- hydroxy-5-isoxazole- acetic)] (isoxazole amino acid)	<i>Amanita muscaria</i> , <i>A. pantheria</i> (mushroom) (Agaricaceae); highly toxic, hallucinogenic; fly agaric reputed aphrodisiac	Non-NMDA-Glu-R (K-R) agonist (cf. Kainic acid) (iGlu- R, NMDA-Glu-R) [insecticidal, narcosis-potentiating, neurotoxic]
[Kynurenic acid (= 4- Hydroxy-2- quinolinecarboxylic acid)] (quinoline carboxylic acid)	Metabolic product of Tryptophan via Kynurenine cyclization by Kynurenine Aminotransferases I & II (KATI & KATII)	non-NMDA-Glu-R antagonist (NMDA-Glu-R) [anti- excitotoxic]
[NBQX (= 2,3-Dihydroxy- 6-nitro-7-sulfamoyl- benzo(f)quinoxaline)] (quinoxaline)	Synthetic	Non-NMDA-Glu-R (AMPA-R) antagonist [ameliorates 3- Nitropropionate-induced neurodegeneration, ameliorates EAE (mouse MS model)]
[Willardine derivatives] (uracil amino acids)	Synthetic	Non-NMDA-Glu-R agonists
Inhibitory glutamate receptor (iGlu-R)		3.3C
1-Glutamate (= (+)- α - Amino-1-glutaric acid) (α -amino acid)	All organisms; numerous plant sources; <i>Brassica</i> (Brassicaceae), <i>Ceratonia</i> , <i>Glycine</i> , <i>Lupinus</i> (Fabaceae) spp.	iGlu-R agonist (non-NMDA- and NMDA-Glu-R agonist)

(continued)

Table 3.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited (other targets) in vivo effects
[Ibotenic acid (= α -Amino-3-hydroxy-5-isoxazoleacetic)] (isoxazole α -amino acid)	<i>Amanita muscaria</i> , <i>A. pantheria</i> (mushroom) (Agaricaceae); highly toxic, hallucinogenic; fly agaric reputed aphrodisiac	iGlu-R (non-NMDA- and NMDA-Glu-R) [insecticidal, narcosis-potentiating, neurotoxic]
Quisqualic acid (= (S)- α -Amino-3,5-dioxo-1,2,4-oxadiazolidine-2-propionic acid) (oxadiazolidine amino acid)	<i>Quisqualis chinensis</i> , <i>Q. indica</i> (Combretaceae) [seed]	iGlu-R agonist (pulmonate molluscs) (KATII, mGlu1a-R, mGlu5a-R, non-NMDA-Glu-R) [anthelmintic, excitatory]
Gly-R		3.3D
Alkaloid		3.3Da
Brucine (= 10, 11-Dimethoxystrychnine) (indole)	<i>Strychnos aculeata</i> , <i>S. ignatii</i> , <i>S. nuxvomica</i> (Loganiaceae)	Gly-R antagonist [bitter, toxic]
Calycanthine (pyrrolidine); structure determined (1960) by Robert Burns Woodward (USA, Nobel Prize, Chemistry, 1965)	<i>Calycanthus</i> spp. (Calycanthaceae) [seed], <i>Palicourea alpina</i> (Rubiaceae) [leaf, stem]	Gly-R antagonist [convulsant, strychnine-like, toxic]
Colchicine (tricyclic); synthesis (1963) by R.B.Woodward (USA, Nobel Prize, Chemistry, 1965)	<i>Colchicum autumnale</i> , <i>C. spp.</i> , <i>Gloriosa superba</i> (Liliaceae); named for Colchis, homeland of sorceress & herbalist Medea	α 1Gly-R antagonist (64), α 1G-R antagonist (324) (GABAA-R, microtubule tubulin) [irritant, carcinogen, teratogen, tubulin and cell division inhibitor, toxic]
Corymine (indole)	<i>Hunteria zeylanica</i> (Apocynaceae) [leaf]	Gly-R antagonist (non-competitive, chloride channel blocker) (11) [CNS stimulant, potentiates convulsions by Strychnine & Picrotoxin]
Deformylcorymine (indole)	<i>Hunteria zeylanica</i> (Apocynaceae) [leaf]	Gly-R antagonist (non-competitive, chloride channel blocker) (37; 55)
N-Demethyl-3-epi-dihydrocorymine (indole)	<i>Alstonia glaucescens</i> (Apocynaceae) [stem bark]	Gly-R antagonist (37; <100) (GABAA-R)
(-)-Laudanidine (benzylisoquinoline)	<i>Papaver somniferum</i> (opium poppy) (Papaveraceae)	Gly-R antagonist [Strychnine-like, toxic]
(+)-Laudanidine (benzylisoquinoline)	<i>Machilus obovatifolia</i> (Lauraceae), <i>Thalictrum dasycarpum</i> (Ranunculaceae)	Gly-R [Strychnine-like, toxic]
Laudanine (= (\pm)-Laudanidine) (benzylisoquinoline)	<i>Xylopiya pancheri</i> (Annonaceae), <i>Papaver somniferum</i> (opium poppy) (Papaveraceae)	Gly-R antagonist [Strychnine-like, toxic]
Pleiocarpamine (indole)	<i>Hunteria zeylanica</i> (Apocynaceae) [leaf]	Gly-R antagonist (>100)

(continued)

Table 3.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Strychnine (indole); Heinrich Otto Wieland (Germany, Nobel Prize, 1927, bile acids); structure & synthesis by Robert Burns Woodward (USA, Nobel Prize, 1965, Chemistry)	<i>Strychnos nux-vomica</i> [seed] (nux-vomica), <i>S. ignatii</i> (ignatius bean), <i>S. icaja</i> , <i>S. tieute</i> , <i>S. triplinervia</i> (Loganiaceae); Adolph Hitler took anti-flatulence pills containing Strychnine & Atropine. He also took Methamphetamine & Cocaine medications	Gly-R antagonist ($\alpha 7nACh-R$) [bitter, CNS stimulant, toxic]; South African Mrs Daisy De Melker poisoned 2 husbands with Strychnine & thence her son with arsenic (1923, 1927 & 1932)
Terpene		3.3Dt
Picrotin (tutinolide sesquiterpene lactone)	<i>Anamirta paniculata</i> (= <i>A. cocculus</i> ; <i>Menispermum oculus</i>), <i>Tinomisium philippinense</i> (Menispermaceae) [drupe]	Gly-R competitive antagonist (GABAA-R) [CNS stimulant, barbiturate antidote, insecticide]
Picrotoxin (= mixture of Picrotin and Picrotoxinin) (tutinolide sesquiterpene lactone)	<i>Anamirta paniculata</i> (= <i>A. cocculus</i> ; <i>Menispermum oculus</i>), <i>Tinomisium philippinense</i> (Menispermaceae) [drupe]	Gly-R competitive antagonist (GABAA-R) [CNS stimulant, barbiturate antidote, insecticide]
Picrotoxinin (= Dehydropicrotin) (tutinolide sesquiterpene lactone)	<i>Anamirta paniculata</i> (= <i>A. cocculus</i> ; <i>Menispermum oculus</i>), <i>Tinomisium philippinense</i> (Menispermaceae) [drupe]	Gly-R competitive antagonist (GABAA-R) [CNS stimulant, barbiturate antidote, insecticide, nematocide]
Other		3.3Do
β -Alanine (= 3-Aminopropionic acid) (amino acid)	<i>Lunaria</i> spp. (honesty) (Brassicaceae), <i>Iris tingitana</i> (Iridaceae) [seed]	Gly-R ligand (effect reversed by Gly-R antagonist Strychnine) (GABA-R) [neurotoxic]
Glycine (α -amino acid)	All organisms; numerous plant sources; <i>Arachis</i> , <i>Ceratonia</i> , <i>Glycine</i> , <i>Lupinus</i> , <i>Phaseolus</i> (Fabaceae)	Strychnine-sensitive Gly-R agonist (Strychnine-insensitive NMDA Glu-R co-agonist)
Non-plant reference		3.3Dn
[<i>N</i> -Demethyl-3- <i>epi</i> -dihydrocorymine] (indole)	Semi-synthetic from Corymine	Gly-R chloride antagonist (non-competitive, chloride channel blocker) (37)
[Dihydrocorymine] (indole)	Semi-synthetic from Corymine	Gly-R chloride antagonist (non-competitive, chloride channel blocker) (34)
[Nicardipine] (arylamino pyridine)	Synthetic	Gly-R Cl ⁻ channel (at 1–10) (V-gated Ca ²⁺ entry, GABAA-R Cl ⁻ channel)
[Nifedipine] (aryl dihydropyridine)	Synthetic	Gly-R Cl ⁻ channel (at 1–10) (DHP–Ca ²⁺ –CH) [antihypertensive]
[Nitrendipine] (Dihydropyridine=DHP)	Synthetic	Gly-R Cl ⁻ channel (at 1–10) (Ca ²⁺ channel blocker) [antihypertensive]
[Taurine (= 2-Aminoethane-sulphonic acid)] (β -amino acid)	Animals	Gly-R agonist (GABAA-R)

(continued)

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Table 3.3 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part/</i>	<i>Enzyme/process inhibited (other targets) in vivo effects/</i>
[Verapamil] (aryl tertiary amine)	Synthetic	Gly-R Cl ⁻ channel (at 10) (1- type Ca ²⁺ CH) [antianginal, antiarrhythmic (class IV), antihypertensive, coronary vasodilator]
Serotonin (5HT3-R)		3.3E
Alkaloid		3.3Ea
Ibogaïne (= 12- Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> , <i>Voacanga thouarsii</i> (Apocynaceae)	5HT3-R ligand (4) NMDA- Glu-R antagonist (antagonist Dizocilpine displacement) [1] (AD-R, mACh-R, D-R, 5HT-R, 5HT-TR, NE-TR, κO-R, V-D-TR, V-MA-TR) [anticonvulsant, CNS activity, hallucinogen, inhibits morphine dependence]
Serotonin (= 5- Hydroxytryptamine) (indole)	<i>Phoenix dactylifera</i> (Arecaceae), <i>Ananas comosus</i> (Bromeliaceae), <i>Hippophae rhamnoides</i> (Elaeagnaceae), <i>Mucuna pruriens</i> (Fabaceae), <i>Juglans regia</i> (Juglandaceae), <i>Musa sapientum</i> (Musaceae), <i>Lycopersicon esculentum</i> , <i>Solanum tuberosum</i> (Solanaceae), <i>Urtica dioica</i> (Urticaceae) (Solanaceae), <i>Theobroma cacao</i> (Sterculiaceae)	5HT3-R agonist [0.2], channel activation (2) (5HT1-R, 5HT1A-R, 5HT2-R) [CNS stimulatory NT]
Tryptophan (= α-Amino- indole-3-propionic acid) (amino acid)	In all organisms	Precursor of 5HT (Serotonin); crosses blood-brain barrier (BBB) (unlike 5HT) [for depression, treatment of aggression]
(+)-Tubocurarine (= curare active principle) (bisbenzylisoquinoline)	<i>Chondrodendron tomentosum</i> (curare, pareira), <i>C. spp.</i> (Menispermaceae) [bark]; S. Am. Indian arrow poison curare component	5HT3-R antagonist [138 nM] (nAChR) [toxic, skeletal muscle relaxant]
Phenolic		3.3Ep
Jensenone (acylphloroglucinol)	<i>Eucalyptus jensenii</i> (gum tree) (Myrtaceae)	[antifeedant effect blocked by 5HT3-R antagonist Ondansetron]
Non-plant reference		3.3En
[Fluoxetine] (trifluorophenoxy phenyl tertiary amine)	Synthetic	5HT3-R antagonist [7] (5HT uptake inhibitor) [antidepressant]
[Granisetron] (indazole carboxamide)	Synthetic	5HT3-R antagonist [1 nM] [antiemetic]
[Imipramine] (dibenzazepine tertiary amine)	Synthetic	[Ondansetron (5HT3-R antagonist) & Mianserine (5HT2-R antagonist) block antinociceptive effect]

(continued)

Table 3.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
[Litoxetine]	Synthetic	5HT ₃ -R antagonist [85 nM] (5HT uptake inhibitor) [antidepressant, antiemetic]
[Metoclopramide] (benzamide)	Synthetic	5HT ₃ antagonist (D ₂ -R antagonist) [controls migraine-associated nausea & vomiting]
[2-Methylserotonin (= 2-Methyl-5HT) (indole)]	Synthetic	Specific 5HT ₃ -R agonist
[Mirtazepine] (pyrazinopyridobenzazepine)	Synthetic	5HT ₃ -R antagonist (5HT ₂ -R antagonist) [antidepressant]
[Ondansetron] (imidazole carbazole)	Synthetic	5HT ₃ -R antagonist [antiemetic]
[Tropisetron] (tropane indole)	Synthetic	5HT ₃ -R antagonist [antiemetic]
[VC-605] (quinoxaline)	Synthetic	Potent 5HT ₃ -R antagonist (pig ileum) (1000× >Ondansetron)

Table 3.4 Sigma and vanilloid receptors

Hormone effect Compound (class)	Plant (family) part	Process inhibited (other target inhibited) in vivo effects
Sigma Receptors (σ-R)		3.4A
Alkaloid		3.4Aa
Hydrastine (phthalideisoquinoline)	<i>Berberis vulgaris</i> , <i>Mahonia aquifolium</i> (Berberidaceae), <i>Corydalis stricta</i> (Papaveraceae), <i>Hydrastis canadensis</i> (Ranunculaceae)	Displaces σ -R agonist Noscapine [antiseptic, non-narcotic antitussive, haemostatic for uterine haemorrhage]
Ibogaine (= 12-Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> , <i>Voacanga thouarsii</i> (Apocynaceae)	σ 1-R ligand [9], σ 2-R ligand [0.2] (D-R, D-TR, 5HT-TR, NMDA-Glu-R, V-D-TR, O-R, V-MA-TR, V-gated Na ⁺ channel) [anti-addictive, anti-convulsant, CNS activity, hallucinogen]
Ibogamine (indole)	<i>Tabernanthe iboga</i> (Apocynaceae); West African stimulant & aphrodisiac	σ 1-R [\sim 1], σ 2-R [0.1] (O-R, V-gated Na ⁺ channel) [brachycardiac activity, cytotoxic, hypotensive]
Narceine (ring-opened isoquinoline)	<i>Papaver somniferum</i> (opium) (Papaveraceae)	Displaces σ -R agonist Noscapine [non-narcotic antitussive, hypotensive, peristalsis stimulant, respiratory stimulant]
Narcotoline (= Desmethylnoscapine) (phthalideisoquinoline)	<i>Papaver somniferum</i> (opium) (Papaveraceae)	Displaces σ -R agonist Noscapine [non-narcotic antitussive, respiratory stimulant, spasmolytic]

(continued)

Table 3.4 (Continued)

Hormone effect Compound (class)	Plant (family) part	Process inhibited (other target inhibited) in vivo effects
Noscapine (= Methoxyhydrastine; Narcosine; α -Narcotine; Opianine) (phthalideisoquinoline)	<i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [latex]	σ -R agonist [7 nM] [antitumour, apoptotic, non-narcotic antitussive, spasmolytic]
Papaverine (benzylisoquinoline)	<i>Rauwolfia serpentina</i> (Apocynaceae), <i>Papaver bracteatum</i> , <i>P. somniferum</i> (opium poppy) (Papaveraceae) [latex]	Displaces σ -R agonist Noscapine (cAMP PDE) [antinociceptive, non-narcotic antitussive, SM relaxant, spasmolytic, vasodilator]
Tabernanthine (= 13-Methoxyibogamine) (indole)	<i>Conopharyngia</i> (<i>Tabernaemontana</i>) spp., <i>Stemmadenia</i> spp., <i>Tabernanthe iboga</i> (Apocynaceae)	σ 1-R [\sim 1], σ 2-R [0.2] (CBZ-R, V-gated Na ⁺ channel, O-R) [CNS activity]
Phenolic		3.4Ap
Hypericin (= Hypericum red) (bianthraquinone)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae)	σ -R agonist (\sim 1) [antidepressant effect overcome by Rimcazole]
Non-plant reference		3.4An
[Acromelic acid A] (kainoid pyrrolidine)	<i>Clitocybe acromelaga</i> (mushroom)	Non-NMDA-Glu-R (K-R) agonist [excitatory (0.3), excitotoxic (3) cf. Kainic acid (70)]
[N-(+)-Allylnormetazocine] (benzomorphan)	Synthetic	σ -R agonist [analgesic, anti-tussive, narcotic, protectant against gastric & duodenal ulcer]
[(2 <i>R-trans</i>)-2-Butyl-5-heptylpyrrolidine] (pyrrolidine)	<i>Streptomyces longisporosuber</i> (fungus)	σ -R ligand – σ 1-R (2 nM), σ 2-R (23 nM) (D2-R)
[Dextromethorphan] (isoquinoline, morphine analogue)	Synthetic; cough suppressant abused as the “DMX” recreational drug	σ -R agonist (NMDA-Glu-R, D-TR) [antitussive, anxiolytic, psychoactive]
[1,2-Di-(2-tolyl)guanidine (= DTG)] (guanidine)	Synthetic	σ -R agonist [antitussive, protectant against gastric & duodenal ulcer]
[Haloperidol (= 1-(3- <i>p</i> -Fluorobenzoylpropyl)-4- <i>p</i> -chlorophenyl-4-hydroxypiperidine)] (aryl piperidine)	Synthetic	σ -R antagonist (D2-R, NMDA-Glu-R) [antidyskinetic (in Tourette Syndrome), antipsychotic]
[Ifenprodil (= 4-Benzyl- α -(<i>p</i> -hydroxyphenyl)- β -methyl-1-piperidine neethanol)] (benzyl-piperidine phenol)	Synthetic	σ -R agonist [cerebral & peripheral vasodilator]
[Metazocine] (benzomorphan)	Synthetic	σ -R agonist [analgesic, antitussive, narcotic, protectant against gastric & duodenal ulcer]

(continued)

Table 3.4 (Continued)

Hormone [effect/ Compound (class)]	Plant (family) part	Process inhibited (other target inhibited) in vivo effects
[Pentazocine] (benzomorphan)	Synthetic	σ -R agonist [analgesic, antiamnesic, antitussive, narcotic, protectant against gastric & duodenal ulcer; Naloxone inhibits NMDA- potentiating effect]
[Rimcazole] (piperazinyl carbazole)	Synthetic	σ -R antagonist (D-TR)
Vanilloid receptor (Capsaicin receptor) (VAN-R)		3.4B
Alkaloid		3.4Ba
Evodiamine (indoloquinazoline alkaloid)	<i>Araliopsis tabouensis</i> (Araliaceae), <i>Evodia rutaecarpa</i> (Rutaceae)	VAN-R agonist [bronchoconstrictive (3), diuretic, diaphoretic, tachykinin release]
Piperine (= (E,E)-1- Piperinoylpiperidine) (piperidine)	<i>Piper nigrum</i> (pepper), <i>P. spp.</i> (Piperaceae)	VAN-R (VR-1) agonist [hot taste of pepper; vasoconstrictive, blocks gastric emptying]
Rutaecarpine (indoloquinazoline alkaloid)	<i>Evodia rutaecarpa</i> , <i>Hortia arborea</i> (Rutaceae)	Inactive as VAN-R antagonist (200) (cf. Evodiamine) [hypotensive]
Phenolic		3.4Bp
Capsaicin (= <i>trans</i> -8-Methyl- <i>N</i> -[4-hydroxy-3- methoxyphenylmethyl]-6- nonenamide; <i>trans</i> -8- Methyl- <i>N</i> -vanillyl-6-non- enamide) (vanilloid phenolic)	<i>Capsicum annuum</i> , <i>C. frutescens</i> (paprika) (Solanaceae); <i>Zingiber officinale</i> (Zingiberaceae); capsicum spray use in law enforcement as an alternative to “deadly force” but war use forbidden; primary afferent neuron deactivation for chronic pain relief	VAN-R (e.g. V1-R) agonist (sensory neuron) [1] (V-K ⁺ CH, V-Na ⁺ CH, TYR) [burning pain sensation, broncho- constrictive (1), desensitizes sensory neurons, irritant, tachykinin release, topical analgesic]
Capsaicinoids (vanilloid phenolics)	<i>Capsicum</i> spp. (Solanaceae)	VAN-R agonists
Gingerols (phenylpropane ketones)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	VAN-R agonists (COX, 5-LOX) (OD-R)
Shogaols (phenylpropanoids)	<i>Zingiber officinale</i> (ginger) [rhizome] (Zingiberaceae)	VAN-R agonists (COX, 5-LOX) [AI, PAI]
Terpene		3.4Bt
Cinnamodial (dialdehyde sesquiterpene)	<i>Cinnamosma fragrans</i> [bark], <i>Warburgia salutaris</i> [wood] (Canellaceae)	VAN-R ligand (0.6) [insect antifeedant]
Resiniferatoxin (= <i>Euphorbia</i> factor RL ₉ ; Resiniferol vanillate & phenylacetate diester) (daphnane diterpenoid diester)	<i>Euphorbia poisonii</i> , <i>E. resinifera</i> , <i>E. unispina</i> (Euphorbiaceae); primary afferent neuron deactivation for chronic pain relief	VAN-R agonist (nociceptive neurons) [2 nM] (PKC) [secondary tumour promoter, irritant, bladder sensory fibre desensitization]

(continued)

Table 3.4 (Continued)

<i>Hormone /effect/ Compound (class)</i>	<i>Plant (family) / part/</i>	<i>Process inhibited (other target inhibited) / in vivo effects/</i>
Resiniferonol (= <i>Euphorbia</i> factor RL ₂₀) (daphnane diterpenoid)	<i>Euphorbia resinifera</i> (Euphorbiaceae)	Inactive as VAN-R ligand (cf. Resiniferatoxin)
Other		3.4Bo
Anandamide (= <i>N</i> - Arachidonylethanolamine) (unsaturated FA amide)	<i>Theobroma cacao</i> (cocoa) (Sterculiaceae) [seed] (low amounts); endogenous mammalian Cannabinoid R agonist	VAN-R agonist [2] [stimulates Ca ²⁺ influx (2)] (CBI-R agonist)
Non-plant reference		3.4Bn
[Capsazepine] (benzazepine)	Synthetic	VAN-R antagonist [0.1]
[Hebelomic acid F] (dialdehyde sesquiterpene)	<i>Hebeloma senescens</i> (mushroom)	VAN-R ligand (19)
[Olvanil (= <i>N</i> -Vanillyl-9- oleamide) (vanilloid phenolic)	Synthetic (cf. Capsaicin)	VAN-R agonist (Anandamide transport)
[Ruthenium Red (=Ruthenium oxychloride ammoniated)] (ruthenium complex)	Synthetic	VAN-R antagonist

4 Ion pumps, ligand- and voltage-gated ion channels

4.1 Introduction

As outlined in Chapter 3, cell excitability can in part be determined by the maintenance of gradients of Na^+ , K^+ and Cl^- ions. Differential plasma membrane (PM) permeabilities to such ions and the gradients of ion concentration contribute to the transmembrane potential difference (ψ_m), which is typically about -0.1 volt (V) (inside with respect to the outside). In addition, the cytosolic free concentration of Ca^{2+} is extremely low ($0.1 \mu\text{M}$ in resting cells and about $10 \mu\text{M}$ in excited cells) as compared to concentrations of Na^+ , Cl^- and K^+ of about 10, 10 and 100 mM, respectively, in the cytosol and about 100, 100 and 10 mM, respectively, in the extracellular milieu. These huge ion gradients are maintained through the operation of ion pumps such as the adenosine 5'-triphosphate (ATP)-energized Ca^{2+} pump (Ca^{2+} -ATPase) and the Na^+ and K^+ pump (Na^+ , K^+ -ATPase).

Conversely, cellular perturbation can occur through the opening or closing of PM-located or endoplasmic reticulum (ER) membrane-located ion channels. These include voltage-gated ion channels (ion-specific protein channels that open or close in response to changes in ψ_m) or ligand-gated ion channels that open through the conformational change-inducing binding of a ligand molecule to the corresponding protein ion channel complex. Ligands gating specific ion channels include various neurotransmitters (NTs) (as described in Chapter 3) or cytosolic “second messenger” molecules generated through signalling such as (channel ion specificity in parentheses) adenosine 3',5'-cyclic monophosphate (cAMP) (Na^+), guanosine 3',5'-cyclic monophosphate (cGMP) (Na^+), inositol-1,4,5-triphosphate (IP_3) (Ca^{2+}), Ca^{2+} (Ca^{2+}), cyclic adenosine 5'-diphosphate ribose (cADPR) (Ca^{2+}), nicotinic acid adenine dinucleotide 2'-phosphate (NAADP) (Ca^{2+}) and sphingolipid (Ca^{2+}).

4.2 Ion pumps

Ca^{2+} pumps (Ca^{2+} -ATPases) are located on the PM and on the ER membrane and pump Ca^{2+} out of the cell or into the lumen of the ER, respectively. This process is driven by the hydrolysis of ATP and involves the successive phosphorylation and dephosphorylation of an aspartyl residue of the Ca^{2+} -ATPase. In the dephosphorylated state (state 1), the pump binds Ca^{2+} tightly at a site oriented towards the cytosol but in the phosphorylated state (state 2) this site has a lower affinity for Ca^{2+} and is oriented towards the other side of the membrane (i.e. towards the outside of the cell or towards the ER lumen). Ca^{2+} is accordingly released in state 2, the pump reverts to state 1 through dephosphorylation and the cycle continues.

The PM Ca^{2+} -ATPase is activated by the Ca^{2+} -calmodulin complex (calmodulin being a key Ca^{2+} -binding regulatory protein) and the ER Ca^{2+} -ATPase is stimulated by the

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phosphorylated form of an ER membrane protein, phospholamban, that is phosphorylated by cAMP-dependent protein kinase (PKA), these representing “feedback” mechanisms regulating how excited cells revert to the resting, unexcited state. The Ca^{2+} -ATPase belongs to the “P-type ATPase” family as does the Na^+ , K^+ -ATPase. The best-known plant inhibitor of the Ca^{2+} -ATPase is the sesquiterpene secondary tumour promoter thapsigargin (Table 4.1).

The H^+ , K^+ -ATPase is a P-type ATPase proton (H^+) pump responsible for acidification of the stomach. Inhibition of this pump by the tannin pentagalloylglucose may be the basis for the efficacy of *Paeonia Radix* (dried roots of *Paeollia filciflora*) for treatment of gastritis and peptic ulcers (Table 4.1).

The Na^+ , K^+ -ATPase catalyzes the ATP-dependent, coupled transport of K^+ into cells and of Na^+ out of cells. This involves the successive phosphorylation and dephosphorylation of an aspartyl residue of the Na^+ , K^+ -ATPase and the mechanism is similar to that of the Ca^{2+} -ATPase. In the dephosphorylated state (state 1), the pump binds Na^+ tightly at a site oriented towards the cytosol but in the phosphorylated state (state 2) this site has a lower affinity for Na^+ and is oriented towards the outside of the cell. Na^+ is accordingly released to the outside in state 2 and the pump now binds K^+ at an outside-accessible site. The pump then reverts to state 1 through dephosphorylation, K^+ is released from its binding site that is now oriented towards the cytosol and the cycle continues.

The Na^+ , K^+ -ATPase generates the Na^+ and K^+ gradients required for transmembrane potential-based neuronal signalling and cell perturbation by signalling molecules that open specific ion channels. However the Na^+ gradient generated by the Na^+ , K^+ -ATPase can also be used to “drive” the transport of other solutes. Thus in intestinal cells a Na^+ -dependent glucose transporter on the intestinal lumen side binds glucose on the outside in a process dependent upon Na^+ binding to the transporter (state 1). The transporter consequently undergoes a change in conformation to state 2 in which the binding sites are oriented towards the intestinal cell cytosol. The Na^+ concentration inside the cell being relatively low, Na^+ is released and glucose is accordingly also released inside the cell. This active Na^+ -dependent glucose transporter is called a Na^+ /glucose symporter (i.e. Na^+ and glucose move in the same direction into the cell) and is driven by the Na^+ gradient set up at the expense of ATP (the cellular “energy currency”) through the operation of the Na^+ , K^+ -ATPase. A similar mechanism is involved for Na^+ -dependent iodide (I^-) uptake by the Na^+ / I^- symporter and chloride (Cl^-) uptake by the Na^+ - K^+ - 2Cl^- co-transporter (symporter) (Table 4.5).

Na^+ / Ca^{2+} antiporter (Na^+ / Ca^{2+} TR). The Na^+ gradient generated by the Na^+ , K^+ -ATPase can also be used to pump Ca^{2+} out of cells across the PM, this being effected by a Na^+ / Ca^{2+} antiporter that exchanges Ca^{2+} going out for Na^+ coming back in and moving “downhill” from a high Na^+ concentration outside to a low Na^+ concentration inside the cell. The best-known plant inhibitors of the Na^+ , K^+ -ATPase are the cardiac glycosides (cardioactive steroid glycosides) such as *Digitalis* (foxglove) digitoxin, *Strophanthus* ouabain and *Nerium oleander* (oleander) oleandrin (Table 4.1). The cardiac glycosides inhibit the dephosphorylation step of the Na^+ , K^+ -ATPase cycle and hence block coupled Na^+ and K^+ transport. The foxglove “digitalis” preparation is a centuries old remedy for cardiac insufficiency, the mechanism of the cardiotoxic effect involving the following successive events: digitalis inhibits the Na^+ , K^+ -ATPase \rightarrow cytosolic Na^+ concentration increases \rightarrow Na^+ gradient decreases \rightarrow coupled Na^+ / Ca^{2+} transport decreases \rightarrow increased cytosolic Ca^{2+} concentration \rightarrow increased cardiac muscle contraction.

Ouabain is now known to be an endogenous hormonal regulator in humans deriving from the adrenal cortex (in response to angiotensin II) and from the hypothalamus. Ouabain

binding to the Na^+ , K^+ -ATPase induces a tyrosine kinase (TK)-mediated signalling pathway leading to regulation of the transcription of specific genes (see Chapter 8).

Na^+/H^+ antiporter (Na^+/H^+ TR). The Na^+ gradient is also used to pump protons (H^+) out of cells via the Na^+/H^+ antiporter which thus prevents cellular acidification. In reperfusion of ischaemic hearts the Na^+/H^+ antiporter decreases cellular acidity and increases cytosolic Na^+ concentration (which thence increases cytosolic Ca^{2+} in myocytes).

4.3 Voltage-gated Na^+ channels

Voltage-gated Na^+ channels are critical for cell excitability and neurotransmission by movement of action potentials. As outlined in Chapter 3, the transmembrane potential (ψ_m) at a particular point on a nerve axon PM is typically negative at rest. However depolarization at an immediately adjoining part of the membrane (through an advancing action potential “train” of depolarization) will cause voltage-gated Na^+ channels to open and hence cause the membrane to depolarize at that point. However depolarization causes the Na^+ channel to temporarily “inactivate” and voltage-gated K^+ channels to open with the consequence that the ψ_m now hyperpolarizes (i.e. goes more negative as K^+ exits). The ψ_m “overshoots” slightly and then depolarizes slightly to return to the original “resting” value at that particular point on the membrane. The transient inactivation of the voltage-gated Na^+ channels establishes a unidirectional movement of the action potential down the axon or otherwise along an excitable cell PM.

Voltage-gated Na^+ channels are made up of four bundles of six transmembrane helices with every fourth helix having a basic (positively charged) voltage-sensing amino acid sequence. Depolarization causes this “positive patch” to be electrostatically attracted towards the now more negative outer side of the membrane with a consequent subtle effect on protein complex conformation and an opening of the Na^+ channel. Voltage-gated K^+ and Ca^{2+} channels operate in a similar fashion.

Inactivation of the Na^+ channel is blocked by the *Veratrum* steroidal alkaloid veratridine and by the highly toxic diterpenoid alkaloid aconitine from *Aconitum* species, these toxins causing the Na^+ channel to stay open and hence disrupting neurotransmission. A variety of toxic diterpenoid alkaloids related to aconitine and having aconitine-like effects include aconifine, bishaconitine, delphinine, falaconitine, indaconitine, jesaconitine, mesaconitine and pseudoaconitine. The diterpenoid alkaloids lappaconitine, *N*-deacetylappaconitine and ajacine block the Na^+ channel and thus can act as antagonists of aconitine. The plant monoterpene pyrethrins I and II are insecticidal by keeping the voltage-gated Na^+ channel in a persistent open state and a number of synthetic pyrethrins are used as insecticides. A variety of other synthetic compounds (e.g. DDT) and naturally occurring toxins from spiders, frogs, gastropods and fish also interfere with the voltage-gated Na^+ channel (Table 4.2).

The potent “puffer fish” toxin tetrodotoxin is a potent inhibitor of most voltage-gated Na^+ channels (K_d values 1–10 nM) (Table 4.2). A variety of voltage-gated Na^+ channels have been resolved from various tissues as follows (subtypes in parentheses): brain (types I, II, IIA, VI), skeletal muscle ($\mu 1$), sympathetic ganglia (PN1), heart (h1) and dorsal root ganglia (PN3/SNS). These channels are variously blocked by tetrodotoxin, the least sensitive being the voltage-gated Na^+ channels of heart (IC_{50} 6 μM) and dorsal root ganglia (IC_{50} 60 μM).

In addition to the voltage-gated Na^+ channels described above and the NT-opened Na^+ channels described in Chapter 3, second messenger-gated Na^+ channels are also involved in signalling. Thus cAMP-gated Na^+ channels are involved in signalling in olfactory and taste perception and cGMP-gated Na^+ channels mediate signalling in vision (Chapter 5).

4.4 Ligand-regulated and voltage-gated K^+ channels

Voltage-gated K^+ channels are critical to transmembrane potential- and Ca^{2+} -mediated signalling. Voltage-regulated K^+ channels are critically involved in action potentials as described above and such channels are blocked by the legume quinolizidine alkaloid sparteine (lupinidine) as well as by various synthetic psychoactive compounds with disparate effects such as amitriptyline, chlorpromazine, imipramine and phencyclidine.

While some K^+ channels are voltage-gated, others are modulated by G proteins (that are in turn regulated by particular hormones such as dopamine or adenosine) (see Chapter 5) and others are subject to Ca^{2+} -dependent activation. A Ca^{2+} -dependent K^+ channel is opened by the lignan nordihydroguaiaretic acid (NDGA).

ATP-sensitive K^+ channels (K_{ATP} channels) are blocked by ATP and are involved in regulation of muscle, synapses and endocrine secretion. Inhibition of K_{ATP} channels in pancreatic β -cells leads to depolarization, Ca^{2+} elevation and insulin secretion. K_{ATP} channels are inhibited by the synthetic carbamoylmethyl benzoic acid drug rugrepiglinide and synthetic sulphonylurea drugs (such as glibenclamide, gliclazide and glimipiride). These drugs are used in treating type 2 diabetes mellitus (mature age diabetes) in which there is an insufficiency of insulin production as well as a decreased responsiveness to insulin (insulin resistance). K_{ATP} channels are also inhibited by the legume-derived quinolizidine alkaloid sparteine (Table 4.3).

4.5 Voltage-gated Ca^{2+} channels

Ca^{2+} is a major “second messenger” in eukaryote cells, the cytosolic free concentration of Ca^{2+} being elevated in response to depolarization and to many hormones and NTs. Intracellular and PM voltage-gated Ca^{2+} channels are accordingly involved in Ca^{2+} -mediated signalling.

PM-located voltage-gated Ca^{2+} channels of various kinds (L, N, P, Q, R and T classes) have been resolved of which the L-type Ca^{2+} channels are the best studied. The voltage-gated Ca^{2+} channels are homologous to the voltage-gated Na^+ and K^+ channels described above and open in response to adjacent depolarization of the ψ_m . The L-type Ca^{2+} channels are blocked by various synthetic drugs including phenylalkylamines (e.g. verapamil), benzothiazepines (e.g. diltiazem) and dihydropyridines (e.g. azidopine and nifedipine) (Table 4.3).

In skeletal muscle open voltage-gated L-type Ca^{2+} channels can interact directly with muscle ER (sarcoplasmic reticulum) ryanodine receptors to open the ryanodine receptor Ca^{2+} channel and thence elevate cytosolic Ca^{2+} concentration from sarcoplasmic reticulum Ca^{2+} stores. However in neurons and cardiac muscle activation of PM voltage-gated Ca^{2+} channels indirectly activates ryanodine receptor Ca^{2+} channels as outlined in the section on “Ligand-gated Ca^{2+} channels”.

4.6 Ligand-gated Ca^{2+} channels

While skeletal muscle ryanodine receptors are involved in excitation – contraction coupling through direct interactions with voltage-gated Ca^{2+} channels, in other cell types ryanodine receptor Ca^{2+} channels located on the ER membrane are opened by cADPR in a Ca^{2+} -CaM-dependent fashion. Ca^{2+} and plant metabolites such as the diterpenoid alkaloid ryanodine and the methylxanthine caffeine promote opening of the ryanodine receptor Ca^{2+} channel. Ryanodine can also negatively modulate the receptor (Table 4.4).

The second messengers cADPR (in which both N^1 and N^6 of adenine are ribosylated) and NAADP (in which the nicotinamide of oxidized nicotinamide adenine dinucleotide

phosphate (NADP⁺) is replaced by nicotinic acid) are synthesized by adenosine 5'-diphosphate (ADP)-ribosyl cyclase from oxidized nicotinamide adenine dinucleotide (NAD⁺) and NADP⁺, respectively. Both cADPR and NAADP release Ca²⁺ from the ER via specific ER receptors that are ligand-gated Ca²⁺ channels. Thus cADPR and NAADP act as second messengers for cholecystokinin (CCK) to trigger elevation of cytosolic Ca²⁺ in pancreatic acinar cells leading to digestive enzyme secretion (noting that CCK can also activate phospholipase A₂ (PLA₂) and phospholipase D (PLD) activity) (Table 4.4).

A more general mechanism for release of Ca²⁺ from the ER is via channels that are gated by the second messenger IP₃. Thus in pancreatic acinar cells acetylcholine (ACh) acts via metabotropic, G-protein-coupled, muscarinic acetylcholine receptors (mACh-Rs) (as opposed to the ionotropic ACh receptors described in Chapter 3) to activate phospholipase C (PLC). PLC generates IP₃ and diacylglycerol (DAG) by hydrolyzing the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate (PI_{4,5}P₂). IP₃ binds to the ER IP₃-receptor (an IP₃-gated channel) thereby elevating cytosolic free Ca²⁺ concentration and ultimately triggering digestive enzyme secretion. As will be outlined in Chapters 5 and 8, a variety of hormones can variously act to increase cytosolic free Ca²⁺ concentration through activating PLC and thence generating IP₃.

4.7 Chloride transport and voltage-regulated chloride channels

Na⁺-K⁺-2Cl⁻ co-transporter (symporter). Chloride (Cl⁻) is transported into cells (e.g. from the blood across the basolateral membrane into intestinal epithelial cells) by a Na⁺-K⁺-2Cl⁻ co-transporter (symporter) driven by the Na⁺ gradient generated as a result of the operation of the Na⁺, K⁺-ATPase (Na⁺/K⁺-antiporter pump). Chloride (Cl⁻) can then be secreted from cells (e.g. across the apical membrane into the lumen of the intestine) via the cystic fibrosis transmembrane conductance regulator (CFTR), this process being regulated in various ways by hormonal agonists elevating the cytosolic concentrations of the second messengers cAMP and Ca²⁺ as outlined in the section on “cystic fibrosis transmembrane conductance regulator (CFTR)”.

Cystic fibrosis transmembrane conductance regulator (CFTR). The CFTR is a Cl⁻ channel and consists of two 6-transmembrane α -helix domains linked by a cytosolic portion consisting of two nucleotide-binding domains (NBD1 and NBD2) and a regulatory domain (R). The CFTR belongs to the “ATP-binding cassette” (ABC) family of solute transporters (other examples being the P-glycoprotein solute transporters (PGPs) involved in multidrug resistance (MDR) to chemotherapy of cancer cells or malaria-causing *Plasmodium falciparum* cells) (Chapter 13). Opening and closing of the CFTR Cl⁻ channel involves energy from ATP hydrolysis due to successive operation of the ATP-binding domains NBD1 and NBD2. However this cycle is hormonally regulated as outlined below.

Hormones acting via G-linked receptors and generating an adenylate cyclase-activating G α s-GTP complex cause an elevation of cAMP which regulates the operation of CFTR. Elevated cAMP activates PKA which phosphorylates the CFTR regulatory domain R, this resulting in an activation of the CFTR. However hormones causing an elevation of cytosolic free Ca²⁺ also modulate the process. Thus elevation of cytosolic Ca²⁺ results in opening of Ca²⁺-regulated K⁺ channels (see Section 4.3) causing K⁺ efflux and cell hyperpolarization (cell interior more negative with respect to the outside). Hyperpolarization in turn favours the exit of negatively charged chloride ion (Cl⁻) from the cell via the CFTR Cl⁻ channel.

Cholera toxin is an ADP ribosyl transferase that ADPribosylates G α s-GTP, this inhibiting the G α s subunit GTP-hydrolyzing activity and thus preventing reversion to the inactive

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G α s–GDP form. Accordingly, cAMP levels are greatly elevated, PKA remains activated and CFTR is persistently activated, resulting in the sustained NaCl and water loss (diarrhoea) associated with cholera. Conversely, in cystic fibrosis (CF) (affecting 1 in 2000 newborn Caucasians), insufficient CFTR is emplaced at the apical membrane (the most common cause being a mutation preventing proper folding of the newly synthesized CFTR). Insufficient CFTR in the lungs results in mucous secretion leading to bacterial infection and lung damage. Approaches to CF include gene therapy and channel-interacting drugs (e.g. Cl⁻ channel openers and Na⁺ channel blockers).

Voltage-regulated chloride channels (ClCs). Since the resolution of the voltage-regulated ClC ClC-0 from electric organ of *Torpedo marmorata* (electric eel), a multiplicity of human ClCs have been resolved (ClC-1 to ClC-7, ClCKa and ClCKb). Defective ClC-5 yields Dent's disease (hypercalciuria, nephrolithiasis and low MW proteinuria). Defective ClCKb yields type III Bartter's syndrome (renal tubular malfunction, hypovolemia, hyponatremia and hypotension). The ClCs are involved in regulation of cell anion balance, pH, excitability and volume.

Table 4.1 Ca²⁺-ATPase, H⁺, K⁺-ATPase and Na⁺, K⁺-ATPase

Compound (class)	Plant (family) part	Enzyme / process inhibited (other targets) in vivo effects
Ca²⁺-ATPase (Ca²⁺/H⁺ antiporter pump)		4.1A
Alkaloid		4.1Aa
Nantenine (aporphine isoquinoline)	<i>Uvaria chamae</i> (Annonaceae), <i>Platycapnos spicata</i> (Papaveraceae)	Ca ²⁺ -ATPase (ATP-K ⁺ CH, Ca ²⁺ -CH, Ca ²⁺ -K ⁺ CH, Na ⁺ , K ⁺ -ATPase)
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Argemone</i> , <i>Bocconia</i> , <i>Chelidonium</i> , <i>Corydalis</i> , <i>Eschscholtzia</i> , <i>Glaucaum</i> , <i>Macleaya</i> , <i>Papaver</i> , <i>Sanguinaria</i> (Papaveraceae), <i>Fumaria</i> (Fumariaceae), <i>Zanthoxylum</i> (Rutaceae), <i>Pteridophyllum</i> (Sapindaceae) spp.	Ca ²⁺ -ATPase (70) (ATPase, CDPK, Diamine oxidase, MLCK, PKA, PKC, VAS-R) [antibacterial, AI]
Phenolic		4.1Ap
<i>cis</i> - <i>E</i> -3-Butylidene-4, 5,6,7-tetrahydro-6,7- dihydroxy-1(3H)- isobenzofuranone (benzofuranone)	<i>Polygonum multiflorum</i> (Polygonaceae) [root]	Ca ²⁺ -ATPase (160)
<i>trans</i> - <i>E</i> -3-Butylidene-4, 5,6,7-tetrahydro-6,7- dihydroxy-1(3H)- isobenzofuranone (benzofuranone)	<i>Polygonum multiflorum</i> (Polygonaceae) [root]	Ca ²⁺ -ATPase (260)
Ellagic acid (= Benzoic acid; Lagistase) (phenolic acid lactone)	Widespread [leaf]; ellagitannin product	Activates Ca ²⁺ -ATPase (at 50) (MLCK, PKA, PKC, p60 ^{src} TK) [anti-mutagen, haemostatic]
[6]-Gingerol (phenol)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	Activates Ca ²⁺ -ATPase (at 50) COX (PGS) [antiemetic, antiseratogenic]

(continued)

Table 4.1 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
[8]-Gingerol (phenol)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	Activates Ca ²⁺ -ATPase
α-Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	Ca ²⁺ -ATPase (CDPK, HIV-1 PR, H-R, MLCK, PKA) [antibacterial, AI, antiulcer]
(<i>E</i>)-2,3,5,4'- Tetrahydroxystilbene 2- <i>O</i> -β-D-glucopyranoside (stilbene phenolic glycoside)	<i>Polygonum multiflorum</i> (Polygonaceae) [root]	Ca ²⁺ -ATPase (240)
Terpene		4.1At
Gossypol (dimeric phenolic sesquiterpenoid)	<i>Gossypium</i> spp. (cotton), <i>Montezuma speciosissima</i> , <i>Thespesia populnea</i> (Malvaceae) [seed]	Ca ²⁺ -ATPase (CAMA, PK) [antifungal, antitumour, inhibits spermatogenesis]
Thapsigargin (guaianolide sesquiterpene lactone)	<i>Thapsia garganica</i> (Apiaceae)	Ca ²⁺ -ATPase [activates basophils, mast cells, neutrophils, secondary tumour promoter]
Other		4.1Ao
Calmodulin (= Ca ²⁺ - binding regulator protein; CaM) (18 kDa protein; (Ca ²⁺) ₄ -CaM)	Universal in eukaryotes; activated hydrophobic Ca ²⁺ ₄ -CaM form	Activates Ca ²⁺ -ATPase – PM Ca ²⁺ -ATPase (animals), PM & ER Ca ²⁺ -ATPase (plants) (10 nM) (activates PP2B, CAMKI-IV, MLCK, NADK, PhosbK)
Non-plant reference		4.1An
[Cyclopiazonic acid] (pentacyclic alkaloid mycotoxin)	<i>Aspergillus</i> & <i>Penicillium</i> spp. (fungi)	ER Ca ²⁺ -ATPase (HIV-1 PR, HIV-2 PR)
H⁺, K⁺-ATPase		4.1B
Phenolic		4.1Bp
Pentagalloylglucose (tannin)	<i>Acer</i> (Aceraceae), <i>Rhus</i> , <i>Cotinus</i> , <i>Schinus</i> (Anacardiaceae), <i>Terminalia</i> (Combretaceae), <i>Quercus</i> (Fagaceae), <i>Geranium</i> (Geraniaceae), <i>Nuphar</i> (Nymphaeaceae), <i>Epilobium</i> , <i>Fuchsia</i> (Onagraceae), <i>Paeonia</i> (Paeoniaceae), <i>Rosa</i> (Rosaceae), <i>Camellia</i> (Theaceae) spp.	H ⁺ , K ⁺ -ATPase (0.2, 10) (αGase; NADH DH, Na ⁺ , K ⁺ -ATPase) [anti-gastritis, anti-peptic ulcer]
Salvianolic acid A (stilbene, phenylpropanoid)	<i>Salvia miltiorhiza</i> (Lamiaceae)	H ⁺ , K ⁺ -ATPase [anti-peptic ulcer, inhibits gastric H ⁺ secretion]
Na⁺, K⁺-ATPase (Na ⁺ /K ⁺ -antipporter pump)	J. Skou (Denmark, Nobel Prize, Chemistry, 1997, Na⁺, K⁺-ATPase)	4.1C
Alkaloid		4.1Ca
Cassaine (diterpenoid alkaloid)	<i>Cassia carnaval</i> , <i>Erythrophleum guineense</i> , <i>E. suaveolens</i> [bark] (Fabaceae)	Na ⁺ , K ⁺ -ATPase [anaesthetic, cardiotonic, toxic]

(continued)

Table 4.1 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Cassaidine (diterpenoid alkaloid)	<i>Erythrophleum guineense</i> , <i>E. suaveolens</i> (Fabaceae) [bark]	Na ⁺ , K ⁺ -ATPase [anaesthetic, cardiotonic, cardiotoxic, convulsant]
Erythrophleguine (= 6- α - Hydroxycassamine) (diterpenoid alkaloid)	<i>Erythrophleum guineense</i> , <i>E. suaveolens</i> (Fabaceae) [bark]	Na ⁺ , K ⁺ -ATPase [cardiotonic, diuretic]
Harmaline (= 3,4- Dihydroharmine; Harmidine) (indole)	<i>Banisteria caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae)	Na ⁺ , K ⁺ -ATPase (NMDA- Glu-R inverse agonist) [anti- Parkinson's, ataxic, excitatory, hallucinogenic]
Nantenine (aporphine isoquinoline)	<i>Uvaria chamae</i> (Annonaceae), <i>Platycapnos spicata</i> (Papaveraceae)	Na ⁺ , K ⁺ -ATPase (ATP-K ⁺ CH, Ca ²⁺ -ATPase, Ca ²⁺ -CH, Ca ²⁺ -K ⁺ CH)
Shihunidine (benzofuranone tetrahydropyrrole)	<i>Dendrodium loddigesii</i> (Orchidaceae) [stem]	Na ⁺ , K ⁺ -ATPase
Shihunine (benzofuranone tetrahydropyrrole)	<i>Banisteriopsis caapi</i> (ayahuasca) (Malpighiaceae), <i>Dendrodium loddigesii</i> , <i>D. lohohense</i> , <i>D. pierardii</i> (Orchidaceae) [stem]	Na ⁺ , K ⁺ -ATPase
Phenolic		
Butein (= 2',4',3,4- Tetrahydroxychalcone) (chalcone)	<i>Dalbergia odorifera</i> , <i>Robinia pseudoacacia</i> , <i>Vicia faba</i> (Fabaceae) [wood]; glycosides in <i>Coreopsis douglasii</i> , <i>Bidens</i> spp. (Asteraceae) [flower], <i>Butea monosperma</i> , <i>B. frondosa</i> (Fabaceae) [flower]	4.1Cp Na ⁺ , K ⁺ -ATPase (<73) (EGF- RTK, F ₁ -ATPase, p60 ^{src} TK) [yellow pigment]
Fisetin (= 5-Deoxy- quercetin; 3,7,3',4'- Tetrahydroxyflavone) (flavonol)	<i>Rhus cotinus</i> , <i>R. rhodantha</i> (Anacardiaceae), <i>Acacia</i> spp., <i>Dalbergia odorifera</i> , <i>Glycine max</i> (Fabaceae) [heartwood]; as glycosides in <i>Rhus succedanea</i> (Anacardiaceae) [wood], <i>Trifolium subterraneum</i> (Fabaceae)	Na ⁺ , K ⁺ -ATPase (<56) (CDPK, ITDI, LOX, NADH DH, NEP, MLCK, PKA, PKC succinate DH) [allergenic, antibacterial, inhibits SM contraction & histamine release]
Galangin (= 3,5,7- Trihydroxyflavone) (flavonol)	<i>Escallonia</i> spp. (Saxifrageaceae), <i>Alpinia officinarum</i> (Zingiberaceae), Betulaceae, Lamiaceae, Salicaceae [bud], ferns [leaf]	Na ⁺ , K ⁺ -ATPase (<148) (CDPK, COX, MLCK, PKA) [antibacterial]
Luteolin (= 5,7,3',4'- Tetrahydroxyflavone) (flavone)	Widespread in leaves e.g. <i>Vitis vinifera</i> (grape) (Vitaceae) [leaf]; widespread as glycosides in Brassicaceae, Fabaceae, Lamiaceae, Scrophulariaceae [aerial]	Na ⁺ , K ⁺ -ATPase (<28), (ACE, AR, CDPK, ITDI, MLCK NADH DH, NEP, PKA, PKC, succinate DH, TOPII) [antibacterial, AI, nodulation signal]
Myricetin (= 3,5,7,3',4',5'- Hexahydroxyflavone) (flavonol)	<i>Haplopappus canescens</i> (Asteraceae), <i>Azadirachta indica</i> (neem), <i>Soymida febrifuga</i> (Meliaceae); glycosides in <i>Vaccinium</i> (Ericaceae), <i>Myrica</i> (Moraceae), <i>Primula</i> (Primulaceae), <i>Camellia</i> (Theaceae) spp.	Na ⁺ , K ⁺ -ATPase (<25) (CDPK, F ₁ -ATPase, IKK, 5- LOX, MLCK, NADH DH, NEP, PKA, succinate DH, TOPII) [antibacterial, antigonadotropic]

(continued)

Table 4.1 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Pentagalloylglucose (tannin)	<i>Paeonia filciflora</i> (Paeoniaceae) [dried root, <i>Paeonia Radix</i>]; anti-peptic ulcer plant	Na ⁺ , K ⁺ -ATPase (3) (H ⁺ , K ⁺ -ATPase, NADH DH) [anti-gastritis, anti-peptic ulcer]
Quercetagetin (= 6-Hydroxyquercetin; 3,5,6,7,3',4'- Hexahydroxyflavone) (flavonol)	<i>Eupatorium gracile</i> , <i>Tagetes</i> spp. (Asteraceae), other Asteraceae [flower], <i>Acacia catechu</i> (Fabaceae); glycosides in <i>Tagetes erecta</i> (marigold) (Asteraceae) [flower]	Na ⁺ , K ⁺ -ATPase (< 50) (AR, CDPK, F ₁ -ATPase, MLCK, PKA, TOPII) [antibacterial, yellow pigment]
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	Na ⁺ , K ⁺ -ATPase (< 26) (AR, cAMP PDE, CaM, F ₁ -ATPase, LOX, MDR-TR, NEP, PK, PS – EF-1α, RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
Terpene		4.1Ct
Asclepin (cyclic bridged cardiac glycoside)	<i>Asclepias curassavica</i> , <i>A.</i> spp. (Asclepiadaceae)	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Calactin (cyclic bridged cardiac glycoside)	<i>Asclepias curassavica</i> , <i>Calotropis procera</i> (Asclepiadaceae)	Na ⁺ , K ⁺ -ATPase [cardiotonic, stored by some insects for their defence, toxic]
[Carbenoxolone (= 18β- Glycyrrhetic acid hydrogen succinate)] (triterpene)	Metabolite of 18β-Glycyrrhetic acid	Na ⁺ , K ⁺ -ATPase (11βHSDH) [sodium retention per ↑ cortisol & ALDO-R activation as with 18β-Glycyrrhetic acid]
Convallatoxin (= Strophanthidin 3-O-α-1-rhamnoside) (cardenolide, cardiac glycoside)	<i>Convallaria majalis</i> (lily of the valley) [leaf], <i>Ornithogalum umbellatum</i> (star of Bethlehem) (Liliaceae), <i>Antiaris toxicaria</i> (Moraceae)	Na ⁺ , K ⁺ -ATPase (0.8) [cardiotonic, toxic]
Cymarín (= Strophanthidin 3-O-β-D-cymaroside) (cardenolide, cardiac glycoside)	<i>Strophanthus hispidus</i> , <i>S. kombé</i> , <i>Apocynum</i> spp. (Apocynaceae), <i>Castilleja elastica</i> (Moraceae), <i>Adonis vernalis</i> (Ranunculaceae)	Na ⁺ , K ⁺ -ATPase (0.3) [cardiotonic, toxic]
Diginatigenin (cardenolide)	<i>Digitalis lanata</i> , <i>D. lutea</i> (Scrophulariaceae) [leaf]; aglycone of Lanatoside D	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Digitalis (leaf extract)	<i>Digitalis purpurea</i> (foxglove) (Scrophulariaceae) [leaf extract] – William Withering (English physician & botanist) reported cardiotonic use for cardiac insufficiency- induced oedema (dropsy) (1785)	Na ⁺ , K ⁺ -ATPase – due to Digitoxin, Digitoxigenin, Digoxigenin, Gitoxigenin, Gitoxin [cardiotonic, toxic]

(continued)

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Table 4.1 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Digitoxin (=Digitoxigenin 3- <i>O</i> -tridigitoxoside) (cardenolide, steroid triterpene glycoside)	<i>Digitalis lanata</i> , <i>D. purpurea</i> (foxglove) (Scrophulariaceae) [digitalis]; high dose yields cloudy “yellow” vision & red-green perception changes (xanthopsia) – anti-epileptic use affected late “yellow” period of Vincent Van Gogh?	Na ⁺ , K ⁺ -ATPase (0.2) [60 nM] [bitter, cardiotoxic, cytotoxic (<0.1), toxic]
Digitoxigenin (cardenolide, steroid triterpene)	<i>Digitalis lanata</i> , <i>D. purpurea</i> (foxglove) (Scrophulariaceae); aglycone of Digitoxin & Lanatoside A	Na ⁺ , K ⁺ -ATPase (14 pM; 0.2) [cardiotoxic, cytotoxic (<0.1), toxic]
Digoxin (= Digoxigenin 3- <i>O</i> -tridigitoxoside) (cardenolide, steroid triterpene glycoside)	<i>Digitalis lanata</i> , <i>D. orientalis</i> , (Scrophulariaceae)	Na ⁺ , K ⁺ -ATPase (0.6) (PS) [50 nM] [cardiotoxic, cytotoxic (<0.1), toxic]
Digoxigenin (cardenolide, steroid triterpene)	<i>Digitalis lanata</i> , <i>D. orientalis</i> , <i>D. purpurea</i> (foxglove) (Scrophulariaceae); aglycone of Digoxin & Lanatoside C	Na ⁺ , K ⁺ -ATPase (0.3) [cardiotoxic, toxic]
Gitaloxigenin (cardenolide, steroid triterpene)	<i>Digitalis lanata</i> , <i>D. purpurea</i> (foxglove) (Scrophulariaceae)	Na ⁺ , K ⁺ -ATPase [cardiotoxic, toxic]
Gitoxigenin (cardenolide)	<i>Nerium oleander</i> (Apocynaceae), <i>Cryptostegia grandifolia</i> (Asclepidaceae), <i>Digitalis lanata</i> , <i>D. purpurea</i> (Scrophulariaceae); aglycone of Gitoxin & Lanatoside B	Na ⁺ , K ⁺ -ATPase [cardiotoxic, toxic]
Gitoxin (= Gitoxigenin 3- <i>O</i> -tridigitoxoside) (cardenolide, cardiac glycoside)	<i>Digitalis lanata</i> , <i>D. purpurea</i> (foxglove) (Scrophulariaceae)	Na ⁺ , K ⁺ -ATPase [cardiotoxic, toxic]
18β-Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (licorice) (Fabaceae) [rhizome, root]	Na ⁺ , K ⁺ -ATPase (ALDO-R, CBG, CORT-R, EST-R, 11βHSDH, SBG) [elevated cortisol, hypermineralo-corticoidism]
Glycyrrhizic acid (=Glycyrrhinic acid; Glycyrrhizin; Glycyrrhizinic acid) (triterpene saponin)	<i>Glycyrrhiza glabra</i> (licorice) (Fabaceae) [rhizome, root]	Na ⁺ , K ⁺ -ATPase (ALDO-R, CBG, CORT-R, EST-R, 11βHSDH, SBG) [anti-ulcerogenic, expectorant, sweet]
Gypenoside (triterpene glycoside)	<i>Gynostemma pentaphyllum</i> (Cucurbitaceae)	Na ⁺ , K ⁺ -ATPase (63) [apoptotic, antineoplastic, cytotoxic]
Hellebrigenin 3-acetate (bufodienolide)	<i>Bersama abyssinica</i> (Melianthaceae)	Na ⁺ , K ⁺ -ATPase
Lanatoside A (= Digitoxigenin glycoside) (cardenolide, cardiac glycoside)	<i>Digitalis lanata</i> , <i>D. lutea</i> , <i>D. viridiflora</i> (Scrophulariaceae) [leaf]	Na ⁺ , K ⁺ -ATPase [cardiotoxic, toxic]

(continued)

Table 4.1 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Lanatoside B (= Gitoxigenin glycoside) (cardenolide, cardiac glycoside)	<i>Digitalis lanata, D. lutea</i> (Scrophulariaceae) [leaf]	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Lanatoside C (= Digoxigenin glycoside) (cardenolide, cardiac glycoside)	<i>Digitalis lanata, D. lutea</i> (Scrophulariaceae) [leaf]	Na ⁺ , K ⁺ -ATPase [cardiotonic, cytotoxic (< 0.1), toxic]
Lanatoside D (= Diginatigenin glycoside) (cardenolide, cardiac glycoside)	<i>Digitalis lanata, D. lutea</i> (Scrophulariaceae) [leaf]	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Neriifolin (cardenolide, cardiac glycoside)	<i>Cerbera odollam, Thevetia nerifolia,</i> <i>T. peruviana, T. thevetioides</i> (yellow oleander) (Apocynaceae) [seed]	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Oleandrin (cardenolide, cardiac glycoside)	<i>Nerium oleander</i> (oleander) (Apocynaceae) [leaf]	Na ⁺ , K ⁺ -ATPase [cardiotonic, diuretic, toxic]
Oleandrigenin (cardenolide)	<i>Nerium oleander</i> (oleander) (Apocynaceae) [leaf]; aglycone of Oleandrin	Na ⁺ , K ⁺ -ATPase [cardiotonic, diuretic, toxic]
Ouabain (= Ouabagenin 3-O-1-rhamnoside; g-Strophanthidin) (cardenolide, cardiac glycoside, triterpene glycoside)	<i>Acokanthera ouabaio, A. schimperi,</i> <i>Strophanthus gratus</i> [seed] (Apocynaceae); endogenous animal Na⁺, K⁺-ATPase regulator	Na ⁺ , K ⁺ -ATPase (0.8) [5–40 nM] [cardiotonic, cytotoxic (< 0.1), natriuretic, toxic]
Ouabagenin (cardenolide)	<i>Acokanthera ouabaio, A. schimperi,</i> <i>Strophanthus gratus</i> [seed] (Apocynaceae); Ouabain aglycone; endogenous animal Na⁺, K⁺-ATPase regulator	Na ⁺ , K ⁺ -ATPase (2.4) [cardiotonic, toxic]
Peruvoside (= Cannogenin 3-O- α -1- thevetoside) (cardenolide, cardiac glycoside)	<i>Thevetia nerifolia, T. peruviana</i> (trumpet flower) (Apocynaceae) [seed]	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Proscillaridin A (bufadienolide cardiac glycoside)	<i>Scilla (Urginea) maritima</i> (Liliaceae) [bulb]	Na ⁺ , K ⁺ -ATPase [cardiotonic, cytotoxic (6 nM), toxic]
Saikosaponins A, B1-4, C, D & E (triterpene saponin)	<i>Bupleurum</i> spp. (Apiaceae) [root]	Na ⁺ , K ⁺ -ATPase
Scilliroside (= Scillirosidin 3-O- β -D- glucoside) (bufadienolide cardiac glycoside)	<i>Scilla (Urginea) maritima</i> (Liliaceae)	Na ⁺ , K ⁺ -ATPase [bitter, cardiotonic, rodenticide, toxic]
Scillaren A (= Scillarenin 3-O-glucosylrhamnoside; Transvaalin) (bufadienolide, triterpene glycoside)	<i>Scilla (Urginea) maritima</i> (Liliaceae)	Na ⁺ , K ⁺ -ATPase [bitter, cardiotonic, toxic]

(continued)

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Table 4.1 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
(25 <i>R,S</i>)-5 α -Spirostan-3 β -ol 3- <i>O</i> -glucosyl-[glucosyl]-galactoside (tetrasaccharide steroidal saponin)	<i>Allium chinense</i> (Liliaceae) [bulb]	Na ⁺ , K ⁺ -ATPase (40) (cAMP PDE)
Strophanthidin (cardenolide, triterpene)	<i>Strophanthus hispidus</i> , <i>S. kombé</i> (Apocynaceae), <i>Convallaria majalis</i> (Liliaceae), <i>Corchorus olitorius</i> (Tiliaceae); aglycone of Convallatoxin, Cymarin & Strophanthin	Na ⁺ , K ⁺ -ATPase (0.6) [cardiotonic, toxic]
Strophanthin (cardiac glycoside, cardenolide)	<i>Strophanthus hispidus</i> , <i>S. kombé</i> (Apocynaceae)	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Strophanthin K (cardiac glycoside, cardenolide)	<i>Strophanthus kombé</i> (Apocynaceae)	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Thesiuside (bufadienolide triterpene)	<i>Thesium lineatum</i> (Santalaceae); toxic plant (sheep poisoning)	Na ⁺ , K ⁺ -ATPase [toxic]
Thevetin A (= Cannogenin 3- <i>O</i> -gentiobiosylthevetoside) (cardenolide, cardiac glycoside)	<i>Thevetia nerifolia</i> (yellow oleander) (Apocynaceae) [seed]	Na ⁺ , K ⁺ -ATPase [toxic]
Thevetin B (= Cerberoside; Digitoxigenin 3- <i>O</i> -gentiobiosylthevetoside; Thevanil) (cardenolide, cardiac glycoside)	<i>Cerbera odollam</i> , <i>Thevetia nerifolia</i> (yellow oleander) (Apocynaceae) [seed]	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
Tyledosides C, D & F (bufadienolide triterpene)	<i>Tylecodon</i> spp. (Crassulaceae)	Na ⁺ , K ⁺ -ATPase [toxic]
Non-plant reference		
[Bufalin] (bufadienolide steroid)	<i>Bufo asiaticus</i> (Chinese toad) (dried venom = Ch'an Su, Senso)	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
[Cinobufagin] (bufadienolide steroid)	<i>Bufo asiaticus</i> (Chinese toad) (dried venom = Ch'an Su, Senso)	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
[Cinobufotalin] (bufadienolide steroid)	<i>Bufo asiaticus</i> (Chinese toad) (dried venom = Ch'an Su, Senso)	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
[Ethacrynic acid (= [4-(Methylenebutyryl)-2,3-dichlorophenoxy] acetic acid)] (chlorophenoxy acid)	Synthetic	Na ⁺ , K ⁺ -ATPase [diuretic]
[Gamabufotalin] (bufadienolide steroid)	<i>Bufo vulgaris formosus</i> (Japanese toad) (venom)	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
[Palytoxin] (polyhydroxypyran)	<i>Palythoa</i> spp. (zooanthid coral); Palytoxin is the most poisonous non-protein compound known	Na ⁺ , K ⁺ -ATPase (0.1) – opens ion channel on both sides of PM [cardiotonic, vasoconstrictant, very toxic]

(continued)

Table 4.1 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
[Resibufogenin] (bufadienolide steroid)	<i>Bufo</i> sp. (toad) (venom)	Na ⁺ , K ⁺ -ATPase [cardiotonic, toxic]
[2,4',5',6'- Tetrahydroxychalcone] (chalcone)	Semi-synthetic	Na ⁺ , K ⁺ -ATPase (< 15)
[3,3',4'- Trihydroxyflavone] (flavonol)	Semi-synthetic	Na ⁺ , K ⁺ -ATPase (30) (CDPK, MLCK, PKA)
Na⁺/Ca²⁺ antiporter (Na⁺/Ca²⁺ TR)		4.1D
[N-Acetyl sphingosine] (ceramide)	Animal	Na ⁺ /Ca ²⁺ TR (at 10)
[N-Hexanoyl sphingosine] (sphingolipid)	Semi-synthetic	Na ⁺ /Ca ²⁺ TR (at 10)
Sphingosine (= 1,3- Dihydroxy-2-amino-4- octadecene; 4- Sphingenine) (sphingolipid)	Universal; precursor of SIP, ceramide, sphingomyelin, glucosylcerebroside, globoside and ganglioside sphingolipids	Na ⁺ /Ca ²⁺ TR (at 3) (SPH-R, LTP)
Na⁺/H⁺ antiporter (Na⁺/H⁺ TR)		4.1E
Phenolic		4.1Ep
[Alpinumisoflavone] (prenyl isoflavone)	Semi-synthetic from Erythrinin B	Na ⁺ /H ⁺ TR (at > 60) [cytotoxic]
Erythrinin B (= Wighteone) (prenyl isoflavone)	<i>Argyrocytisus battandieri</i> [leaf], <i>Erythrina variegata</i> [bark], <i>Laburnum anagyroides</i> [leaf], <i>Lupinus albus</i> , <i>L. spp.</i> (Fabaceae) [fruit, leaf], <i>Maclura cochinchinensis</i> (Moraceae) [root]	Na ⁺ /H ⁺ TR (at 4) [antifungal, cytotoxic, phytoalexin]
[Erythrinin B triacetate (= Wighteone triacetate)] (prenyl isoflavone)	Semi-synthetic from Erythrinin B	Na ⁺ /H ⁺ TR (at 7) [cytotoxic]
Euchrenone b10 (prenyl isoflavone)	<i>Erythrina variegata</i> (Fabaceae) [bark]	Na ⁺ /H ⁺ TR (at 3) [cytotoxic]
1,3,5-Trihydroxy-4- (3-methylbut-2- enyl)xanthen-9-one (prenyl isoflavone)	<i>Maclura cochinchinensis</i> (Moraceae) [root]	Na ⁺ /H ⁺ TR (at 7) [cytotoxic]
Terpene		4.1Et
[25-Hydroxycholesterol] (sterol)	Generated by cooking from Cholesterol	Na ⁺ /H ⁺ TR (HMGCoAR)

Table 4.2 Voltage-gated Na⁺ channel

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) / in vivo effects
Voltage-gated sodium ion channel (V-Na⁺CH)		4.2
Alkaloid		4.2a
3-Acetylaconitine (diterpene)	<i>Aconitum flavum</i> (Ranunculaceae)	V-Na ⁺ CH activator (cf. Aconitine), site 2 [1] [antinociceptive (5×> morphine), antiarthritic, arrhythmic, hypotensive, slows heart rate, toxic]
Aconifine (= 10-Hydroxy-aconitine; Nagarine)	<i>Aconitum karakolicum</i> , <i>A. nagarum</i> (Ranunculaceae) [root]	Effects like Aconitine (V-Na ⁺ CH activator) [toxic]
Aconitine (= Acetylbenzoylaconine) (diterpene alkaloid)	<i>Aconitum carmichaelii</i> , <i>A. napellus</i> (wolfsbane), <i>A. spp.</i> (Ranunculaceae) [root, other parts]; the first poison wolfsbane made by Hecate from the froth of Cerberus	V-Na ⁺ CH activator (neurotoxin binding site 2 of α-subunit) (abolishes inactivation; causes channel to stay open) [1] (nACh-R) [antinociceptive (0.1), arrhythmic (at 10 nM), hypotensive, slows heart rate, very toxic]
Ajacine (= N-Acetyl-anthranilic acid ester of lycocotinine) (diterpene alkaloid)	<i>Aconitum spp.</i> , <i>Consolida ajacis</i> (Ranunculaceae)	V-Na ⁺ CH inhibitor (cf. Lappaconitine) [antiepileptiform, hypotensive]
Ajmaline (= Raugalline; Rauwolfine) (indole)	<i>Melodinus balansae</i> , <i>Rauwolfia serpentina</i> [root], <i>R. spp.</i> , <i>Tonduzia longifolia</i> (Apocynaceae), <i>Pausinystalia johimbe</i> (Rubiaceae)	V-Na ⁺ CH inhibitor (7) [antiarrhythmic, coronary artery dilatory]
6-Benzoylheteratisine (diterpene alkaloid)	<i>Aconitum spp.</i> (Ranunculaceae) [aerial, tuber]	V-Na ⁺ CH antagonist (abolishes Aconitine effect at 10) (Heteratisine inactive at 30) [antiarrhythmic, AI]
Bikhaconitine (diterpene alkaloid)	<i>Aconitum ferox</i> , <i>A. spicatum</i> , <i>A. violaceum</i> (Ranunculaceae) [root]	V-Na ⁺ CH (cf. Aconitine) [respiratory depressant, arrhythmogenic, toxic]
Cevadine (steroidal alkaloid)	<i>Schoenocaulon officinale</i> [seed], <i>Veratrum viride</i> (Liliaceae) [root]	V-Na ⁺ CH activator (abolishes inactivation; causes channel to stay open) [toxic]
Cocaine (= Benzoylmethylecgonine; Methylbenzoylecgonine) (tropane)	<i>Erythroxylum coca</i> (coca), <i>E. recurrens</i> , <i>E. steyermarkii</i> , <i>E. brouvianum</i> [leaf], <i>E. monogynum</i> [root] (Erythroxylaceae) [leaf]; 1.5 million US Cocaine users	V-Na ⁺ CH (inactivated form) blocker (catecholamine transport inhibition) [central nervous system (CNS) stimulant, local anaesthetic, mydriatic, narcotic]
Coronaridine (= Carbomethoxyibogamine) (indole)	<i>Tabernaemontana coronaria</i> , <i>Tabernanthe iboga</i> (Apocynaceae)	V-Na ⁺ CH antagonist [16] (O-R) [cytotoxic, diuretic, oestrogenic]
N-Deacetylappaconitine (diterpene alkaloid)	<i>Aconitum spp.</i> , <i>Delphinium spp.</i> (Ranunculaceae) [aerial, tuber]; metabolite derived from Lappaconitine	V-Na ⁺ CH inhibitor [antinociceptive, hypotensive, anti-arrhythmic, lowers heart rate]

(continued)

Table 4.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Delphinine (diterpene alkaloid)	<i>Atragene siberica</i> [root], <i>Delphinium staphisagria</i> [seed] (Ranunculaceae) [root]	Effects like Aconitine (V-Na ⁺ CH activator) [arrhythmogenic, bradycardic, hypotensive, respiratory depressant, toxic (Aconitine > Delphinine)]
Deoxyaconitine (diterpene alkaloid)	<i>Aconitum</i> spp. (Ranunculaceae)	Effects like Aconitine (V- gated Na ⁺ channel activator)
Falacnitine (=Pyropseudoaconitine) (diterpene alkaloid)	<i>Atragene falconeri</i> , (Ranunculaceae) [root]	Effects like Aconitine (V-Na ⁺ CH activator) [arrhythmogenic, convulsant, hypotensive, respiratory depressant, toxic]
Germidine (steroidal alkaloid)	<i>Schoenocaulon officinale</i> , <i>Veratrum album</i> , <i>V. viride</i> [rhizome] (Liliaceae)	V-Na ⁺ CH (TTX-resistant) activator [toxic; positive chronotropy & inotropy]
Harmaline (= 3,4- Dihydroharmine; Harmidine; 1-Methyl-7- methoxy-3,4 dihydro- β-carboline) (indole alkaloid)	<i>Banisteria caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum</i> <i>harmala</i> (Zygophyllaceae) [seed]	V-Na ⁺ CH antagonist [12] [ataxic, hallucinogenic, tremorigenic]
Harmine (= Banisterine; Leucoharmine; Telepathine; Yageine) (indole alkaloid)	<i>Banisteria caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Peganum</i> <i>harmala</i> , <i>Tribulus terrestris</i> (Zygophyllaceae) [seed]	V-Na ⁺ CH antagonist [11] [CNS stimulant, hallucinogenic]
Heteratisine (diterpene alkaloid)	<i>Aconitum heterophyllum</i> , <i>A. zeraschanicum</i> (Ranunculaceae) [aerial, tuber]	V-Na ⁺ CH antagonist (weak) [antiarrhythmic, AI, short hypertension, altered respiration]
Hypaconitine (= 3-Deoxymesaconitine) (diterpene alkaloid)	<i>Aconitum callianthum</i> , <i>A. carmichaelii</i> , <i>A. napellus</i> (Ranunculaceae)	V-Na ⁺ CH activator (cf. Aconitine), site 2 [1] [AI, antinociceptive (5× < Aconitine), arrhythmic, AP blocker, toxic]
Ibogaine (= 12-Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> (iboga), <i>Voacanga thouarsii</i> (Apocynaceae)	V-Na ⁺ CH [8; 9] (O-R) [anti- addictive, anti-convulsant, hallucinogenic]
Ibogamine (indole)	<i>Tabernanthe iboga</i> (iboga) (Apocynaceae)	V-Na ⁺ CH [8] (O-R, σ) [brachycardiac activity, cytotoxic, hypotensive]
Indaconitine (= 15-Deoxyaconitine) Pyropseudoaconitine) (diterpene alkaloid)	<i>Atragene falconeri</i> , <i>A. ferox</i> , <i>A. chasmanthum</i> (Ranunculaceae) [root]	Effects like Aconitine (V-Na ⁺ CH activator) [arrhythmogenic, hypotensive, respiratory depressant, toxic]
Jesaconitine (diterpene alkaloid)	<i>Aconitum carmichaelii</i> , <i>A. fischeri</i> , <i>A. sachalinense</i> , <i>A. subcuneatum</i> (Ranunculaceae)	Like Aconitine (V-Na ⁺ CH activator) [analgesic, slows heart, slows respiration, hypotensive, toxic]

(continued)

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Table 4.2 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Enzyme/process inhibited (other targets) in vivo effects </i>
Lappaconitine (diterpene alkaloid)	<i>Aconitum excelsum</i> , <i>A. orientale</i> , <i>A. ranunculaeifolium</i> , <i>A. septentrionale</i> , <i>A. simontanum</i> , <i>Delphinium</i> spp. (Ranunculaceae) [aerial, tuber]	V-Na ⁺ CH inhibitor [12] [AI, arrhythmic, antinociceptive (100× < Aconitine), anti- epileptiform, toxic (< Aconitine), respiratory inhibition]
Liriodenine (aporphine isoquinoline)	<i>Annona</i> spp., <i>Fissistigma</i> <i>glaucescens</i> , <i>Guatteria scadens</i> [fruit oil] (Annonaceae)	V-Na ⁺ CH (0.7)
Mesaconitine (= 3α- Hydroxyhyapaconitine) (diterpene alkaloid)	<i>Aconitum carmichaelii</i> , <i>A. napellus</i> , <i>A. spp.</i> (Ranunculaceae) [root, other parts]	V-Na ⁺ CH activator (cf. Aconitine; neurotoxin binding site 2 of α-subunit) (abolishes inactivation; causes channel to stay open) [AI, antinociceptive, arrhythmogenic, hypotensive, slows heart rate, very toxic]
Napelline (= Luciculine) (diterpene)	<i>Aconitum carmichaelii</i> , <i>A. napellus</i> , <i>A. spp.</i> (Ranunculaceae) [aerial, tuber]	V-Na ⁺ CH antagonist [antiarrhythmic, AI, hypotensive, altered respiration]
Pseudoaconitine (diterpene alkaloid)	<i>Atragene falconeri</i> , <i>A. ferox</i> , <i>A. spicatum</i> (Ranunculaceae) [root]	V-Na ⁺ CH activator (effects like Aconitine) [arrhythmogenic, hypotensive, respiratory depressant, toxic]
Quinidine (= Cinchinidine; Cinchocatine; Cinchonan-9-ol) (quinoline)	<i>Olea europaea</i> (olive), <i>Ligustrum</i> <i>vulgare</i> (Oleaceae) [leaf], <i>Cinchona officinalis</i> , <i>C. succirubra</i> , <i>C. tucujensis</i> , <i>Remijia</i> sp. (Rubiaceae)	V-Na ⁺ channel blocker (56) [antiarrhythmic, antimalarial]
(-)-Sparteine (= Lupinidine) (quinolizidine)	<i>Anagyris foetida</i> , <i>Baptisia</i> sp., <i>Cytisus scoparius</i> , <i>Lupinus</i> spp., <i>Piptanthus nanus</i> , <i>Sarothamnus</i> sp., <i>Spartium junceum</i> (Fabaceae), <i>Aconitum napellus</i> (Ranunculaceae)	V-Na ⁺ CH blocker (169) (nAChR agonist) [antiarrhythmic, diuretic, insect feeding stimulant, hypoglycaemic, oxytocic, toxic]
Tabernanthine (= 13-Methoxyibogamine) (indole)	<i>Conopharyngia</i> (<i>Tabernaemontana</i>) spp., <i>Stemmadenia</i> spp., <i>Tabernanthe</i> <i>iboga</i> (Apocynaceae)	V-Na ⁺ CH [8] (CBZ-R, O-R, σ-R) [CNS activity]
Veratridine (= 3-Veratroyl veracevine) (steroidal alkaloid)	<i>Schoenocaulon officinale</i> [seed], <i>Veratrum album</i> , <i>V. viride</i> [rhizome] (Liliaceae) (Liliaceae)	V-Na ⁺ CH activator (abolishes inactivation; causes channel to stay open) [toxic; parent alcohol Veracevine (= Protocevine) insecticidal]
Veratrine (= mixture of Cevadine, Cevine, Cevadilline, Sabadine & Veratridine) (steroidal alkaloid mixture)	<i>Schoenocaulon officinale</i> [seed], <i>Veratrum viride</i> [root] (Liliaceae)	V-Na ⁺ CH activator

(continued)

Table 4.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Yohimbine (= Aphrodine; Corynine; Hydroergotocin; Quebrachine) (indole)	<i>Catharanthus lanceus</i> [plant], <i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia</i> <i>yohimbe</i> (yohimbe) (Rubiaceae) [bark]	V-Na ⁺ CH ligand (22) (α 1A-R, α 2A-R, 5HT-R) [blocks vas deferens contraction [0.2]; Clonidine antagonism; antidepressant, aphrodisiac, mydriatic, toxic]
Phenolic		4.2p
Capsaicin (= <i>trans</i> -8-Methyl- <i>N</i> -[[4-hydroxy-3-methoxyphenyl)methyl]-6-nonenamide; <i>trans</i> -8-Methyl- <i>N</i> -vanillyl-6-nonenamide) (vanilloid phenolic)	<i>Capsicum annuum</i> (sweet pepper, paprika), <i>C. frutescens</i> (Solanaceae) [fruit], <i>Zingiber officinale</i> (Zingiberaceae)	V-Na ⁺ CH (VAN-R, V-K ⁺ CH) [burning sensation, bronchoconstrictive (1), desensitizes sensory neurons, irritant, tachykinin release, topical analgesic]
Daidzein (= 4',7-Dihydroxyisoflavone) (isoflavone)	<i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Phaseolus coccineus</i> , <i>Trifolium repens</i> , <i>Ulex europaeus</i> (Fabaceae)	V-Na ⁺ CH ligand (195) (GABAA-R)
Dihydrokawain (=Dihydronoson; Dihydrokavain) (phenolic derivative)	<i>Piper methysticum</i> (kava, yaqona) (Piperaceae) [root]; kava (yaqona = yangona) traditional Fiji drink	V-Na ⁺ CH ligand (30 nM)
Dihydromethysticin (phenolic derivative)	<i>Piper methysticum</i> (kava, yaqona) (Piperaceae) [rhizome, root]	V-Na ⁺ CH ligand (30 nM) [spasmolytic]
Genistein (= Genisteol; Prunetol; Sophoricol; 4', 5,7-Trihydroxyisoflavone) (isoflavone)	<i>Genista</i> spp., <i>Trifolium subterraneum</i> , <i>T. brachycalycinum</i> , <i>Phaseolus lunatus</i> (Fabaceae), <i>Prunus</i> spp. (Rosaceae) [wood]	V-Na ⁺ CH ligand (60) (GABAA-R, HISK, lipase, peroxidase, PK, RTK) [antifungal, oestrogenic]
Kawain (= Gonosan; Kavain) (phenolic derivative)	<i>Piper methysticum</i> (kava, yaqona) (Piperaceae) [root]	V-Na ⁺ CH ligand (30 nM) [AI, local anaesthetic, antimycotic, spasmolytic]
Terpene		4.2t
Asebotoxins I, II (grayanotoxin-type diterpenes)	<i>Pieris japonica</i> (Ericaceae)	V-Na ⁺ CH activator (open state) [toxic]
Asebotoxins III (grayanotoxin-type diterpene)	<i>Pieris japonica</i> (Ericaceae)	V-Na ⁺ CH activator (open state) [toxic]
Grayanotoxin I (=Acetylandromedol; Andromedotoxin; Asebotoxin; G-1; Rhodotoxin) (grayanotoxin diterpene)	<i>Kalmia latifolia</i> , <i>Leucothoe grayana</i> , <i>L. spp.</i> , <i>Rhododendron</i> spp. (Ericaceae); in honey from Rhododendron-feeding bees	V-Na ⁺ CH activator [hypotensive, toxic]
Grayanotoxin II (grayanotoxin diterpene)	<i>Kalmia latifolia</i> , <i>Leucothoe grayana</i> , <i>L. spp.</i> , <i>Rhododendron</i> spp. (Ericaceae); in honey from <i>Rhododendron</i> -feeding bees	V-Na ⁺ CH activator [hypotensive, toxic]
Grayanotoxin III (grayanotoxin diterpene)	<i>Kalmia latifolia</i> , <i>Leucothoe grayana</i> , <i>L. spp.</i> , <i>Pieris japonica</i> [leaf], <i>Rhododendron</i> spp. (Ericaceae); in honey from <i>Rhododendron</i> -feeding bees	V-Na ⁺ CH activator [hypotensive, toxic]

(continued)

Table 4.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Grayanotoxins (~30 isolated) (grayanotoxin diterpenes)	<i>Kalmia latifolia</i> , <i>Leucothoe grayana</i> , <i>L. spp.</i> , <i>Rhododendron</i> spp. (Ericaceae); in honey from <i>Rhododendron</i> -feeding bees	Related Grayanotoxins I–III are V-Na ⁺ CH activators [hypotensive, toxic]
Pyrethrin I (= Chrysanthemum monocarboxylic acid pyrethrolone ester) (monoterpene)	<i>Tanacetum (Chrysanthemum) cinerariifolium</i> (pyrethrum) (Asteraceae); Leopold Ruzicka (Croatia/Switzerland, Nobel Prize, 1939, Chemistry, polymethylenes & terpenes)	V-Na ⁺ CH activator (persistent open state) [allergic dermatogenic, CNS active, insecticidal, respiratory depressant, toxic]
Pyrethrin II (= Chrysanthemum dicarboxylic acid monomethyl ester pyrethrolone ester) (monoterpene)	<i>Tanacetum (Chrysanthemum) cinerariifolium</i> (pyrethrum) (Asteraceae)	V-Na ⁺ CH activator (persistent open state) [allergic dermatogenic, CNS active, insecticidal, respiratory depressant, toxic]
Other		4.2o
Docosapentaenoic acid (= C22:6n-3) (unsaturated FA)	Widespread in plant oils	V-Na ⁺ CH ligand (30) [antiarrhythmic]
Eicosapentaenoic acid (C20:5n-3) (unsaturated FA)	Widespread in plant oils	V-Na ⁺ CH ligand (30) [antiarrhythmic]
Eicosatetraenoic acid (C20:4n-3) (unsaturated FA)	Widespread in plant oils	V-Na ⁺ CH ligand (30) [antiarrhythmic]
Linoleic acid (unsaturated FA)	Widespread in plant oils	V-Na ⁺ CH ligand (30) [antiarrhythmic]
Linolenic (unsaturated FA)	Widespread in plant oils	V-Na ⁺ CH ligand (30) [antiarrhythmic]
γ1-Zeathonin (4 disulphide cysteine knot polypeptide)	<i>Zea mays</i> (Poaceae) [seed]	V-Na ⁺ CH blocker [cf. non-plant <i>Conus</i> sp. μ-Conotoxins]
γ2-Zeathonin (4 disulphide cysteine knot polypeptide)	<i>Zea mays</i> (Poaceae) [seed]	V-Na ⁺ CH blocker [cf. non-plant <i>Conus</i> sp. μ-Conotoxins]
Non-plant reference		4.2n
[AaIT] (polypeptide)	<i>Androctonus australis</i> (Buthid scorpion venom)	V-Na ⁺ CH activator [1–3 nM]
[μ-Agatoxin-I] (cystine knot polypeptide)	Spider venom	V-Na ⁺ CH activator (blocks channel inactivation) [toxic]
[Allethrin I (= Allethrolone ester of Chrysanthemum monocarboxylic acid)] (monoterpene, cyclopropane carboxylic acid ester)	Synthetic Type I pyrethroid analogue of Pyrethrin I	V-Na ⁺ CH (esp. TTX-resistant) activator (persistent open state, hyperexcitation) [insecticidal, proconvulsant, toxic]
[Allethrin II (= Allethrolone ester of Chrysanthemum monocarboxylic acid)] (monoterpene, cyclopropane carboxylic acid ester)	Synthetic Type I pyrethroid analogue of Pyrethrin I	V-Na ⁺ CH (esp. TTX-resistant) activator (persistent open state, hyperexcitation) [insecticidal, proconvulsant, toxic]

(continued)

Table 4.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
[Amiloride] (pyrazine carboxamide)	Synthetic	V-Na ⁺ CH
[Anthopleurins A & B (= sea anemone toxins ApA & ApB)] (polypeptide)	<i>Anthopleura xanthogrammica</i> (sea anemone)	V-Na ⁺ CH ligand (blocks Na ⁺ current decay)
[Atracotoxins] (polypeptides)	Funnel web spiders (Australia)	V-Na ⁺ CH activators (persistent open state, inactivation inhibited)
[Batrachotoxinin A] (steroid alkaloid)	<i>Phyllobates</i> sp. (South American poison dart frog) [skin]	V-Na ⁺ CH activator (persistent open state, inactivation inhibited)
[Batrachotoxinin-A-20 α-benzoate] (steroid alkaloid)	Semi-synthetic from Batrachotoxinin A	V-Na ⁺ CH activator (persistent open state, inactivation inhibited) (28 nM)
[Batrachotoxins (many others)] (steroid alkaloids)	Frog; also found in bird feathers (passerine birds, Pitohui spp., Itohui spp. – sequestered from a toxic source for self-defence)	V-Na ⁺ CH activators (persistent open state, inactivation inhibited)
[Brevetoxins A, B & C (= BTXs A, B & C)] (polyalicyclic polyether)	<i>Pyrodiclus brevis</i> (<i>Gymnodinium breve</i>) (toxic “red tide” dinoflagellate)	V-Na ⁺ CH activator [lipid- soluble, toxic]
[Bukatoin (α- type Scorpion toxin)] (polypeptide)	<i>Buthus martensi</i> (scorpion)	V-Na ⁺ CH activator (blocks channel inactivation) [toxic]
[δ-Conotoxin] (polypeptide)	<i>Conus textile</i> (poisonous sea mollusc)	V-Na ⁺ CH activators (persistent open state, inactivation inhibited)
[μ-Conotoxin] (polypeptide)	<i>Conus</i> sp. (poisonous sea mollusc)	V-Na ⁺ CH blocker
[DDT (= α,α-Bis (p- chlorophenyl)-β,β,β- trichloroethane)] (chlorinated aromatic)	Synthetic; Paul Müller (Switzerland, Nobel Prize, Medicine, 1948, DDT as insect contact poison)	V-Na ⁺ CH activator (persistent open state) [insecticidal, toxic]
[Deltamethrin] (brominated cyclopropane carboxylic acid ester)	Synthetic Type II (α-cyano group) pyrethroid	V-Na ⁺ CH (both TTX- sensitive & TTX-resistant) activator (persistent open state; depolarization, block, paralysis) [insecticide, proconvulsant, toxic]
[Dibucaine] (quinoline carboxamide tertiary amine)	Synthetic	V-Na ⁺ CH blocker (inhibits AP) (23) [allergic contact dermatitogenic, local anaesthetic, antiarrhythmic]
[Fenvalerate (= Phenvalerate)] (chlorinated aryl carboxylic acid ester)	Synthetic Type II (α-cyano group) analogue of Pyrethrin I	V-Na ⁺ CH (both TTX- sensitive & TTX-resistant) activator (persistent open state; depolarization, block, paralysis) [insecticide, proconvulsant, toxic]
[Flunarizine] (aryl piperazine)	Synthetic	V-Na ⁺ CH blocker (Ca ²⁺ channel blocker) [antinociceptive]

(continued)

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Table 4.2 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Enzyme/process inhibited (other targets) in vivo effects </i>
[Geographutoxin II (= GTXII)] (polypeptide)	<i>Conus geographicus</i> (cone shell mollusc)	V-Na ⁺ CH blocker (at 0.1–1)
[Lamotrigine] (aryl triazine)	Synthetic	V-Na ⁺ CH blocker [anticonvulsant, antinociceptive]
[Lidocaine (= 2-Diethylamino)- <i>N</i> -(2,6-dimethylphenyl)-acetamide)] (aryl tertiary amine)	Synthetic	V-Na ⁺ CH blocker (inhibits AP) (204, 326) [allergic contact dermatitogenic, local anaesthetic, antiarrhythmic]
[Permethrin] (chlorinated aryl cyclopropane carboxylic acid ester)	Synthetic Type I pyrethroid analogue of Pyrethrin I	V-Na ⁺ CH (esp. TTX-resistant) activator (persistent open state, hyperexcitation) [insecticidal, proconvulsant, toxic]
[Pumiliotoxin B] (alkaloid)	Frog skin	V-Na ⁺ CH activator
[Robustoxin] (42 residue, 4 disulphide cysteine knot polypeptide)	<i>Atrax robustus</i> (Sydney funnel web spider) [venom]	V-Na ⁺ CH ligand
[Saxitoxin (= mussel/clam poison; STX)] (guanidinium tricyclic imine)	<i>Gonyaulax catenella</i> , <i>G. tumarensis</i> (“red tide” dinoflagellates) [contaminates clam, mussel, scallop]	V-Na ⁺ CH blocker [toxic]
[β-Scorpion toxins] (polypeptides)	Scorpion venom	V-Na ⁺ CH blockers (block channel activation) [toxic]
[Tetracaine] (benzoic acid ester tertiary and secondary amine)	Synthetic	V-Na ⁺ CH blocker (inhibits AP) (0.7) [local anaesthetic, topical anaesthetic]
[Tetrodotoxin (= Fugu poison; TTX)] (guanidinium alicyclic)	<i>Spheroides rubripes</i> (puffer fish) (Tetraodontidae) [liver, ovary] – notwithstanding careful preparation about 100 fatalities per year from Japanese puffer fish delicacy fugu	V-Na ⁺ CH blocker [1–10 nM] [extremely toxic]
[Versutoxin] (cysteine knot polypeptide)	<i>Hadronyche versuta</i> (Australian Blue Mountains funnel web spider)	V-Na ⁺ CH activator (slows channel inactivation)

Table 4.3 Ligand- and voltage-gated K⁺ channels

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Enzyme/process inhibited (other targets) in vivo effects </i>
ATP-sensitive K⁺ channel (ATP-K⁺CH)		4.3A
Alkaloid		4.3Aa
ATP (nucleoside triphosphate)	Universal; synthesized by Lord Todd (UK, Nobel Prize, Chemistry, 1957, nucleotides)	ATP-K ⁺ CH

(continued)

Table 4.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Caffeine (= 1,3,7-Trimethylxanthine; Coffeine; Guaranine; Thein; Theine) (purine, methylxanthine); the plant bioactive most consumed by humans?	<i>Ilex paraguayensis</i> (maté) (Aquifoliaceae), <i>Coffea arabica</i> , <i>Coffea</i> spp. (coffee) (Rubiaceae) [coffee bean], <i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Cola acuminata</i> (cola) (Sterculiaceae) [seed], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	ATP-K ⁺ CH (A ₁ AD-R, A ₂ AD-R, cAMP PDE, cGMP PDE, ryanodine R) [bitter; cardiac, CNS & respiratory stimulant, diuretic, smooth muscle relaxant, vasodilator]
Nantenine (aporphine isoquinoline)	<i>Uvaria chamae</i> (Annonaceae), <i>Platycodon spicatus</i> (Papaveraceae)	Activates ATP-K ⁺ CH (Ca ²⁺ -ATPase, Ca ²⁺ -CH, Ca ²⁺ -K ⁺ CH, Na ⁺ , K ⁺ -ATPase)
(-)-Sparteine (= Lupinidine) (quinolizidine alkaloid)	<i>Anagyris foetida</i> , <i>Baptisia</i> sp., <i>Cytisus scoparius</i> , <i>Lupinus luteus</i> , <i>L. nigra</i> , <i>Piptanthus nanus</i> , <i>Sarothamnus</i> sp., <i>Spartium junceum</i> (Fabaceae), <i>Aconitum napellus</i> (Ranunculaceae)	ATP-K ⁺ CH [171] (V-Na ⁺ CH) [cardiotonic, depolarizes, diuretic, insect feeding stimulant, oxytocic, toxic]
Phenolic		4.3Ap
(-)-Epiatzelechin (flavan-3-ol)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial], <i>Camellia sinensis</i> (Theaceae) [leaf]	ATP K ⁺ CH ligand (> 10) (α1A-R, α2A-R, βA-R, D2-R, COX-1, 5HT1A R, O R) [AI with carrageenin-induced paw edema]
Ethyl gallate (phenolic)	<i>Phyllanthus urinaria</i> (Euphorbiaceae), <i>Haematoxylum campechianum</i> (Fabaceae) [leaf]	Opens ATP-K ⁺ CH (Ca ²⁺ -K ⁺ CH) [hyperpolarizes, SM relaxant]
Methyl gallate (phenolic)	<i>Phyllanthus urinaria</i> (Euphorbiaceae), <i>Acacia farnesiana</i> (Fabaceae) [plant]	Opens ATP-K ⁺ CH (Ca ²⁺ -K ⁺ CH) [hyperpolarizes, SM relaxant]
Pedunculagin (= 2,3 Hexahydroxydiphenoyl 4,5- hexahydroxydiphenoyl glucose) (ellagitannin)	<i>Casuarina stricta</i> (Casuarinaceae), <i>Quercus</i> sp. (Fagaceae), <i>Potentilla</i> sp., <i>Rubus</i> spp. (Rosaceae), <i>Stachyurus praecox</i> (Stachyuraceae), <i>Camellia japonica</i> (Theaceae)	ATP-K ⁺ CH ligand (> 10) (α2A-R, βA-R, D1-R, GPT, O-R) [inhibits Epinephrine-induced adipocyte lipolysis]
β-1,2,3,4,6-Penta-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark], <i>Geranium thunbergii</i> (Geraniaceae), <i>Paeonia lactiflora</i> (Paeoniaceae)	ATP-K ⁺ CH ligand (> 10) (α2A-R, D1-R, D2-R, O-R)
Tellimagrandin I (= 4,5 Hexahydroxydiphenoyl 2,3-digalloylglucose) (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Quercus</i> (Fagaceae), <i>Syzygium</i> , <i>Feijoa</i> , <i>Psidium</i> , <i>Eucalyptus</i> (Myrtaceae), <i>Fuchsia</i> (Onagraceae), <i>Geum</i> , <i>Rosa</i> , <i>Tellima</i> (Rosaceae), <i>Stachyurus</i> (Stachyuraceae), <i>Camellia</i> (Theaceae) spp.	ATP-K ⁺ CH ligand (> 10) (α1A-R, α2A-R, D2-R, GPT, O-R) [inhibits Epinephrine-induced adipocyte lipolysis]
β-1,2,4,6-Tetra-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark]	ATP-K ⁺ CH ligand (> 10) (α2A-R, βA-R, D2-R, O-R)

(continued)

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Table 4.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Terpene		4.3At
Betulinic acid (lupene triterpene); so far isolated from some 460 plant species, indicative of the plant distribution complexity dimension	Widespread; <i>Diospyros</i> (Ebenaceae), <i>Rhododendron</i> (Ericaceae), <i>Psophocarpus</i> (Fabaceae), <i>Syzygium</i> (Myrtaceae), <i>Solanum</i> (Solanaceae), <i>Clerodendrum</i> (Verbenaceae)	ATP-K ⁺ CH ligand (8) (CDPK, HIV-1 PR, PKA, PKC) [antineoplastic]
Other		4.3Ao
Ethyl- α -D-glucopyranoside (sugar)	<i>Clerodendrum mandarinorum</i> (Verbenaceae) [root bark]	ATP-K ⁺ CH ligand (8)
Non-plant reference		4.3An
[Amantadine (= 1-Aminoadamantane)] (polyalicyclic amine)	Synthetic	ATP-K ⁺ CH [120]
[Glibenclamide (= Glyburide)] (aryl sulphonylurea)	Synthetic	ATP-K ⁺ CH [1 nM; 2 nM] (CFTR) [antidiabetic, \uparrow insulin secretion]
[Gliclazide (= Diamicon)] (aryl sulphonylurea)	Synthetic	ATP-K ⁺ CH [antidiabetic, \uparrow insulin secretion]
[Glimepiride] (aryl sulphonylurea)	Synthetic	ATP-K ⁺ CH [antidiabetic, \uparrow insulin secretion]
[Glipizide] (pyrazinecarboxamido arylsulphonylurea)	Synthetic	ATP-K ⁺ CH [antidiabetic, hypoglycaemic, \uparrow insulin secretion]
[Repaglinide] (carbamoylmethyl benzoic acid)	Synthetic	ATP-K ⁺ CH [antidiabetic, \uparrow insulin secretion]
Ca²⁺-dependent K⁺ channel (Ca²⁺-K⁺ CH)		4.3B
Alkaloid		4.3Ba
Caffeine (= 1,3,7-Trimethylxanthine; Coffeine; Guaranine; Thein; Theine) (purine, methylxanthine)	<i>Ilex paraguayensis</i> (Aquifoliaceae), <i>Coffea arabica</i> , <i>Coffea</i> spp. (Rubiaceae), <i>Paullinia cupana</i> (Sapindaceae), <i>Cola acuminata</i> (Sterculiaceae) [seed], <i>Camellia sinensis</i> (Theaceae) [leaf]	Activates Ca ²⁺ -K ⁺ CH (A ₁ AD-R, A ₂ AD-R, cAMP PDE, cGMP PDE, ryanodine R) [cardiac, CNS & respiratory stimulant, diuretic, smooth muscle relaxant, vasodilator]
Nanténine (aporphine isoquinoline)	<i>Uvaria chamae</i> (Annonaceae), <i>Platycapnos spicata</i> (Papaveraceae)	Activates Ca ²⁺ -K ⁺ CH (ATP-K ⁺ CH, Ca ²⁺ -ATPase, Ca ²⁺ -CH, Na ⁺ , K ⁺ -ATPase)
[Paxilline] (indole)	<i>Acremonium lolii</i> -infected <i>Lolium perenne</i> (perennial rye grass)	Ca ²⁺ -K ⁺ CH (IP ₃ -R; precursor of mACh-R agonist & tremorgen Lolitrem B) [tremorgen mycotoxin]
Theophylline (= 1,3-Dimethylxanthine) (methylxanthine)	<i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Theobroma cacao</i> (Sterculiaceae) [seed], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	Activates Ca ²⁺ -K ⁺ CH (AD-R, cAMP PDE) [cardiac stimulant, coronary vasodilator, diuretic, smooth muscle relaxant, anti-asthmatic]

(continued)

Table 4.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
Phenolic		
Ethyl gallate (phenolic)	<i>Phyllanthus urinaria</i> (Euphorbiaceae), <i>Haematoxylum campechianum</i> (Fabaceae) [leaf]	4.3Bp Opens Ca^{2+} - K^+ CH (ATP- K^+ CH) [hyperpolarizes, SM relaxant]
Methyl gallate (phenolic)	<i>Phyllanthus urinaria</i> (Euphorbiaceae)	Opens Ca^{2+} - K^+ CH (ATP- K^+ CH) [hyperpolarizes, SM relaxant]
Nordihydroguaiaretic acid (= NDGA) (lignan)	<i>Guaicum officinale</i> , <i>G. sanctum</i> <i>Larrea</i> spp. (Zygophyllaceae) [resin]	Opens Ca^{2+} - K^+ CH (V- Ca^{2+} CH, V- K^+ CH) [antibacterial, antifungal, antioxidant, antitumour]
Terpene		
Dehydrosoyasaponin I (triterpene glycoside)	<i>Desmodium adscendens</i> (Fabaceae); Ghana anti-asthma herb	4.3Bt Opens Ca^{2+} - K^+ CH [0.1] (from inside only)
Voltage-gated potassium ion channel (V-K^+CH)		
Alkaloid		
Caffeine (= 1,3,7-Trimethylxanthine; Coffeine; Guaranine; Thein; Theine) (purine, methylxanthine)	<i>Ilex paraguayensis</i> (Aquifoliaceae), <i>Coffea</i> spp. (Rubiaceae), <i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Cola acuminata</i> (Sterculiaceae), <i>Camellia sinensis</i> (Theaceae)	4.3Ca V- K^+ CH (A_1 AD-R, A_2 AD-R, cAMP PDE, cGMP PDE (ryanodine R) [cardiac, CNS & respiratory stimulant, diuretic, smooth muscle relaxant, vasodilator]
Quinine (quinoline)	<i>Cinchona officinalis</i> , <i>C.</i> spp., <i>Remijia pedunculata</i> (Rubiaceae)	V- K^+ CH (MDR-TR) [antifibrillatory, antimalarial, very bitter]
(-)-Sparteine (= Lupinidine) (quinolizidine alkaloid)	<i>Anagyris foetida</i> , <i>Baptisia</i> sp., <i>Cytisus scoparius</i> , <i>Lupinus luteus</i> , <i>L. nigra</i> , <i>Piptanthus nanus</i> , <i>Sarothamnus</i> , <i>Spartium</i> spp. (Fabaceae), <i>Aconitum napellus</i> (Ranunculaceae)	V- K^+ CH (ATP- K^+ CH) [cardiotonic, depolarizes, diuretic, insect feeding stimulant, oxytocic, toxic]
Phenolic		
Capsaicin (= <i>trans</i> -8-Methyl- <i>N</i> -[[4-hydroxy-3-methoxyphenyl)methyl]-6-nonenamide; <i>trans</i> -8-Methyl- <i>N</i> -vanillyl-6-nonenamide) (vanilloid phenolic)	<i>Capsicum annuum</i> (sweet pepper, paprika) [fruit], <i>C. frutescens</i> (Solanaceae), <i>Zingiber officinalis</i> (Zingiberaceae)	4.3Cp V- K^+ CH (VAN-R, V- Na^+ CH) [burning sensation, bronchoconstrictive (1), desensitizes sensory neurons, irritant, tachykinin release, topical analgesic]
Inositol hexaphosphate (= IP ₆ ; Phytic acid) (cyclitol hexaphosphate)	Widespread esp. in seeds of Brassicaceae (oilseed), Fabaceae & Poaceae (grain seed)	V- K^+ CH (plant stomatal guard cell inward rectifying) [ABA induces IP ₆ → V- K^+ CH block → stomatal closure; hypocalcemic]
Nordihydroguaiaretic acid (= NDGA) (lignan)	<i>Guaicum officinale</i> , <i>G. sanctum</i> <i>Larrea</i> spp. (Zygophyllaceae) [resin]	V- K^+ CH (10) (Ca^{2+} - K^+ CH (V- Ca^{2+} CH)[antibacterial, antifungal, antioxidant, antitumour]
Procyanidins (condensed tannins)	Widespread; <i>Crataegus monogyna</i> , <i>C. oxyacantha</i> (Rosaceae)	Activate V- K^+ CH

(continued)

Table 4.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited (other targets) in vivo effects
Terpene Azadirachtin (limonoid nortriterpene)	<i>Azadirachta indica</i> (neem tree) (Meliaceae); multi-millennial Indian anti-insect use; cited over plant resource rights of indigenous people	4.3Ct V-K ⁺ CH (ECMOX) [insect antifeedant]
Other Acetophenone (= Acetylbenzene) (aryl ketone)	<i>Cistus ladaniferus</i> (Cistaceae), <i>Orthodon</i> (Lamiaceae), <i>Stirlingia</i> (Proteaceae), <i>Populus</i> (Salicaceae), <i>Urtica</i> (Urticaceae) spp.	4.3Co Abolishes V-K ⁺ CH block by Zn ²⁺ (OD-R) [hypnotic, odorant]
Non-plant reference [4-Aminopyridine] (aminopyridine)	Synthetic	4.3Cn V-K ⁺ CH [depolarizes]
[Amitriptyline] (dibenzoheptene tertiary amine)	Synthetic	V-K ⁺ CH [antiemetic, depolarizes, tranquilizer]
[Chlorpromazine] (phenothiazine tertiary amine)	Synthetic	V-K ⁺ CH [depolarizes, tricyclic antidepressant]
[α -Dendrotoxin] (7 kDa protein; 6 Cys)	<i>Dendroaspis angusticeps</i> (green mamba snake venom)	V-K ⁺ CH (Kv1.1, Kv1.2 & Kv1.6 channels) (at nM)
[Dendrotoxin K] (7 kDa protein; 6 Cys)	<i>Dendroaspis polylepis</i> (black mamba snake venom)	V-K ⁺ CH (Kv1.1 channel) (at nM)
[Imipramine] (dibenzazepine tertiary amine)	Synthetic	V-K ⁺ CH [depolarizes, tricyclic antidepressant]
[Phencyclidine (= PCP; 1-(1-Phenylcyclohexyl)- piperidine) (piperidine, tertiary amine)	Synthetic; drug of abuse (angel dust); addictive, dangerous, psychotic effects	V-K ⁺ CH (5HT-TR, NMDA- Glu-R) [analgesic, anaesthetic, depressant, psychotic, schizophrenia mimetic]
[Tetraethylammonium] (quaternary ammonium cation)	Synthetic	V-K ⁺ CH [depolarizes]
[Verapamil] (aromatic tertiary amine)	Synthetic	V-K ⁺ CH (L-type Ca ²⁺ channel) [antianginal, antiarrhythmic, anti-hypertensive, coronary vasodilator]

Table 4.4 Voltage- and ligand-gated Ca²⁺ channels and Na⁺/Ca²⁺ antiporter

Compound (class)	Plant (family) part	Target / process inhibited (other targets) in vivo effects
Voltage-gated calcium ion channel (V-Ca²⁺ CH)		4.4A
Alkaloid Antioquine (bisbenzylisoquinoline)	<i>Guatteria boliviana</i> (Annonaceae) [stem bark]	4.4Aa L-type Ca ²⁺ CH blocker

(continued)

Table 4.4 (Continued)

Compound (class)	Plant (family) part	Target/process inhibited (other targets) in vivo effects/
Berberamine (= Berberine) (bisbenzylisoquinoline)	<i>Berberis aquifolium</i> , <i>B. thunbergii</i> , <i>B. vulgaris</i> , <i>Mahonia aquifolium</i> (Berberidaceae), <i>Atherosperma moschatum</i> (Monimiaceae)	V-Ca ²⁺ (nACh-R antagonist)
Crychine (pavine)	<i>Cryptocarya chinensis</i> (Lauraceae)	Ca ²⁺ CH (V- & R-regulated)
7-O-Demethylisothalicberine (bisbenzylisoquinoline)	<i>Berberis chilensis</i> (Berberidaceae)	Ca ²⁺ CH [cardiodepressor, chronotropic (180), negative inotropic (150)]
Dauricine (bisbenzylisoquinoline)	<i>Menispermum dauricum</i> , <i>M. canadense</i> (Menispermaceae)	L-type V-Ca ²⁺ CH (nACh-R antagonist) [AI, anaesthetic, toxic]
Daurisoline (bisbenzylisoquinoline)	<i>Menispermum dauricum</i> (Menispermaceae)	P-type Ca ²⁺ channel (CaM, CaM-PDE) [inhibits ADP- induced PA]
Dictamnine (= Dictamine) (furoquinoline)	<i>Adiscanthus fusciflorus</i> , <i>Aegle marmelos</i> , <i>Afraegle paniculata</i> , <i>Casimiroa edulis</i> , <i>Dictamnus albus</i> , <i>D. dasycarpus</i> , <i>Esenbeckia</i> spp., <i>Flanderia</i> spp., <i>Geigeria</i> spp., <i>Glycosmis</i> spp., <i>Haplophyllum</i> spp., <i>Ruta graveolens</i> (rue), <i>Zanthoxylum</i> spp. (Rutaceae)	V-Ca ²⁺ CH & norepinephrine-induced Ca ²⁺ CH opening (SM) (DNA) [vasorelaxant; phototoxic contact dermatitis, photo- induced genotoxicity]; contributes to rue phototoxic phytodermatitis
Ethaverine (benzylisoquinoline)	<i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [opium exudate]	L-type Ca ²⁺ CH [blocks catecholamine secretion]
Evodiamine (indole)	<i>Araliopsis tabouensis</i> (Araliaceae), <i>Evodia rutaecarpa</i> (Rutaceae)	Ca ²⁺ CH (Phenylephrine- α 2A-R-regulated) [vasorelaxant]
Glaucine (= Boldine dimethyl ether) (aporphine isoquinoline)	<i>Annona squamosa</i> (Annonaceae), <i>Dicentra eximia</i> , <i>Corydalis ambigua</i> (Fumariaceae), <i>Beilschmiedia podagrica</i> (Lauraceae), <i>Eschscholzia californica</i> , <i>Glaucium flavum</i> (Papaveraceae)	V-Ca ²⁺ CH (cAMP PDE) [antitussive, hypotensive]
Harman (= 1-Methyl- β -carboline) (β -carboline, indole)	<i>Passiflora edulis</i> , <i>P. incarnata</i> (Passifloraceae), <i>Sickingia rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> , <i>Zygophyllum fabago</i> (Zygophyllaceae)	L-type Ca ²⁺ CH ligand (α 1- A-R, BZ-R, DNA, 5HT2-R) [convulsant, cytotoxic]
Harmine (= Banisterine; Leucoharmine; Telepathine; Yageine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> (Zygophyllaceae)	L-type Ca ²⁺ CH (α 1A-R, MAO-A) [CNS stimulant, hallucinogenic; WW2 Nazi Gestapo use as "truth drug"]

(continued)

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Table 4.4 (Continued)

Compound (class)	Plant (family) / part/	Target/process inhibited (other targets) / in vivo effects/
Hernandezine (=Thalicimine; Thaliximine) (bisbenzylisoquinoline)	<i>Stephania hernandiifolia</i> (Menispermaceae) [fish poison use], <i>Thalictrum simplex</i> (Ranunculaceae)	V-Ca ²⁺ CH [AI]
Lacinilene C 7-methyl ether (sesquiterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae)	Enhances Ca ²⁺ movement per V-Ca ²⁺ CH [likely causative agent of cotton dust-induced byssinosis]
Laudanosine (= Laudanine methyl ether) (benzylisoquinoline)	<i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [opium exudate]	L-type Ca ²⁺ CH ligand (26), (α 1A-R, GABAA-R, μ 1O-R) [analgesic, convulsive, hypotensive, tetanic, toxic]
Liriodenine (= Spermatheridine) (benzylisoquinoline)	Widespread; <i>Annona cherimolia</i> , <i>A. spp.</i> , <i>Guatteria scadens</i> (Annonaceae), <i>Liriodendron tulipifera</i> , <i>Magnolia obovata</i> (Magnoliaceae)	L-Ca ²⁺ CH (at 0.1–100) (α 1A-R) [vasodilator]
Nanténine (aporphine isoquinoline)	<i>Uraria chamae</i> (Annonaceae), <i>Platycodon spicata</i> (Papaveraceae)	Ca ²⁺ -CH (ATP-K ⁺ CH, Ca ²⁺ -ATPase, Ca ²⁺ -K ⁺ CH, Na ⁺ , K ⁺ -ATPase)
Norshinsunine (aporphine isoquinoline)	<i>Annona cherimolia</i> , <i>A. glabra</i> , <i>A. squamosa</i> (Annonaceae)	L-Ca ²⁺ CH (at 0.1–100) (α 1A-R) [vasodilator]
Papaveraldine (benzylisoquinoline)	<i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [opium exudate]	[V-gated Ca ²⁺ entry inhibition]
Papaverine (benzylisoquinoline)	<i>Rauwolfia serpentina</i> (Apocynaceae), <i>Papaver bracteatum</i> , <i>P. somniferum</i> (opium poppy) (Papaveraceae) [opium flower exudate]	L-Ca ²⁺ CH (34) (A-R, cAMP PDE, cGMP PDE, Na ⁺ K ⁺ ATPase) [spasmolytic, SM relaxant, vasodilator, coronary vasodilator, antitussive]
Ryanodine (diterpene pyrrole alkaloid)	<i>Ryania speciosa</i> (Flacourtiaceae)	L-Ca ²⁺ CH (45) (RY-R) [insecticide, vasoconstrictant per RY-R agonist action]
Taxine A (aryl tertiary amine)	<i>Taxus baccata</i> (yew) (Taxaceae) [leaf]	L-Ca ²⁺ CH (0.6)
Tetramethylpyrazine (pyrazine)	<i>Ligusticum wallichii</i> (Apiaceae), <i>Glycine max</i> , <i>Glycyrrhiza glabra</i> [root] (Fabaceae), <i>Capsicum annuum</i> (Solanaceae), <i>Camellia sinensis</i> (Theaceae) [leaf]	V-Ca ²⁺ CH & IP ₃ -mediated ↑ cytosolic Ca ²⁺ [hypotensive, vascular relaxant]
(+)-Tetrandine (bisbenzylisoquinoline)	<i>Cissampelos pareira</i> , <i>Cyclea pellata</i> , <i>Stephania tetrandia</i> , <i>S. discolor</i> (Menispermaceae)	V-Ca ²⁺ CH (L-Ca ²⁺ CH) [also inhibits Bradykinin- & Angiotensin II- induced, IP ₃ - mediated ↑ cytosolic Ca ²⁺ , analgesic, AI, antipyretic, antitumour, apoptotic]
[Thaligrisine] (bisbenzyltetra- hydroisoquinoline)	Semi-synthetic	L-Ca ²⁺ CH (diltiazem displacement) [2] (α 1A-R)
Thaliporphine (aporphine isoquinoline)	<i>Neolitsea konishii</i> (Lauraceae)	↑ DHP-sensitive (L-type) Ca ²⁺ influx [positive inotropic, vasoconstrictant]

(continued)

Table 4.4 (Continued)

Compound (class)	Plant (family) part	Target/process inhibited (other targets) in vivo effects/
Phenolic		4.4Ap
Cinnamophilin (= -(8 <i>R</i> , 8' <i>S</i>)-4,4'- Dihydroxy-3,3'- dimethoxy-7-oxo-8,8'- neolignan) (neolignan)	<i>Cinnamomum philippense</i> (Lauraceae)	V-Ca ²⁺ CH (at 1–15) (TXA2- R) [PAI, relaxant]
8-Epiblechnic acid (= des(α-Carboxy-3,4- dihydroxyphenethyl) lithospermic acid) (benzofuran)	<i>Salvia miltiorrhiza</i> (Lamiaceae)	Ca ²⁺ CH (ER) [hypotensive, vasodilator]
Fargesone A & B (monoeoxylignans)	<i>Magnolia fargesii</i> (Magnoliaceae)	Ca ²⁺ CH
Hyperforin (phloroglucinol)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae); major herbal antidepressant	P-Ca ²⁺ CH (at 0.8)
Kurarinone (flavanone)	<i>Sophora angustifolia</i> , <i>S. flavescens</i> (Fabaceae) [root]	Ca ²⁺ CH [vasodilatory]
Liriodendrin (lignan)	<i>Liriodendrum tulipifera</i> (Magnoliaceae) [bark], <i>Boerhaavia diffusa</i> (Nyctaginaceae) [root], <i>Penstemon deustus</i> (Scrophulariaceae)	Ca ²⁺ CH
NDGA (lignan)	<i>Guaicum officinale</i> , <i>G. sanctum</i> <i>Larrea</i> spp. (Zygophyllaceae) [resin]	V-Ca ²⁺ CH (3) (Ca ²⁺ -K ⁺ CH, V-K ⁺ CH) [antibacterial, antifungal, antioxidant, antitumour]
Paeoniflorin (benzoyl polycyclic glycoside)	<i>Paeonia albiflora</i> , <i>P. lactiflora</i> , <i>P. mouton</i> , <i>P. officinalis</i> , <i>P. suffricosa</i> (Paeoniaceae)	L-Ca ²⁺ CH [inhibits atrial contraction induced by Veratrine and Veratridine; antiallergic, anti- coagulant, PAI]
Pd-Ia (= 3'-Angeloyloxy- 4'-acetoxy-3',4'- dihydroselesin) (coumarin)	<i>Peucedanum praeruptorum</i> (Apiaceae) ["Qian hu"]	Ca ²⁺ CH [inhibits Concanavalin A-induced anaphylactic mediator release from mast cells (79)]
Pd-C-II (coumarin)	<i>Peucedanum decursivum</i> (Apiaceae) ["Qian hu"]	Ca ²⁺ CH [inhibits Concanavalin A-induced anaphylactic mediator release from mast cells (100)]
Pd-C-III (coumarin)	<i>Peucedanum decursivum</i> (Apiaceae) ["Qian hu"]	Ca ²⁺ CH [inhibits Concanavalin A-induced anaphylactic mediator release from mast cells (102)]
Pd-C-IV (coumarin)	<i>Peucedanum decursivum</i> (Apiaceae) ["Qian hu"]	Ca ²⁺ CH [inhibits Concanavalin A-induced anaphylactic mediator release from mast cells (73)]
Tinctormine (quinochalcone C-glycoside)	<i>Carthamus tinctorius</i> (Asteraceae)	Ca ²⁺ CH [yellow pigment]

(continued)

Table 4.4 (Continued)

Compound (class)	Plant (family) part	Target/process inhibited (other targets) in vivo effects
(-)-Trachelogenin (lignan)	<i>Arctium lappa</i> , <i>Cnicus benedictus</i> (Asteraceae), <i>Ipomoea cairica</i> (Convolvulaceae)	Ca ²⁺ -CH (HIV-1 RT)
Vexibinol (flavanone)	<i>Sophora flavescens</i> (Fabaceae) [root]	Ca ²⁺ CH [vasodilatory]
Visnadin (= Cardine; Carduben; Provismine; Vibeline; Visnamine) (dihydropyranocoumarin)	<i>Ammi visnaga</i> , <i>Anethum</i> sp., <i>Ferula</i> sp. (Apiaceae)	Ca ²⁺ CH [coronary vasodilator, spasmolytic]
Terpene		4.4At
Abscisic acid (= ABA; Abscisin II; Dormin) (sesquiterpene)	Universal in plants as growth regulator; high in <i>Persea</i> <i>gratissima</i> (avocado) (Lauraceae) [fruit], <i>Gossypium hirsutum</i> (cotton) (Malvaceae) [fruit]	Activates V-Ca ²⁺ CH (ABA → H ₂ O ₂ → ⊕ V-Ca ²⁺ CH (plant stomata) [regulates abscission, bud dormancy & stomatal closure]
14-Acetoxycedrol (= 14- Acetyl 8,14-cedranediol) (sesquiterpene)	<i>Juniperus squamata</i> (Pinaceae)	V-gated Ca ²⁺ channel blocker [vasorelaxant]
14-Acetoxy-7β-(3'- ethylcrotonoyloxy)- notonipetranone (terpene)	<i>Tussilago farfara</i> (coltsfoot) (Asteraceae) [bud]	L-Ca ²⁺ CH [1] (PAF-R) [blocks PAF- & carageenan- induced oedema]
1,9-Dideoxyforskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae)	Ca ²⁺ CH (nACh-R antagonist, MDR, inactive as AC activator)
Farnesol (linear sesquiterpene)	Widespread in plant oils	N-type Ca ²⁺ CH (at 0.3)
3β-Formyloxyurs-11-en- 18,13β-olide (triterpene)	<i>Eucalyptus camaldulensis</i> (Myrtaceae) [leaf]	Ca ²⁺ CH [spasmolytic]
Forskolin (labdane diterpenoid)	<i>Coleus barbatus</i> , <i>C. forskohlii</i> (Lamiaceae)	Ca ²⁺ CH (AC activator, nACh-R antagonist, MDR) [hypotensive per arterial SM relaxation, increases cAMP, increases heart rate]
Fraxinellone (degraded limonoid nortriterpene)	<i>Melia azedarach</i> (Meliaceae), <i>Dictamnus dasycarpus</i> (Rutaceae)	V-Ca ²⁺ CH [vasorelaxant]
Ginsenoside Rf (triterpene glycoside saponin)	<i>Panax ginseng</i> (ginseng) (Araliaceae) [root]	N-Ca ²⁺ CH (via PTX- sensitive Go/Gi-linked R) (40) [antistress]
Ginsenosides Rb1, Rc, Re, Rf & Rg1 (triterpene glycoside saponins)	<i>Panax ginseng</i> (ginseng) (Araliaceae) [root]	V-Ca ²⁺ CH (at 100) [antistress, inhibit adrenal chromaffin cell catecholamine secretion]
Jatrophone (jatrophone A diterpene)	<i>Jatropha elliptica</i> , <i>J. gossypifolia</i> (Euphorbiaceae)	L-Ca ²⁺ CH [antitumour, uterine relaxant]
Lacinilene C 7-methyl ether (sesquiterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [bract, cotton dust]	↑ Ca ²⁺ influx per V-Ca ²⁺ CH [implicated in cotton dust- induced byssinosis of cotton workers, tracheal SM constrictant]

(continued)

Table 4.4 (Continued)

Compound (class)	Plant (family) part	Target/process inhibited (other targets) in vivo effects
Panaxadiol saponins (triterpene saponins)	<i>Panax ginseng</i> (ginseng) (Araliaceae) [root]	[L-, T- & B-Ca ²⁺ CH (at 1000–1500)]
Panaxatriol saponins (triterpene saponins)	<i>Panax ginseng</i> (ginseng) (Araliaceae) [root]	[L-, T- & B-Ca ²⁺ CH (at 200–300)]
<i>Panax</i> saponins (triterpene saponins)	<i>Panax notoginseng</i> (Araliaceae) [root]	Ca ²⁺ CH
S-Petasin (sesquiterpene)	<i>Petasites formosanus</i> (Asteraceae)	L-Ca ²⁺ CH [hypotensive]
Stevioside (= Steviol triglycoside) (kaurane diterpene glycoside)	<i>Stevia phlebophylla</i> , <i>S. rebaudiana</i> (Asteraceae) [leaf]; sweetener in Thailand	Ca ²⁺ CH (sweet)
Ursolic acid lactone (triterpene)	<i>Eucalyptus camaldulensis</i> (Myrtaceae) [leaf]	Ca ²⁺ CH [spasmolytic]
Ursolic acid lactone acetate (triterpene)	<i>Eucalyptus camaldulensis</i> (Myrtaceae) [leaf]	Ca ²⁺ CH [spasmolytic]
Xanthorrhizol (sesquiterpene)	<i>Iostephane heterophylla</i> (Asteraceae), <i>Curcuma xanthorrhiza</i> , <i>Zingiber officinale</i> (Zingiberaceae)	V-Ca ²⁺ CH & R-regulated Ca ²⁺ CH [vascular relaxant]
Other		4.4Ao
α-L-Rha-(1→4)-O-β-D- Glc-(1→6)-β-D-Glc (trisaccharide)	<i>Schefflera bodinieri</i> (Araliaceae) [leaf, root]	L-Ca ²⁺ CH ligand (8) [3] (5HT2-R)
<i>Psychotria</i> Cyclopsychotride A (31 aa; 3 kDa; cyclic protein)	<i>Psychotria longipes</i> (Rubiaceae)	↑ intracellular Ca ²⁺ (NT- independent) (NT-R)
<i>Purularia</i> thionin (5 kDa protein)	<i>Purularia pubera</i> (buffalo nut) Santalaceae) [nut]	↑ Ca ²⁺ influx [induces AA & prolactin release, toxic]
<i>Viscum</i> Viscotoxins (A2, A3, B, ThiVa1, ThiVa2) (5 kDa; 6 Cys; thionin protein)	<i>Viscum album</i> (mistletoe) (Viscaceae) [leaf & stem]	Action via Ca ²⁺ CH (blocked by Verapamil) [cytotoxic]
Non-plant reference		4.4An
[Azidopine] (1,4-dihydropyridine)	Synthetic dihydropyridine (DHP)	L-type Ca ²⁺ CH [5 nM]
[6-Benzylaminopurine (= BAP)] (purine)	Synthetic	↑ DHP-sensitive (L-type) Ca ²⁺ influx (moss) (at 1 nM) [plant cytokinin – antisenescence, growth regulator, mitogenic]
[ω-Conotoxin] (protein)	<i>Conus</i> (gastropod) [venom]	N-type Ca ²⁺ CH
[3,4-Dihydropapaverine] (benzylisoquinoline)	Semi-synthetic	DHP-binding & L-type Ca ²⁺ CH blocker (diltiazem displacement) (104) (α1A-R)
[Diltiazem] (aryl benzothiazepin)	Synthetic	L-type Ca ²⁺ CH [antianginal, antiarrhythmic, antihypertensive, coronary vasodilator]

(continued)

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Table 4.4 (Continued)

Compound (class)	Plant (family) / part/	Target/process inhibited (other targets) / in vivo effects/
[Gabapentin (= 1-(Aminomethyl)- cyclohexaneacetic acid)] (alicyclic amine carboxylic acid)	Synthetic	V-Ca ²⁺ CH (via GABA(B)-R) [anticonvulsant]
[Haloperidol] ((fluorobenzoyl hydroxypiperidino chlorobenzene))	Synthetic	V-Ca ²⁺ CH (D2-R)
[Kinetin (= <i>N</i> -6- Furfurylaminopurine) (purine)]	Generated from DNA breakdown	↑ DHP-sensitive (L-type) Ca ²⁺ influx (moss); ↑ Azidopine binding [130 pM] [plant cytokinin – antisenescent, growth regulator, mitogenic]
[8-Methoxydiltiazem] (benzothiazepine)	Synthetic	L-type Ca ²⁺ CH blocker (>Diltiazem)
[<i>N</i> -Methylpapaverine] (benzylisoquinoline)	Semi-synthetic	[V-gated Ca ²⁺ entry inhibition]
[Nicardipine] (arylamino pyridine)	Synthetic	V-gated Ca ²⁺ entry (GABAA-R & Gly-R Cl ⁻ channels)
[Nifedipine] (aryl dihydropyridine)	Synthetic	DHP-Ca ²⁺ CH (Gly-R Cl ⁻ channel); [L-type Ca ²⁺ CH (0.8 nM; 90 nM; antihypertensive]
[Nimodipine] (aryl dihydropiperidine)	Synthetic	Ca ²⁺ CH blocker [antihypertensive, vasodilator]
[Nitrendipine] (Dihydropyridine)	Synthetic	Ca ²⁺ CH blocker [0.3 nM] (Gly-R Cl ⁻ channel) [antihypertensive]
[Papaverinol] (benzylisoquinoline)	Semi-synthetic	[V-gated Ca ²⁺ entry inhibition]
[Prymnesin-1, Prymnesin- 2] (long-chain acetylenic, polycyclic, aliphatic)	<i>Prymnesium parvum</i> (“red tide” dinoflagellate) [toxic]	[Ca ²⁺ -enhanced ichthyotoxic – Ca ²⁺ (300 nM), + Ca ²⁺ (3nM)]
Tetrahydropapaverine (tetrahydro-benzo isoquinoline)	Semi-synthetic	DHP-binding & L-type Ca ²⁺ CH (102) (α1A-R)
[Tetrahydropapaveroline] (benzoisoquinoline)	Semi-synthetic	DHP-binding Ca ²⁺ CH blocker L-type Ca ²⁺ channel blocker (weak)
[Verapamil] (aryl tertiary amine)	Synthetic	L-type Ca ²⁺ CH (6 nM) (Gly-R Cl ⁻ channel) [L-type Ca ²⁺ CH (30 nM; 5); antianginal, antiarrhythmic, antihypertensive, coronary vasodilator]

(continued)

Table 4.4 (Continued)

Compound (class)	Plant (family) part	Target/process inhibited (other targets) in vivo effects/
IP₃-gated Ca²⁺ channel (IP₃ receptor) (IP₃-R)		
4.4B		
Helenalin (pseudoguaianolide sesquiterpene lactone)	<i>Anaphalis</i> , <i>Arnica</i> , <i>Balduina</i> , <i>Eupatorium</i> , <i>Gaillardia</i> , <i>Helenium</i> spp., <i>Inula helenium</i> (Asteraceae)	Potentiates IP ₃ -R-dependent ER Ca ²⁺ release (AROM) [toxic]
Inositol 1,4,5-triphosphate (= IP ₃) (phosphorylated cyclitol)	Universal in plants & animals	Opens IP ₃ -R [IP ₃ -specific ER Ca ²⁺ release]
[Paxilline] (indole)	<i>Acremonium lolii</i> -infected <i>Lolium perenne</i> (perennial rye grass)	IP ₃ -R (Precursor of mACh-R agonist & tremorgen Lolitrem B) [tremorgen mycotoxin]
NAADP-gated Ca²⁺ channel (NAADP receptor) (NAADP-R)		
4.4C		
Nicotinic acid adenine dinucleotide 2'-phosphate (= NAADP) (adenine nucleotide)	Universal in animals; likely universality in plants (NAADP-induced Ca ²⁺ release)	Opens NAADP-R [NAADP-specific ER Ca ²⁺ release]
ER Ca²⁺-induced channel Ca²⁺ release channel		
4.4D		
Caffeine (= 1,3,7-Trimethylxanthine; Coffeine; Guaranine; Thein; Theine) (purine, methylxanthine)	<i>Ilex paraguayensis</i> (maté) (Aquifoliaceae), <i>Coffea</i> spp. (Rubiaceae), <i>Paullinia cupana</i> (Sapindaceae), <i>Cola acuminata</i> (Sterculiaceae), <i>Camellia sinensis</i> (Theaceae) [leaf]	Opens ER Ca ²⁺ channel (A ₁ AD-R, A ₂ AD-R, ATP-, Ca ²⁺ - & V-K ⁺ CH, cAMP PDE, cGMP PDE, RY-R) [stimulant, diuretic, smooth muscle relaxant, vasodilator]
[Eudistomin D] (pyridinoindole)	From marine tunicate <i>Eudistoma olivaceum</i>	Opens non-RYR, caffeine-opened Ca ²⁺ channel
[9-Methyl-7-bromo-eudistomin] (pyridinoindole)	Semi-synthetic from tunicate-derived Eudistomin D	Opens non-RYR, caffeine-opened Ca ²⁺ channel (1000× > Caffeine)
Ryanodine-gated Ca²⁺ channel (Ryanodine receptor) (RY-R)		
4.4E		
Abscisic acid (= ABA) (sesquiterpene)	Universal in plants as abscission, dormancy & stomatal closure phytohormone; John Cornforth (Australia, UK, Nobel Prize, 1975, Chemistry, terpenes)	Induces cADPR-mediated RY-R opening [leaf abscission, bud dormancy, stomatal closure]
Caffeine (= 1,3,7-Trimethylxanthine; Coffeine; Guaranine; Thein; Theine) (purine, methylxanthine)	<i>Ilex paraguayensis</i> (maté) (Aquifoliaceae), <i>Coffea arabica</i> (Rubiaceae), <i>Paullinia cupana</i> (Sapindaceae), <i>Cola acuminata</i> (Sterculiaceae), <i>Camellia sinensis</i> (Theaceae)	Opens RY-R (A ₁ AD-R, A ₂ AD-R, ATP-, Ca ²⁺ - & V- K ⁺ CH, cAMP PDE, cGMP PDE) [stimulant, diuretic, smooth muscle relaxant, vasodilator]
Calmodulin (= Ca ²⁺ -binding regulator protein; CaM) (18 kDa protein; (Ca ²⁺) _i -CaM)	Universal in eukaryotes; activated hydrophobic (Ca ²⁺) _i -CaM form	Promotes cADPR-dependent RY-R opening (activates Ca ²⁺ -ATPase, CaMKI-IV, MLCK, NADK, PhosbK, PP2B)

(continued)

Table 4.4 (Continued)

Compound (class)	Plant (family) / part/	Target/process inhibited (other targets) / in vivo effects/
Cyclic adenosine-5'-diphosphate ribose (= cADPR) (purine nucleotide)	Universal in animals; likely universality in plants (cADPR-induced Ca^{2+} release)	Opens RY-R (Ca^{2+} -CaM participates) [cADPR-specific ER Ca^{2+} release]
Nicotinamide (= Niacinamide; 3-Pyridine carboxylic acid amide) (pyridine)	Universal (in coenzymes NAD^+ & NADP^+ involved in redox reactions)	ADP-ribosyl cyclase (catalyses synthesis of cADPR & NAADP)
Nicotinic acid (= Niacin; Pyridine 3-carboxylic acid) (pyridine)	<i>Oryza sativa</i> (rice seed coat), <i>Solanum tuberosum</i> (potato tuber) (Solanaceae); Fabaceae, Poaceae seed; low in <i>Zea mays</i> (corn seed) (Poaceae) – pellagra from deficiency	Precursor of Nicotinamide [dietary deficiency gives pellagra – diarrhoea, irritability, skin rash, dementia (insane asylum before cure recognized)]
Ryanodine (diterpene, indole alkaloid)	<i>Ryania speciosa</i> (Flacourtiaceae)	Opens RY-R [ER Ca^{2+} release, muscle contraction, vascular constriction]
Non-plant reference		4.4En
[8-Amino-cyclic ADP-ribose (= 8-Amino-cADPR)] (purine nucleotide)	Synthetic	RY-R
[Bromoeudistomin] (pyridinoindole)	Semi-synthetic	RY-R
[Procaine (= 2-Diethylaminoethyl <i>p</i> -aminobenzoate)] (aryl ester, tertiary amine)	Synthetic	RY-R [local anaesthetic]
[Ruthenium red (= $[(\text{NH}_3)_3\text{Ru}-\text{O}-\text{Ru}(\text{NH}_3)_4-\text{O}-\text{Ru}(\text{NH}_3)_3]\text{Cl}_6$) (metal coordination complex)]	Synthetic	RY-R [microscopy dye]
Sphingolipid-gated Ca^{2+} channel (Sphingolipid receptor) (SPH-R)		4.4F
[Psychosine (= D-Galactosyl- β -1,1'-sphingosine)] (sphingolipid)	Widespread lipid mediator in animals; likely to be in plants	Inactive as SPH-R ligand
Sphingosine (= 1,3-Dihydroxy-2-amino-4-octadecene; 4-Sphingenine) (sphingolipid)	Universal; named after the enigmatic Sphinx by discoverer Johann Thudichum (physician, chemist, German)	SPH-R (weak) – phosphorylated by sphingosine kinase \rightarrow SIP
Sphingosine-1-phosphate (= SIP) (sphingolipid)	Universal; likely signaller in plants and fungi as well as animals	SPH-R (SPC-specific ER Ca^{2+} release)
Sphingosylphosphocholine (= SPC) (sphingolipid)	Universal	SPH-R (SPC-specific ER Ca^{2+} release)
Non-plant reference		4.4Fn
[Fumonisin (e.g. Fumonisin B1, B2)] (mycotoxins)	<i>Fusarium moniliforme</i> (fungus) – plant pathogen e.g. plant leaf, <i>Zea mays</i> (corn) (Poaceae) seed	Sphinganine/Sphingosine N-acyltransferase [carcinogenic, toxic]

Table 4.5 CFTR, voltage-gated Cl⁻ channels and Na⁺-K⁺-2Cl⁻ co-transporter

Compound (class)	Plant (family) part	Target/process inhibited (other targets) in vivo effects
CFTR		
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Widespread; <i>Apium</i> , <i>Daucus</i> spp. (Apiaceae), <i>Achillea</i> , <i>Matricaria</i> spp. (Asteraceae), <i>Mentha</i> , <i>Oreganum</i> , <i>Thymus</i> spp. (Lamiaceae), ferns [leaf surface]; <i>Digitaria-exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	4.5A Stimulates CFTR (11) (BZ-R-like R, EST-R, PK, RTK, TPO) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
Daidzein (= 4',7-Dihydroxy-isoflavone) (isoflavone)	<i>Glycine max</i> , <i>Trifolium repens</i> , <i>Ulex europaeus</i> (Fabaceae); 7-O-glucoside (Daidzin) in <i>Baptisia</i> spp., <i>Glycine max</i> , <i>Pueraria</i> spp., <i>Trifolium pratense</i> (Fabaceae)	Stimulates CFTR (DNAP, EST-R, GABAA-R, lipase, TOPII, TPO) [antifungal, phytoestrogen]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxy-isoflavone) (isoflavone)	Widespread; <i>Genista</i> , <i>Glycine</i> , <i>Phaseolus</i> , <i>Trifolium</i> spp. (Fabaceae); <i>Prunus</i> spp. (Rosaceae) [wood], glucosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora japonica</i> (Fabaceae) [pod]	Stimulates CFTR (14) (AD-R, EGF-RTK, GABAA-R, HSK, lipase, MLCK, peroxidase, RTK, TOPII, TPO) [antifungal, oestrogenic]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koelreuteria henryi</i> (Sapindaceae)	Stimulates CFTR (6) (AROM, CDPK, EGF-RTK, EST-R, MLCK, PKA, RTK, TPO)
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	Stimulates CFTR (22) (AR, cAMP PDE, F ₁ -ATPase, 11βHSDH, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, NEP, PK, PS-EF-1α, RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
Rice factor (unknown)	<i>Oryza sativum</i> (Poaceae) [boiled rice seed]	Blocks cAMP-dependent CFTR activation [antidiarrhoea]
Non-plant reference		
[Glibenclamide (= Glyburide)] (aryl sulphonylurea)	Synthetic	4.5An CFTR (ATP-K ⁺ CH) [antidiabetic, ↑ insulin secretion]
[4-Phenylbutyrate] (aryl carboxylic acid)	Synthetic	[Increases PM CFTR expression]
Voltage-gated ClC		
[5-Nitro-2-(3- phenylpropylamino)-benzoic acid (= NPPB)] (arylamino benzoic acid)	Synthetic	4.5B ClC (PSII)

(continued)

Table 4.5 (Continued)

Compound (class)	Plant (family) / part/	Target/process inhibited (other targets) / in vivo effects/
Na⁺-K⁺-2Cl⁻ co-transporter (Na⁺/K⁺/Cl⁻ TR)		4.5C
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Widespread; <i>Apium</i> , <i>Daucus</i> spp. (Apiaceae), <i>Achillea</i> , <i>Matricaria</i> spp. (Asteraceae), <i>Mentha</i> , <i>Oreganum</i> , <i>Thymus</i> spp. (Lamiaceae), ferns [leaf surface]; <i>Digitaria exilis</i> - (fonio, semi-arid zone millet variety) (Poaceae) [seed]	Stimulates Na ⁺ /K ⁺ /Cl ⁻ TR (BZ-R-like R, CFTR, EST-R, PK, RTK, TPO) [antibacterial, AI, diuretic, hypotensive]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	Widespread; <i>Genista</i> , <i>Glycine</i> , <i>Phaseolus</i> , <i>Trifolium</i> spp. (Fabaceae); <i>Prunus</i> spp. (Rosaceae) [wood], glucosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora japonica</i> (Fabaceae)	Stimulates Na ⁺ /K ⁺ /Cl ⁻ TR (AD-R, GABAA-R, HSK, lipase, peroxidase, PK, RTK, TOPII, TPO) [antifungal, oestrogenic]
[Furosemide (= Frusemide; Lasix) (furyl sulphamoyl-anthranilic acid)]	Synthetic	Na ⁺ /K ⁺ /Cl ⁻ TR [antihypertensive, diuretic]

5 Plasma membrane G protein-coupled receptors

5.1 Introduction – signalling via heterotrimeric G proteins

A major hormone signal transduction mechanism involves heterotrimeric guanyl nucleotide-binding protein (G protein) complexes. Hormone binding to a specific plasma membrane (PM)-located G protein-coupled receptor (GPCR) gives a hormone–receptor complex (H–R) that interacts with a PM-located heterotrimeric G protein complex (GDP–G α –G β –G γ) in which the guanyl nucleotide guanosine 5'-diphosphate (GDP) is bound to the G α subunit. This H–R complex–G protein interaction causes release of G β G γ , dissociation of GDP and replacement of GDP on G α with guanosine 5'-triphosphate (GTP) to form an “activated” G α –GTP complex. The active G α –GTP complex activates downstream “effector” enzymes depending upon the specific type of G α (as detailed below). The activation process is reversed through the GTP hydrolysing (GTPase) activity of the G α subunit generating G α –GDP, which can then recombine with G β G γ to re-form the inactive G α –GDP–G β G γ complex.

This reversible activation/deactivation process can be summarized as follows: H + PM R \rightarrow H–R \rightarrow H–R–G α –GDP–G β –G γ interaction \rightarrow H–R + G α –GTP + G β –G γ complex \rightarrow active G α –GTP activates effector proteins \rightarrow downstream effects; deactivation occurs via the GTPase activity of G α so that G α –GTP \rightarrow G α –GDP + P $_i$ \rightarrow G α –GDP binds G β –G γ \rightarrow the inactive GDP–G α –G β –G γ complex is re-formed.

The activation of effector proteins by G α –GTP complexes to ultimately cause the cellular responses to the initial hormone signal depends upon the specific type of G α subunit activated. A variety of G proteins have been resolved and characterized. In addition to their effector protein specificity, the G α subunits can be distinguished by their modification by particular bacterial toxins. Thus the *Vibrio cholerae* (cholera) toxin adenosine 5'-diphosphate (ADP)-ribosylates G α_s , G α_t and G α_{olf} entities, thereby inhibiting their GTPase activity and keeping these proteins in the persistently activated G α –GTP form. The *Bordetella pertussis* (whooping cough) toxin (pertussis toxin) ADP-ribosylates G α_i , G α_o , G α_g and G α_t entities, thereby preventing GDP release and keeping these proteins in the inactive GDP–G α –G β –G γ form. The effector specificities of the different G α proteins and their differential effects on membrane potential and the cytosolic levels of “second messengers” such as adenosine 3',5'-cyclic monophosphate (cAMP), inositol-1,4,5-triphosphate (IP $_3$) and Ca $^{2+}$ are outlined below.

i. G α_s (s for stimulatory) is cholera toxin-sensitive. G α_s –GTP can open Ca $^{2+}$ channels and activates adenylyl cyclase (which catalyses the formation of cAMP from adenosine 5'-triphosphate(ATP)), cAMP thence activating cAMP-dependent protein kinase (PKA) and depolarizing by opening cAMP-gated Na $^+$ channels.

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ii. G α olf (olf for olfactory) is involved in olfaction and is cholera toxin-sensitive. G α olf-GTP activates adenylyl cyclase and hence increases cAMP concentration (with consequent opening of cAMP-gated Na⁺ channels, depolarization, action potential initiation and signalling to the central nervous system (CNS) (see Chapter 10).

iii. G α i (i for inhibitory) is pertussis toxin-sensitive (noting that G α z is a pertussis toxin-insensitive G α i variant). G α i-GTP inhibits adenylyl cyclase (thereby lowering cAMP), opens K⁺ channels (thereby hyperpolarizing) and closes Ca²⁺ channels.

iv. G α o is pertussis toxin-sensitive. G α o-GTP activates phospholipase C (PLC), which catalyses the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PI4,5P₂) to diacylglycerol (DAG) and (IP₃) (IP₃ thence increasing cytosolic Ca²⁺ and Ca²⁺ and DAG consequently activating protein kinase C (PKC)).

v. G α q is pertussis toxin-insensitive and G α q-GTP activates PLC and increases cytosolic Ca²⁺ concentration as described for G α o-GTP.

vi. G α t (α -transducin) is involved in vision and is sensitive to both cholera and pertussis toxins. G α t-GTP is generated as a result of light absorption by rhodopsin (the visual protein opsin covalently linked to the chromophore retinal), retinal isomerization, rhodopsin conformational change and interaction with a G protein complex. G α t-GTP thus generated activates guanosine 3',5'-cyclic monophosphate (cGMP) phosphodiesterase (cGMP PDE), which hydrolyses cGMP to 5'-GMP with the successive consequences that cGMP levels decrease, cGMP-gated Na⁺ channels close and the transmembrane potential (ψ_m) hyperpolarizes (becomes more negative inside with respect to outside). Light-induced hyperpolarization is transmitted to a synapse and thence to the CNS for visual information processing.

vii. G α g (α -gustducin) is involved in sweet and bitter taste perception and is pertussis toxin-sensitive. In some cells sweet tastant-GPCR binding causes formation of G α g-GTP with successive consequences of increased cAMP, PKA activation, K⁺ channel phosphorylation, K⁺ channel closure and PM depolarization. Bitter tastants can also generate G α g-GTP, which activates cAMP/cGMP PDE, thereby lowering cAMP/cGMP levels and causing hyperpolarization via closure of cAMP- or cGMP-gated Na⁺ channels. However the released heterodimer G β G γ can activate PLC, this generating IP₃ which elevates cytosolic Ca²⁺ concentration (Chapters 4, 7 and 10).

5.2 G protein-coupled hormone and neurotransmitter receptors

Many different hormones (Hs) and neurotransmitters (NTs) act via PM-located heterotrimeric GPCRs, this mechanism involving receptors for ATP, adenosine, many peptide hormones, eicosanoids (unsaturated fatty acid derivatives such as prostaglandins, thromboxanes and leukotrienes), endogenous cannabinoid and sigma receptor ligands, catecholamines (such as epinephrine, norepinephrine and dopamine) and other bioactive amines such as histamine, acetylcholine (ACh), 5-hydroxytryptamine (5HT, serotonin), γ -aminobutyric acid (GABA) and glutamate (Glu). It must be noted that ACh, 5HT, GABA and Glu act through "ionotropic" receptors that are NT-gated ion channels as well as acting through "metabotropic" GPCRs. Similarly, sigma receptor ligands act via sigma receptors (σ -Rs) that are either ionotropic (Chapter 3) or metabotropic.

The PM receptors interacting with G proteins are typically composed of seven transmembrane α -helices. Hormone or NT binding to GPCRs ultimately leads to activation of effector proteins by the appropriate G α -GTP complexes and generation of second messengers such as cAMP, IP₃ and Ca²⁺. These second messengers in turn can activate second

messenger-dependent protein kinases (PKs). A transient “memory” of signalling events can occur when the G protein-interacting cytosolic domains of GPCRs are phosphorylated by PKs such as β -adrenergic receptor kinase (BARK) and rhodopsin kinase; subsequent binding of arrestin proteins to such phosphorylated sites prevents receptor–G protein interaction. This so-called receptor “desensitization” mechanism is reversed through the operation of phosphoprotein phosphatases (PPs) that dephosphorylate the receptors, thus returning the receptors to their original state of hormone-inducible reactivity.

Some other aspects of G protein chemistry should be noted. Thus AlF_4^- (fluoraluminate) can bind to G proteins forming an activated $\text{G}\alpha\text{-GDP-AlF}_4^-$ complex that mimics the active $\text{G}\alpha\text{-GTP}$ complex. Similarly, various non-hydrolysable GTP analogues, notably guanosine-5'-[γ -thio]triphosphate ($\text{GTP}[\gamma\text{-S}]$), bind to $\text{G}\alpha\text{s}$ and cause persistent activation. [^{35}S] $\text{GTP}[\gamma\text{-S}]$ has been very useful for radioactively labelling $\text{G}\alpha$ proteins and hence establishing that particular hormones or NTs act via a G protein-coupled mechanism.

5.3 Hormones and neurotransmitters acting via G protein-coupled receptors

A variety of peptide and non-peptide hormones or NTs act via GPCRs to change the concentrations of second messengers (such as cAMP or Ca^{2+}) or to affect K^+ or Ca^{2+} channels. A much larger number of substances (many derived from plants) bind to sweet and bitter taste receptors that interact with G proteins (Chapter 10). As noted in Chapter 3, some hormones or NTs have a multiplicity of receptors that are either “ionotropic” (activatable ion channels) or “metabotropic” (G protein-linked). Further, for a given hormone acting by G protein-linked receptors, the mechanism involved may differ for different receptors that may be expressed only on particular cell types. Thus epinephrine can act through β -adrenergic receptors (via $\text{G}\alpha\text{s}$ to increase cAMP), α 1-adrenergic receptors (via $\text{G}\alpha\text{o}$ to activate PLC, increase IP_3 and hence increase Ca^{2+}) and through α 2-adrenergic receptors (via $\text{G}\alpha\text{i}$ to decrease cAMP). The effects of a variety of peptide and non-peptide hormones and NTs on second messenger levels and ion channels are summarized below (with the H or NT abbreviations and specific receptor (R) sub-types being listed in parentheses).

ia. Peptide hormones increasing cAMP (via $\text{G}\alpha\text{s}$) include: bradykinin, calcitonin, chorionic gonadotropin, corticotropin (adrenocorticotrophic hormone, ACTH), corticotropin-releasing hormone (CRH), follicle-stimulating hormone (FSH), glucagon, glucagon like peptide-1 (GLP-1), histamine (H_2 R), luteinizing hormone (LH), melanocyte-stimulating hormone (MSH), parathyroid hormone (PTH), opioids (e.g. Met-enkephalin (YGGFM), Leu-enkephalin (YGGFL) and β -endorphin), oxytocin, (parathyroid-like hormone), substance P (a tachykinin), thyrotropin (thyroid-stimulating hormone, TSH), LH-release hormone (LHRH), relaxin and vasopressin.

ib. Non-peptides increasing cAMP (via $\text{G}\alpha\text{s}$) include: adenosine (A2A), dopamine (D1), epinephrine (β -adrenergic), melatonin, prostaglandins E1, E2 (PGE1, PGE2) and serotonin (5HT; 5HT1 α , 5HT2 and 5HT4 receptors).

ii. Peptides decreasing cAMP (via $\text{G}\alpha\text{i}$) include: opiates and somatostatin.

ii. Non-peptides decreasing cAMP (via $\text{G}\alpha\text{i}$) include: adenosine (A1 R), dopamine (D2 R), epinephrine (α 2-adrenergic Rs), γ -hydroxybutyrate (GHB R) and PGE1 (PGE1 R).

iii. Peptides increasing cytosolic Ca^{2+} (via $\text{G}\alpha\text{o}$ or $\text{G}\alpha\text{q}$) include: angiogenin, angiotensin II, ATP (P2x and P2 γ Rs), gastrin-releasing peptide, gonadotropin-releasing hormone (GRH), oxytocin, thyrotropin release hormone (TRH) and vasopressin.

iiib. Non-peptides increasing cytosolic Ca^{2+} (via $\text{G}\alpha\text{o}$ or $\text{G}\alpha\text{q}$) include: ACh (muscarinic M_1 , M_2 , M_3 and M_4 Rs), epinephrine (α_1 -adrenergic Rs), GABA (metabotropic GABA B class Rs), Glu (metabotropic Rs), histamine (H_1 R) and serotonin (5HT; metabotropic 5HT $_2$ R).

5.4 Activation of specific G protein-coupled receptors

a. Adenosine

Adenosine binds to adenosine receptors (AD-Rs) (subtypes A_1 , $\text{A}_{2\text{A}}$, $\text{A}_{2\text{B}}$ and A_3). A_1 - and A_3 -R activation gives $\text{G}\alpha\text{i}$ -mediated inhibition of adenylyl cyclase (resulting in decreased cAMP) and $\text{G}\alpha\text{i}/\text{G}\alpha\text{o}$ -mediated activation of a K^+ channel (with a de-excitatory hyperpolarizing effect). $\text{A}_{2\text{A}}$ and $\text{A}_{2\text{B}}$ activation gives $\text{G}\alpha\text{s}$ -mediated stimulation of adenylate cyclase (resulting in elevated cAMP). Adenosine acting via particular receptors variously has cardioprotective, neuroprotective, sedative, anticonvulsant, soporific, vasodilatory and bronchoconstrictive effects. The plant-derived methylxanthines theophylline and caffeine are adenosine A_1 and A_2 receptor antagonists (Table 5.1).

b. Acetylcholine (ACh)

Acetylcholine binds to ionotropic nicotinic ACh receptors (nACh-Rs) (Chapter 3) and to G protein-linked muscarinic ACh receptors (mACh-Rs) (subtypes M_1 , M_2 , M_3 and M_4). M_1 , M_3 and M_4 activation gives $\text{G}\alpha\text{q}$ -mediated PLC activation and thence successive IP_3 elevation, Ca^{2+} elevation and smooth muscle (e.g. ileum) contraction. Cardiac M_2 activation gives $\text{G}\alpha\text{i}$ -mediated K^+ channel opening (causing hyperpolarization) and $\text{G}\alpha\text{o}$ -mediated Ca^{2+} channel closure resulting in cardiac muscle relaxation and hypotension, this being prevented by the plant-derived mACh-R antagonist atropine. Muscarine from the fungus *Amanita* is an agonist of mACh-Rs (Table 5.2). Other plant mACh-R agonists include pilocarpine, pilosine, norarecoline and arecoline. Plant-derived mACh-R antagonists include the tropane alkaloids hyoscamine, atropine (the hyoscamine racemate) and hyoscyne (scopolamine), the benzyloisoquinoline liriodenine and the steroidal alkaloid ebeinone. Muscarinic ACh-R agonists have potential for treatment of Alzheimer's disease.

c. α - and β -Adrenergic receptors

α - and β -Adrenergic receptors mediate the effects of the catecholamines, epinephrine and norepinephrine. A variety of adrenergic receptors have been resolved, namely the β -, α_1 - and α_2 -type adrenergic receptors that are briefly described below.

α_1 -Adrenergic receptors. $\alpha_{1\text{A}}$ -, $\alpha_{1\text{B}}$ - and $\alpha_{1\text{D}}$ -Adrenergic receptor activation gives $\text{G}\alpha/\text{G}\alpha\text{q}$ -mediated PLC activation, this causing increased IP_3 and voltage-gated (V-gated) Ca^{2+} channel activation with resultant increased cytosolic Ca^{2+} and smooth muscle contraction.

α_2 -Adrenergic receptors. $\alpha_{2\text{A}}$ -, $\alpha_{2\text{B}}$ - and $\alpha_{2\text{C}}$ -Adrenergic receptor activation gives $\text{G}\alpha\text{i}$ -mediated adenylate cyclase inhibition (decreasing cAMP) and V-gated Ca^{2+} channel inhibition. α_2 -Adrenergic receptor effects include those of $\alpha_{2\text{A}}$ (analgesic, anaesthetic, hypotensive, NT release inhibitory and sedative) and $\alpha_{2\text{B}}$ (vasoconstrictive).

β -Adrenergic receptors. β_1 -, β_2 -, β_3 - and β_4 -Adrenergic receptor activation gives $\text{G}\alpha\text{s}$ -mediated activation of adenylate cyclase (elevating cAMP). β -Adrenergic receptor activation may also cause G protein-mediated opening of V-gated Ca^{2+} channels. Some

β -adrenergic receptor effects include those of β_1 (increased heart contraction rate and force), β_2 (smooth muscle relaxation and bronchodilation), β_3 (increased adipocyte lipolysis) and β_4 (increased heart contraction rate and force). Well-known β -adrenergic receptor antagonists are the synthetic “ β -blockers” such as propranolol (that lowers blood pressure) (Table 5.3). Well-known plant-derived β -adrenergic receptor agonists are cathine and cathinone (constituents of the Middle Eastern euphoriant and stimulant khat) and ephedrine and pseudoephedrine (that are used as bronchodilators) (Table 5.3).

d. Dopamine receptors (D-Rs)

Dopamine receptors include the D_1 - and D_2 -receptor subtypes, which are further classified as “ D_1 -like” (D_1 - and D_5 -Rs) and “ D_2 -like” (D_2 -, D_3 - and D_4 -Rs).

D_1 -receptor activation gives $G_{\alpha s}$ -mediated activation of adenylate cyclase (elevating cAMP) and G_q -mediated activation of PLC (elevating IP_3 and hence elevating cytosolic Ca^{2+}). D_1 -R activation is excitatory in the CNS and is involved in brain cognitive, cardiovascular and motor function modulation. Dopamine deficiency leads to Parkinson’s disease, which is reversed (but with ultimate dyskinesia) by its immediate metabolic precursor L-DOPA (3-hydroxytyrosine or 3-(3,4-dihydroxyphenyl)-alanine).

D_2 -receptor activation gives $G_{\alpha i}$ -mediated inhibition of adenylate cyclase (decreasing cAMP) and these receptors are involved in schizophrenia and Parkinson’s disease and in control of motor function, cardiovascular function and behaviour by the CNS. The well-known antipsychotics chlorpromazine and haloperidol are D_2 -R antagonists. A number of hallucinogenic indole alkaloids from ergot-infected grasses and cereals are D_2 -R agonists (Table 5.4).

e. Metabotropic GABA (γ -aminobutyric acid) receptors or GABA(B) receptors

γ -Aminobutyric acid (B) receptors are heterodimeric and act via $G_{\alpha i}$ to close Ca^{2+} channels and open K^+ channels with a resultant inhibitory, hyperpolarizing effect. GABA is the major inhibitory NT in the CNS and also acts via ionotropic A and C-type receptors which are inhibitory GABA-gated Cl^- channels (Chapter 3). GABA functions to counterbalance excitatory NTs and imbalance causes epilepsy. Accordingly GABA agonists or GABA elevating compounds are potentially antiepileptic (Table 5.5). The GABA metabolite GHB acts via a GPCR to inhibit adenylate cyclase and decrease cAMP. GHB diminishes alcohol and opiate dependence but has become a drug of abuse in body building, “date rape” and “raving” (Table 5.5).

f. Metabotropic glutamate receptors (mGlu-Rs)

Metabotropic glutamate receptors act via G proteins and a variety of different types have been resolved. Class I (subtypes 1 and 5), Class II (subtypes 2 and 3), Class III (subtypes 4, 6, 7 and 8) and phospholipase D (PLD)-coupled mGlu-Rs couple through G proteins to increase PLC via $G_{\alpha o}/G_{\alpha q}$ (Class I), decrease adenylate cyclase via $G_{\alpha i}$ (Classes II and III) and to increase PLD-coupled mGlu-R. The glutamate receptors are excitatory and agonists can be neurotoxic such as *Amanita*-derived ibotenic acid and the Guam cycad amino acid BMAA (β -N-methylamino-L-alanine), which causes a type of dementia (Table 5.5).

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g. Metabotropic 5HT (serotonin) receptors

Metabotropic 5HT receptors act via G proteins and a multiplicity of such receptors have been resolved, namely type 1A, 1B, 1D, 1E, 1F, 2A, 2B, 2C, 4, 5A, 5B, 6, 5 and 7 5HT receptors (noting that the type 3 5HT receptor is an ionotropic $\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$ channel) (Chapter 3). 5HT receptors 1 and 5 act via $\text{G}\alpha_i$ to decrease adenylyl cyclase (and hence decrease cAMP); 5HT receptor type 2 increases Ca^{2+} via $\text{G}\alpha_q$ (and thence via PLC activation and IP_3 generation); 5HT receptor types 4, 6 and 7 act via $\text{G}\alpha_s$ to activate adenylyl cyclase (and hence increase cAMP). 5HT receptor occupancy is involved in excitatory neurotransmission, stimulation or inhibition of cardiac function, vasodilation, nociception, sensitization of nociceptive neurons, nausea and vomiting. A variety of plant-derived 5HT receptor agonists are hallucinogenic including 5-hydroxy-*N,N*-dimethyltryptamine, *N,N*-dimethyltryptamine, lysergamide, 5-methoxy-*N,N*-dimethyltryptamine and mescaline (3,4,5-trimethoxyphenylethylamine). Various fungus-derived hallucinogens are 5HT receptor agonists including ergotamine and lysergamide (from ergot), LSD (D-lysergic acid diethylamide, a semi-synthetic from ergot-derived lysergamide) and psilocin and psilocybin (from *Psilocybe*) (Table 5.5).

h. Opiate receptors

Opiate receptors are GPCRs mediating the effects of analgesic endogenous opiate peptides. The various opiate receptor types include $\delta 1$, $\delta 2$, κ , $\mu 1$, $\mu 2$ and ORL (opiate receptor-like) receptors. Opiate receptors can act via $\text{G}\alpha_i$ to close Ca^{2+} channels and open K^+ channels (and thereby hyperpolarize). Opiates can also act to increase cAMP via $\text{G}\alpha_s$. Endogenous peptide agonists (receptor subtypes in parentheses) include β -endorphin and derivative enkephalins (that variously bind to δ , κ and μ opiate receptors), endomorphin-1 and endomorphin-2 (μ), dynorphins (κ) and nociceptin (ORL). In addition there are endogenous peptide opiate receptor antagonists. A variety of plant-derived alkaloids are analgesic and narcotic opiate receptor ligands of which the best known are codeine and morphine (from the opium poppy) (Section 1, Appendix) and the semi-synthetic heroin (morphine diacetate) (Table 5.6).

5.5 Leucocyte- and inflammation-related G protein-linked receptors

Various G protein-linked receptors mediate the effects of leucocyte- and inflammation-related hormones and some of these are also targets for plant defensive compounds (Table 5.7). G proteins are involved in platelet aggregation in response to receptor binding by ADP (G_i , G_q), thromboxane A₂ (G_q) and thrombin. ADP acts by simultaneously activating G_i and G_q proteins. Epinephrine promotes platelet aggregation via binding to $\alpha 2$ -adrenergic receptors with consequent $\text{G}\alpha_i$ activation, adenylyl cyclase inhibition and cAMP decrease (see Section 5.4c). Thrombin activates its receptor proteolytically. Collagen causes platelet aggregation via glycoprotein VI receptor tyrosine kinase (RTK) activation; however signal pathway “cross-talk” involving $\text{G}\alpha_q$ is required because in $\text{G}\alpha_q$ -deficient platelets, ADP restores collagen-induced but not thrombin-induced aggregation.

a. ADP receptors

Adenosine 5'-diphosphate activates platelet aggregation through simultaneous binding to P2Y₁ receptors (producing a $\text{G}\alpha_q$ -mediated PLC activation, Ca^{2+} elevation and platelet

shape change) and to P2Y₁₂ receptors (decreasing cAMP via G_{αi}-mediated inhibition of adenylyl cyclase). These events activate fibrinogen receptors (glycoproteins GP IIb/IIIa) and thence platelet aggregation. Coronary thrombosis involving atherosclerotic plaque rupture and platelet aggregation-induced thrombus formation is a major pharmaceutical target.

b. Bradykinin receptors

Bradykinin and related kinin peptides are produced by leucocytes and act via G_{αq} to elevate cytosolic Ca²⁺ and promote nitric oxide (NO) synthesis, smooth muscle contraction, capillary permeability, inflammation and histamine release from mast cells.

c. Chemokine receptors

Chemokine receptors mediate the effects of a large group of chemotactic cytokine peptides that regulate leucocyte trafficking in inflammatory responses, angiogenesis, haematopoiesis and organogenesis. Some chemokine receptors have been subverted by pathogens such as *Plasmodium vivax* and human immunodeficiency virus-1 (HIV-1) for cell entry. The chemokines have been subclassified depending upon conserved cysteine (C) number and disposition into the C, CC, CXC and CX₃C classes. Thus monocyte chemoattractant proteins MCP-1, MCP-2, MCP-3, MCP-4 and MCP-5 are CC chemokines and interleukin-8 (IL-8) is a CXC chemokine. Numerous chemokine receptors have been resolved and these are mostly named after their chemokine class specificity (although this overlaps in some cases), that is, CCRs 1–8, CXCRs 1–5, XCR1 and CX₃CR1. The chemokine receptors are 7-transmembrane (7-TM) α-helix proteins that couple through G_{αi} proteins.

d. Thrombin

Thrombin is a serine protease involved in the blood clotting proteolytic cascade and acts via protease-activated receptors (PARs 1–4). PAR cleavage at an N-terminal region site generates a “tethered” ligand which activates the PAR. The PARs 1 and 2 signal via G_{αi} and G_{αq} proteins to decrease cAMP and elevate Ca²⁺, respectively. Accordingly thrombin, like ADP, induces platelet aggregation. Thrombin is critical to blood clotting, induces synthesis of tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) and is involved in inflammatory and pigmentation diseases.

e. Histamine receptors

Histamine receptors variously mediate the bronchoconstrictant, inflammatory, irritant, vasodilator, gastric pepsin secretion and immune suppression actions of histamine. Associated with the immune response, cytokines cause release of histamine from mast cells. Histamine acts via H₁, H₂, H₃ and H₄ GPCRs. H₁ and H₂ receptors couple via both G_{αs} (elevating cAMP) and G_{αq} (elevating Ca²⁺ in a pertussis toxin-insensitive fashion) and H₃ couples via G_{αi} (decreasing cAMP).

f. Platelet activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphorylcholine, PAF)

Platelet activating factor is a phospholipid-derived signalling compound generated in animal systems by stimulated neutrophils, basophils, platelets and endothelial cells. PAF receptors

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couple via a G protein leading to activation of PLC (elevating Ca^{2+}) and of phospholipase A_2 (PLA_2) (generating arachidonic acid, the precursor of prostaglandins and related compounds). PAF is involved in platelet histamine and 5HT release, leucocyte migration, inflammation and anaphylaxis. Accordingly PAF-R antagonists are potential anti-inflammatory compounds.

g. Prostanoids

Prostanoids derive from cyclooxygenase-catalysed oxidation of the polyunsaturated fatty acid arachidonic acid and include (receptor types in parentheses) prostaglandins PGE1 and PGE2 (EP), PGD1 and PGD2 (DP), PGF 2α (FP), PGI2 (IP) and thromboxane A2 (TP). These receptors couple through G proteins and the receptor subtype G protein $\text{G}\alpha$ specificity and second messenger consequences can be summarized thus (where \uparrow and \downarrow correspond to increase and decrease, respectively): DP (G_s , \uparrow cAMP), EP1 (G_o/G_q , \uparrow Ca^{2+}), EP2 (G_s , \uparrow cAMP), EP3A (G_i , \downarrow cAMP), EP3B (G_s , \uparrow cAMP), EP3C (G_s , \uparrow cAMP), EP3D (G_i , \downarrow cAMP; G_s , \uparrow cAMP; G_q , \uparrow Ca^{2+}), EP4 (G_s , \uparrow cAMP), FP (G_q , \uparrow Ca^{2+}), IP (G_s , \uparrow cAMP; G_q , \uparrow Ca^{2+}), TP α (G_i , \downarrow cAMP; G_q , \uparrow Ca^{2+}) and TP β (G_s , \uparrow cAMP; G_q , \uparrow Ca^{2+}). Prostaglandins are involved in fever, inflammation, pain, immune responses, thrombosis, hypertension, haemostasis, platelet aggregation and in reproductive and bone physiology. A large number of plant-derived substances interfere with prostanoid synthesis (see Chapter 14).

h. Sphingosine-1-phosphate (S1P) receptors

Sphingosine-1-phosphate receptors EDG-1 and EDG-3 bind S1P generated from phosphorylation of sphingosine by sphingosine kinase. The binding of S1P and sphinganine 1-phosphate (dihydrosphingosine 1-phosphate) to EDG-1 promotes chemotaxis via a $\text{G}\alpha_i$ -mediated mechanism.

i. Thromboxane A2 is an arachidonic acid-derived prostanoid agonist of TP α receptors (acting via G_i to decrease cAMP and via G_q to increase Ca^{2+}) and of TP β receptors (acting via G_s to increase cAMP and via G_q to increase Ca^{2+}). Thromboxane A2 is involved in vasoconstriction, inflammation and platelet aggregation (Table 5.7).

5.6 Other G protein-coupled receptors

Many other GPCRs mediate the effects of hormones and NTs involved in a wide variety of responses. Some of these are also targets for plant defensive compounds (Table 5.8) and are listed alphabetically for convenience in the outline presented below. Note that all of the hormones listed below are peptides except for (a) ATP, (c) anandamide, (j) melatonin and (p) some non-peptide sigma receptor ligands.

a. ATP receptors

Adenosine 5'-triphosphate is an excitatory neurotransmitter in the CNS and the peripheral nervous system (PNS). ATP acts via ionotropic P2X receptors (Chapter 3) and also acts through metabotropic G protein-linked P2Y receptors. With respect to P2Y receptors 1–13 that have been distinguished, uridine 5'-triphosphate (UTP) and ATP bind to P2Y2 and P2Y4 and ATP also binds to P2Y11. The signalling mechanism involves $\text{G}\alpha_q$ -mediated cytosolic Ca^{2+} elevation.

b. Bombesin receptors

Bombesin and related peptides such as gastrin-releasing peptide, neuromedin B and somatomedin are autocrine growth factors, anorexigenic and inducers of GI hormone (e.g. gastrin) release. Bombesin acts via $G_{\alpha q}$ to elevate cytosolic Ca^{2+} .

c. Cannabinoid receptors

Cannabinoid receptors include the CB1 receptors (which have a high incidence in the CNS and inhibit adenylyl cyclase, close Ca^{2+} channels and open K^+ channels via $G_{\alpha i}$) and CB2 receptors (which are present in immune cells and act via $G_{\alpha i}$ proteins to inhibit adenylyl cyclase). CB1 and CB2 receptors bind the endogenous ligand anandamide (arachidonylethanolamide) as well as Δ^9 -tetrahydrocannabinol from marijuana (*Cannabis sativa*). Δ^9 -Tetrahydrocannabinol antagonizes the peripheral CB2 receptor but acts as an agonist for the CNS CB1 receptor. Cannabinoid receptor agonists have appetite stimulant and psychoactive effects and have therapeutic potential for relief from nausea and pain.

d. Cholecystokinin (CCK, pancreozymin) receptors

Cholecystokinin receptors are the GPCRs CCK-A and CCK-B. The C-terminal sulfated octapeptide CCK fragment (CCK8) is a major neuropeptide. CCK is involved in anorexia, cardiovascular tonus, central respiratory control, nociception, pancreatic exocrine secretion, gastric emptying, memory, vigilance and emotional states such as anxiety and panic.

e. Cocaine- and amphetamine-regulated transcript (CART) receptor (CART-R)

The cocaine- and amphetamine-regulated transcript receptor is involved in the action of CART as a leptin-induced, hypothalamic anorexigenic (appetite-suppressing) hormone, CNS stimulant and inducer of catecholamine release from presynaptic storage granules.

f. Corticotropin (adrenocorticotrophic hormone, ACTH)

Adrenocorticotrophic hormone derives from the anterior pituitary in response to the leptin- or stress-induced anorexigenic, hypothalamic CRH. Corticotropin (like enkephalins and MSHs) derives from a precursor polypeptide pro-opiomelanocortin. Corticotropin induces the catabolic adrenal cortex corticosteroid cortisol and the mineralocorticoid aldosterone (Chapter 11) and is an important regulator of immune responses including chemotaxis and phagocytosis. Corticotropin acts via GPCRs to activate $G_{\alpha s}$ and increase cAMP in anterior pituitary cells.

g. Gastrin

Gastrin stimulates gastric acid secretion but also has growth-promoting effects on various cell types. Gastrin shares GPCRs with CCK, namely the CCK- A and -B receptors.

h. Glucose-dependent insulinotropic polypeptide (Gastric inhibitory peptide, GIP)

Gastric inhibitory peptide acts via a GPCR on pancreatic β cells to promote insulin secretion. The plant natural products gymnemic acid and phloridzin inhibit D-glucose binding to the GI glucose receptor involved in glucose-stimulated GIP secretion.

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i. Imidazoline receptors (I-Rs)

Imidazoline receptors I1 and I2 are GPCRs. I1 agonists are hypotensive. I-Rs are involved in hypertension, diabetes mellitus and mood disorder pathologies.

j. α -Melanocyte-stimulating hormone (α -MSH, α -melanotropin)

α -Melanocyte-stimulating hormone (MSH) is, like CRH and CART, an anorexigenic (appetite-suppressing) hypothalamic hormone generated in response to Janus kinase/Signal transducers and activators of transcription (JAK/STAT)-mediated signalling from the adipocyte-derived peptide hormone leptin, which reports fat reserve fullness (adiposity). α -MSH derives from the same pro-opiomelanocortin precursor peptide as do the other melanocortin peptide hormones ACTH, corticotropin-like intermediary peptide (CLIP), β -endorphin, Met-enkephalin, β -MSH and γ -MSH. α -MSH acts via GPCRs MC1-R, MC2-R, MC3-R, MC4-R and MC5-R, which couple via G α s to increase cAMP (noting that cholera toxin-sensitive increase in Ca²⁺ can also occur). α -MSH causes darkening in amphibia and fish and melanogenesis in man that is reversed by melatonin (*N*-acetyl-5-methoxytryptamine). The orexigenic peptides Agouti protein and Agouti-related protein compete with anorexigenic α -MSH for a common receptor with opposite effects on appetite.

k. Melatonin (N-acetyl-5-methoxytryptamine; regulin)

Melatonin is an indole-derived anterior pituitary hormone that causes downstream inhibition of α -MSH-induced melanogenesis. Melatonin is anti-amnesic, synchronizes circadian and circannual rhythms and is metabolized to 5-methoxytryptamine. Melatonin acts via GPCRs MT1 and MT2 (which both couple through G α i and cAMP decrease). MT1 may also couple via G α o and G α q to activate PLC (and hence increase cytosolic Ca²⁺) and via G β G γ activation of PLA2. Melatonin can further interact with nuclear receptor superfamily “orphan” retinoid receptors RZR/ROR. Melatonin fluctuates with a circadian rhythm and is elevated in blood during the night. Melatonin is accordingly of social importance in relation to shift work and jet-lag. Melatonin and 5-methoxytryptamine occur in some plants (Table 5.8).

l. Neurotensin (NEUT)

Neurotensin is anorexigenic as a potent stimulator of α -MSH and is antinociceptive. NEUT binds to GPCRs NTS1 and NTS2 which act via G α q to activate PLC and hence elevate cytosolic Ca²⁺.

m. Neuropeptide Y (NPY)

Neuropeptide Y derives from the hypothalamus and functions both in the CNS and peripherally. NPY is orexigenic (pro-feedant, appetite-stimulating), reduces leptin-induced thermogenesis and its synthesis and secretion is inhibited by leptin, by the appetite-suppressing and insulin secretagogue glucagon-like peptide-1 (GLP-1) and by the leptin-induced anorexigenic hormones MSH, CRH and CART. NPY levels rise during starvation. Homozygous ob/ob mice (that make no leptin, the product of the wildtype OB gene product) are hungry, obese and insulin-resistant. Homozygous db/db mice (that make no leptin receptor, the product of the wildtype DB gene) also become obese and diabetic. NPY is elevated in both ob/ob and db/db mice.

n. Oxytocin

Oxytocin is secreted from the posterior pituitary and targets the uterus (stimulating uterine contraction) and mammary tissue (promoting lactation). The oxytocin receptor couples via a G α s to activate adenylyl cyclase and increase cAMP.

o. Parathyroid hormone /parathyroid hormone-related protein receptor (PTH-R)

Parathyroid hormone-related protein receptor is a GPCR that acts via a G α s (and elevation of cAMP) or via G α q (to activate PLC, increase IP₃ and thence increase cytosolic Ca²⁺). PTH increases bone resorption and reabsorption of Ca²⁺ in the kidney with consequent elevation of blood Ca²⁺. Calcitonin, which binds to a GPCR that acts via a G α s to elevate cAMP, has opposing effects to those of PTH.

p. Secretin

Secretin inhibits postprandial gastrin release (thus decreasing gastric acid secretion) and increases pancreatic exocrine secretion (e.g. of bicarbonate). The secretin receptor (like the GLP-1 receptor and vasoactive intestinal peptide (VIP) receptor) acts via G α s and cAMP elevation. A plant agonist for the secretin receptor has been isolated from the Thai anti-ulcer plant *Croton sublyratus* (*plau-loi*) (Table 5.8).

q. Sigma receptor (σ -R)

Sigma receptor ligands bind to metabotropic GPCRs as well as ionotropic σ -Rs (Chapter 3). Endogenous ligands for σ -Rs include some opiates. Sigma-R activation can have antitussive, anxiolytic and ulceroprotective effects. Hypericin from *Hypericum perforatum* (St John's wort) is a σ -R agonist (Table 5.8).

r. Somatostatin (growth hormone-release inhibiting factor, GH-RIF; somatotropin release inhibiting factor, SRIF)

Somatostatin is a hypothalamic hormone that inhibits secretion of growth hormone (somatotropin), gastrin, secretin, glucagon and insulin. Somatostatin acts via GPCRs that decrease cAMP via G α i.

s. Substance P

Substance P acts via tachykinin NK1 and NK2 receptors, these being coupled via G proteins resulting in PLC activation, IP₃ generation and cytosolic Ca²⁺ elevation.

t. Vasopressin (Antidiuretic hormone, ADH)

Antidiuretic hormone is a posterior pituitary peptide hormone that binds to vasoconstrictive V1a receptors (via G α q to activate PLC and thence increase cytosolic Ca²⁺), to V2 receptors (causing kidney water reabsorption via G α s and increased cAMP) and to corticotropin secretion-regulating V1b (V3) receptors (mediated by G α q to activate PLC and thence increase cytosolic Ca²⁺). For bioactive-G protein interactions see Table 5.9.

Table 5.1 Adenosine receptors

Compound (class)	Plant (family) / part/	Receptor affected (other target) / in vivo effects/
Adenosine receptor (AD-R)		5.1A
Alkaloid		5.1Aa
[Acetylhaemanthamine (= Acetyl-3-epicrinamine; Acetylhemanthidine; Acetylnatalensine)] (crinane Amaryllidaceae alkaloid)	Semi-synthetic from Haemanthamine from <i>Haemanthus</i> sp. (Amaryllidaceae)	AD-R ligand – A ₁ selective (PIA displacement) [53], A _{2A} (inactive), A ₃ (inactive)
Adenosine (purine nucleoside)	Universal	AD-R agonist
(-)-Apparicine (indole)	<i>Aspidosperma dasycarpon</i> , <i>Tabernaemontana pachysiphon</i> (Apocynaceae) [leaf]	A ₁ AD-R ligand [μM] (O-R) [analgesic (mouse abdominal relaxant), analeptic, antiviral]
Arborinine (quinoline)	<i>Euodia xanthoxyloides</i> , <i>Fagara lepreurii</i> , <i>Glycosmis arborea</i> , <i>Ruta graveolens</i> , <i>Teclea natalensis</i> (Rutaceae)	AD-R ligand – A ₁ (PIA displacement) [13], A _{2A} (CGS displacement) [6], A ₃ (ABMECA displacement) [<100] [spasmolytic]
Caffeine (= 1,3,7-Trimethylxanthine; Coffeine; Guaranine; Thein; Theine) (purine, methylxanthine); most consumed plant bioactive compound?	<i>Ilex paraguayensis</i> (maté) (Aquifoliaceae), <i>Coffea arabica</i> , <i>Coffea</i> spp. (coffee) (Rubiaceae) [coffee bean], <i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Cola acuminata</i> (cola) (Sterculiaceae) [seed], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	A ₁ AD-R, A ₂ AD-R & A ₃ AD-R antagonist (cAMP PDE, cGMP PDE, ryanodine R) [cardiac, CNS & respiratory stimulant, diuretic, smooth muscle relaxant, increased catecholamine-induced lipolysis (at 0.1–1), vasodilator]
1,7-Dimethylxanthine (= Paraxanthine) (methylxanthine)	<i>Sinomenium acutum</i> (Menispermaceae); major metabolite of Caffeine	A ₁ AD-R & A _{2A} AD-R antagonist [increased catecholamine-induced lipolysis (at 0.1–1)]
Ibogaine (= 12-Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> (iboga), <i>Voacanga thouarsii</i> (Apocynaceae); iboga W. African stimulant & aphrodisiac	AD-R–A ₁ -R ligand (mACh-R, D-R, DTR, 5HTTR, NMDA-Glu-R, O-R) [anti-addictive, anticonvulsant, hallucinogenic]
[8-Phenyltheophylline (= 1,3-Dimethyl-8-phenylxanthine)] (methylxanthine)	Semi-synthetic from Theophylline	A ₁ AD-R antagonist
Theobromine (= 3,7-Dimethylxanthine) (methylxanthine)	<i>Ilex paraguayensis</i> (Aquifoliaceae), <i>Paullinia cupana</i> (Sapindaceae), <i>Cola acuminata</i> , <i>Theobroma cacao</i> (Sterculiaceae), <i>Camellia sinensis</i> (Theaceae)	AD-R antagonist (weak) (cAMP PDE) [cardiac stimulant, diuretic, smooth muscle relaxant, vasodilator]
Theophylline (= 1,3-Dimethylxanthine) (methylxanthine)	<i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Theobroma cacao</i> (Sterculiaceae), <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	AD-R antagonist – A _{2B} [8] (cAMP PDE) [anti-asthmatic, cardiac stimulant, coronary vasodilator, diuretic, SM relaxant]
Tubotaiwine (alkaloid)	<i>Tabernaemontana pachysiphon</i> , <i>Tabernanthe iboga</i> (Apocynaceae) [leaf]	A ₁ AD-R ligand [μM] (O-R) [analgesic (mouse abdominal relaxant)]

(continued)

Table 5.1 (Continued)

Compound (class)	Plant (family) / part/	Receptor affected (other target) / in vivo effects/
Phenolic		5.1Ap
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Lamiaceae, ferns [leaf surface], Widespread; <i>Apium</i> , <i>Daucus</i> spp. (Apiaceae), <i>Achillea</i> , <i>Matricaria</i> spp. (Asteraceae), <i>Mentha</i> , <i>Oreganum</i> , <i>Thymus</i> spp. (Lamiaceae), ferns [leaf surface]; <i>Buddleja officinalis</i> (Loganiaceae), <i>Digitaria exilis</i> (Poaceae) [seed]	AD-R ligand – A ₁ (PIA displacement) [3], A _{2A} (CGS displacement) [8], A ₃ (ABMECA displacement) [<10] (ARH, cAMP PDE, cGMP PDE, AR, CDK2, PK, RTK) [antibacterial, AI, diuretic, hypotensive]
Catechin 3-gallate (gallotannin)	<i>Hamamelis virginiana</i> (Hamamelidaceae), <i>Bergenia stracheyi</i> (Saxifragaceae) [root]	A ₁ AD-R ligand (>10) (D ₁ D-R, D ₂ D-R, 5HT ₁ -R, O-R)
Cirsimaritin (= Cirsimaritin 4'-O-glucoside) (flavone O-glycoside)	<i>Microtea debilis</i> (Phytolaccaceae)	A ₁ AD-R antagonist (3) [may explain anti-proteinuria herbal medicinal use of plant]
Cirsimaritin (= 5,4'-Dihydroxy-6,7-dimethoxyflavone) (flavone)	<i>Microtea debilis</i> (Phytolaccaceae)	AD-R ligand – A ₁ (PIA displacement) [1], A _{2A} (CGS displacement) [3], A ₃ (ABMECA displacement) [2]
2,3-Dihydroquercetin (= 2,3-Dihydro-3,5,7,3',4'-pentahydroxyflavone; Taxifolin) (dihydroflavonol)	Widespread; <i>Acacia catechu</i> (Fabaceae), <i>Polygonum nodosum</i> (Polygonaceae), <i>Salix capraea</i> (Salicaceae), Coniferae; glycosides in <i>Rhododendron</i> (Ericaceae), <i>Astilbe</i> (Saxifragaceae) spp.	AD-R ligand – A ₃ (ABMECA displacement) [2] (LOX, MLCK, PKA, NADH DH, succinate DH) [antibacterial, antifungal, AI, antioxidant]
Flavone (= 2-Phenyl-1,4-benzopyrone) (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula malacoides</i> , <i>P. pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	AD-R ligand – A ₁ (PIA displacement) [3], A _{2A} (CGS displacement) [3], A ₃ (ABMECA displacement) [17] (ARH, COX, 5-LOX (ECMOX) [AI, PAI, inhibits basophil histamine release]
Galangin (= 3,5,7-Trihydroxyflavone) (flavonol)	Betulaceae, Salicaceae, ferns, Lamiaceae, <i>Datisca cannabina</i> (Datisceae), <i>Escallonia</i> spp. (Saxifragaceae), <i>Alpinia officinarum</i> (Zingiberaceae)	AD-R ligand – A ₁ (PIA displacement) [0.9], A _{2A} (CGS displacement) [1], A ₃ (ABMECA displacement) [3] [antibacterial]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	Widespread; <i>Genista</i> , <i>Glycine</i> , <i>Phaseolus</i> , <i>Trifolium</i> spp. (Fabaceae); <i>Prunus</i> spp. (Rosaceae) [wood], glycosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora japonica</i> (Fabaceae)	AD-R ligand – A ₁ (PIA displacement) [5], A _{2A} (CGS displacement) [36], A ₃ (ABMECA displacement) [>100] (GABAA-R, HISK, lipase, peroxidase, PK, RTK) [antifungal, oestrogenic]
Haematoxylin (= Hydroxybrazilin) (polycyclic benzopyran)	<i>Haematoxylon campechianum</i> (Fabaceae) [wood]	AD-R ligand – A ₁ (PIA displacement) [3], A _{2A} (CGS displacement) [>100] A ₃ (inactive) [light exposure yields red pigment]
[3,5,7,3',4',5'-Hexamethoxyflavone (= Hexamethylmyricetin)] (flavonol)	Semi-synthetic from Myricetin	AD-R ligand – A ₃ (ABMECA displacement) [16]

(continued)

Table 5.1 (Continued)

Compound (class)	Plant (family) / part/	Receptor affected (other target) / in vivo effects/
Hispidulin (= Dinatin; Scutellarein 6-methyl ether); 5,7, 4'- Trihydroxy-6- methoxyflavone (flavone)	Asteraceae, Hygrophyllaceae, Lamiaceae [leaf], <i>Citrus sudachii</i> (Rutaceae) [peel], <i>Digitalis orientalis</i> (Scrophulariaceae) [leaf]	A _{2A} AD-R agonist, AD-R ligand – A ₁ (PIA displacement) [2], A _{2A} (CGS displacement) [6], A ₃ (ABMECA displacement) [<10] [↑ platelet cAMP → PAI]
5-Hydroxyflavone (flavone)	<i>Ficus gomelleira</i> (Moraceae) [leaf]	AD-R ligand – A ₁ (PIA displacement) [2], A _{2A} (CGS displacement) [6], A ₃ (ABMECA displacement) [~100] (CDPK, MLCK)
7-Hydroxyflavone (flavone)	<i>Clerodendron phlomidis</i> (Verbenaceae) [flower; leaf]	AD-R ligand – A ₁ (PIA displacement) [3], A _{2A} (CGS displacement) [3], A ₃ (ABMECA displacement) [>100]
7-Hydroxy-3',4'- dimethoxyflavone (flavone)	As precursor of 3,4- methylenedioxy derivative in <i>Piper</i> sp. (Piperaceae)	AD-R ligand – A ₁ (PIA displacement) [19], A _{2A} (CGS displacement) [35], A ₃ (ABMECA displacement) [>100]
5-Hydroxy-7,4'- dimethoxyflavone (flavone)	<i>Biota orientalis</i> (Cupressaceae), <i>Rosmarinus officinalis</i> (Lamiaceae), <i>Piper</i> spp. (Piperaceae)	A ₃ AD-R selective ligand (ABMECA displacement) [<10]
5-(3-Hydroxypropyl)-7- methoxy-2-(3'-methoxy- 4'-hydroxyphenyl)-3- benzo[b]furan- carbaldehyde (benzofuran)	<i>Salvia miltiorrhiza</i> (Lamiaceae)	A ₁ AD-R ligand [17 nM]
[5-Hydroxy-7-methyl-4'- methoxyflavone] (flavone)	Semi-synthetic	AD-R ligand – A ₁ (PIA displacement) [3], A _{2A} (CGS displacement) [28], A ₃ (ABMECA displacement) [7]
Luteolin (5,7,3',4'- Tetrahydroxyflavone) (flavone)	Widespread; Apiaceae, Asteraceae, Brassicaceae, Lamiaceae, Fabaceae, Rutaceae, Scrophulariaceae, Thymelaeaceae [aerial]	A ₁ AD-R antagonist [low μM] (cAMP PDE, iodothyronine deiodinase, PKC, NADH DH, succinate DH, AR, PEP)
Paeoniflorin (phenolic-related glycoside)	<i>Paeonia albiflora</i> , <i>P. lactiflora</i> , <i>P. moutan</i> , <i>P. officinalis</i> , <i>P. suffruticosa</i> (Passifloraceae) [root]	A ₁ AD-R selective agonist [antiallergic, anticoagulant, PAI]
[3,5,7,2',4'- Pentamethoxyflavone (= Pentamethylmorin)] (flavonol)	Semi-synthetic from Morin	AD-R ligand – A ₁ (PIA displacement) [28], A _{2A} (CGS displacement) [47], A ₃ (ABMECA displacement) [3]
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	AD-R ligand – A ₁ (PIA displacement) [3], A _{2A} (CGS displacement) [28], A ₃ (↑ ABMECA binding) (at 10–30) (AR, LOX, PDE, PK) [AI, feeding stimulant, SM contraction, radical scavenger allergenic, antiviral]

(continued)

Table 5.1 (Continued)

Compound (class)	Plant (family) / part/	Receptor affected (other target) / in vivo effects/
Rhamnetin (= 3,5,7,3',4'-Pentahydroxy-flavone 7-methyl ether; Quercetin 7-methyl ether) (flavonol)	<i>Cistus</i> spp. (Cistaceae), Apiaceae, Asteraceae, Euphorbiaceae, Lamiaceae; glycosides in <i>Thalictrum</i> (Ranunculaceae), <i>Rhamnus</i> (Rhamnaceae), <i>Tamarix</i> (Tamaricaceae) spp.	AD-R ligand – A ₃ (ABMECA displacement) [1] (AR, cAMP PDE) [allergenic, antibacterial]
Sakuranetin (= 5,4'-Dihydroxy-7-methoxyflavanone; Naringenin 7-methyl ether) (flavanone)	<i>Daucus</i> (Apiaceae), <i>Betula</i> (Betulaceae), <i>Artemisia</i> , <i>Baccharis</i> (Asteraceae), <i>Ribes</i> (Grossulariaceae), <i>Juglans</i> (Juglandaceae) spp., glycoside in <i>Prunus pumila</i> (Rosaceae)	AD-R ligand – A ₁ (PIA displacement) [8], A _{2A} (CGS displacement) [36], A ₃ (ABMECA displacement) [3] [antifungal]
[3,5,7,4'-Tetra-methoxy-flavone (= Tetramethyl-kaempferol)] (flavone)	Semi-synthetic from Kaempferol	AD-R ligand – A ₁ (PIA displacement) [1], A ₃ (ABMECA displacement) [3]
[3,5,7-Triacetoxylflavone (= 3,5,7-Triacetyl-galangin)] (flavonol)	Semi-synthetic from Galangin	AD-R ligand – A ₁ (PIA displacement) [12], A _{2A} (CGS displacement) [57], A ₃ (ABMECA displacement) [18]
[3,5,7-Trimethoxyflavone] (flavone)	Semi-synthetic	AD-R ligand – A ₁ (PIA displacement) [0.5], A _{2A} (CGS displacement) [6], A ₃ (ABMECA displacement) [1]
[5,6,7-Trimethyl-4'-methoxyflavone (= Tetramethyl-scutellarein)] (flavone)	Semi-synthetic	AD-R ligand – A ₁ (PIA displacement) [1], A ₃ (ABMECA displacement) [4]
Other		5.1Ao
Linoleic acid (unsaturated FA)	Widespread in plant oils	A ₁ AD-R non-competitive inhibitor
Non-plant reference		5.1An
[ABMECA] (purine nucleoside)	Synthetic – cf. Adenosine	A ₃ AD-R selective agonist [0.6 nM]
[CGS] (purine nucleoside)	Synthetic – cf. Adenosine	A ₂ AD-R selective agonist [14 nM]
[N6-Cyclohexyladenosine] (purine nucleoside)	Synthetic – cf. Adenosine	A ₁ AD-R selective agonist [3 nM]
[8-Cyclopentyl-1,3-dipropylxanthine] (alkyl xanthine)	Synthetic – cf. Theophylline	A ₁ AD-R selective antagonist [3 nM], A ₂ AD-R antagonist [51 nM]
[α-Naphthoflavone] (naphthoflavone)	Synthetic – cf. Flavone	AD-R ligand – A ₁ (PIA displacement) [0.8], A _{2A} (CGS displacement) [1], A ₃ (ABMECA displacement) [<10] (ARH)
[β-Naphthoflavone] (naphthoflavone)	Synthetic	A ₁ AD-R selective ligand (PIA displacement) [9]
[PIA (= N6-Phenylisopropyl-adenosine)] (purine nucleoside)	Synthetic – cf. Adenosine	A ₁ AD-R selective agonist [1 nM]

(continued)

Table 5.1 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other target) / in vivo effects
[8-(<i>p</i> -Sulphophenyl)- theophylline] (aryl xanthine)	Synthetic – cf. Theophylline	A ₁ AD-R selective antagonist (polar & excluded from brain by blood brain barrier (BBB))

Table 5.2 Muscarinic acetylcholine receptor

Compound (class)	Plant (family) part	Receptor affected (other target) / in vivo effects
Muscarinic Acetylcholine receptor (mACh-R) – agonists		5.2A
Alkaloid		5.2Aa
Arecaidine (= Arecaine) (dehydropiperidine)	<i>Areca catechu</i> [betel nut] (Palmae), <i>Piper betle</i> [betel pepper leaf] (Piperaceae)	mACh-R agonist – atrial M2 α & ileal M2 β (at 0.01–1) [diaphoretic, laxative, miotic, teniacidal]
Arecoline (dehydropiperidine)	<i>Areca catechu</i> [betel nut] (Palmae), <i>Piper betle</i> [betel pepper leaf] (Piperaceae)	mACh-R agonist – atrial M2 α & ileal M2 β (at 0.01–1) [anthelmintic, cathartic, mutagen, parasympathetic stimulant, teniacidal]
Brucine (= 10,11- Dimethoxystrychnine) (indole)	<i>Strychnos aculeata</i> , <i>S. ignatii</i> , <i>S. nox vomica</i> (Loganiaceae) [bark, seed, wood]	M1 mACh-R allosteric modulator agonist [CNS stimulant]
Guvacine (= <i>N</i> - Demethyl arecaidine; Δ^3 - Tetrahydronicotinic acid) (piperidine)	<i>Areca catechu</i> [betel nut] (Palmae)	mACh-R agonist – atrial M2 α & ileal M2 β (at 0.01–1) (GABA-TR)
Guvacoline (= Guvacine methyl ester) (piperidine)	<i>Areca catechu</i> [betel nut] (Palmae)	mACh-R agonist – rat atrial M2 α & ileal M2 β (at 0.01–1)
Ibogaine (= 12- Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> (iboga), <i>Voacanga thouarsii</i> (Apocynaceae); iboga W. African stimulant & aphrodisiac	mACh-R ligand (AD-R, D-R, DTR, 5HT ₁ TTR, NMDA-Glu-R, O-R) [anti-addictive, anticonvulsant, hallucinogenic]
Liriodenine (benzophenanthridinone)	<i>Annona</i> spp., <i>Guatteria scadens</i> , <i>Fissistigma glaucescens</i> (Annonaceae), <i>Liriodendron</i> , <i>Magnolia</i> (Magnoliaceae) spp.	mAChR antagonist
Pilocarpine (furanone imidazole)	<i>Pilocarpus jaborandi</i> , <i>P. microphyllus</i> , <i>P.</i> spp. (Rutaceae)	mACh-R partial agonist (α 9 nACh-R blocker) [anti-glaucoma, cholinergic, gastric, salivary & lachrymal secretory stimulant, myotic, parasympathomimetic]
Pilosine (imidazole furan)	<i>Pilocarpus microphyllus</i> , (Rutaceae)	mACh-R agonist [parasympathetic agonist increasing gastric, lachrymal & salivary secretion]

(continued)

Table 5.2 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other target) / in vivo effects
Terpene		5.2At
Bodinone (triterpene)	<i>Schefflera bodinieri</i> (Araliaceae) [leaf, root]	mACh-R ligand (0.9) [0.3]
Bodinone glycoside (triterpene glycoside)	<i>Schefflera bodinieri</i> (Araliaceae) [leaf, root]	mACh-R ligand (4) [1]
3-Epioleanolic acid (triterpene)	<i>Ekebergia capensis</i> (Meliaceae); Zulu use as uterotonic to facilitate childbirth	mACh-R agonist [uterine smooth muscle contraction]
<i>Ginkgo biloba</i> extract e.g. EGb-761 (triterpene saponins + flavonoids)	<i>Ginkgo biloba</i> (Ginkgoaceae); anti-glaucoma & alleviates diabetic retinopathy (alloxan-treated rat) (esp. + Zn²⁺);	Reverses aging brain mACh-R loss [AI, AO/FRS, PAF antagonism; ↑ blood flow, blocks angiogenesis, ↓ metastasis, ↓ LDL oxidation]
Oleanolic acid (triterpene)	<i>Lavandula</i> , <i>Ocimum</i> , <i>Origanum</i> , <i>Rosmarinus</i> , <i>Salvia</i> , <i>Thymus</i> spp. (Lamiaceae), <i>Ekebergia capensis</i> (Meliaceae) (Zulu use as uterotonic to facilitate childbirth), <i>Syzygium aromaticum</i> (Myrtaceae)	mACh-R agonist [uterine smooth muscle contraction]
Swertiamarin (seco-iridoid monoterpenes)	<i>Centaurium erythraea</i> , <i>Gentiana</i> spp., <i>Swertia japonica</i> (Gentianaceae) (Japanese bitter stomachic use)	mACh-R antagonist [anticholinergic]
Other		5.2Ao
Acetylcholine (basic non-heterocyclic)	<i>Helianthus annuus</i> (sunflower) (Asteraceae), <i>Spinacia oleracea</i> (spinach) (Chenopodiaceae), <i>Pisum sativum</i> (Fabaceae), <i>Urtica dioica</i> (Urticaceae)	mACh-R agonist [34 nM] (nACh-R, rat α4β2) [natural nACh-R agonist; water resorption & photosynthesis regulation in plants]
Ethyl-α-D-glucopyranoside (sugar)	<i>Clerodendrum mandarinorum</i> (Verbenaceae) [root bark]	mACh-R ligand
2-Methoxy-5-hydroxymethylcyclopentane-1,3,4-triol (cyclitol alicyclic)	<i>Salpianthus arenius</i> (Nyctaginaceae)	mACh-R agonist [parasymphathomimetic]
Non-plant reference		5.2An
[Bethanecol] (tetraalkyl ammonium carbamate)	Synthetic	mACh-R agonist (α9 nACh-R blocker) [cholinergic]
[Carbachol (= Carbamyl choline chloride)] (quaternary ammonium)	Synthetic parasymphathomimetic	mACh-R agonist [cholinergic, myotic, parasymphathomimetic]
[MT2 & MT4] (proteins)	Mamba snake venom	mACh-R allosteric activator agonists
[MTLP-1 (= Muscarinic toxin-like protein)] (polypeptide)	<i>Naja kaouthia</i> (cobra snake)	mACh-R ligand – M3 (Methylscopolamine displacement) (3) [amino acid sequence homology to MTLP-2 from cobra & mamba toxins MT1 & MT4]

(continued)

Table 5.2 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other target) / in vivo effects
[Muscarine] (quaternary ammonium furan)	<i>Amanita muscaria</i> (fly agaric mushroom) (Amanitaceae), <i>Inocybe</i> spp. (mushroom) (Cortinariaceae), <i>Clitocybe</i> spp. (mushroom) (Tricholomataceae)	mACh-R agonist ($\alpha 9$ nACh-R antagonist) [muscarinic cholinergic, lacrimalatory, hypotensive, visual, bowel, bronchial and heart disturbance, toxic]
[Otenzepad] (piperidinylbenzazepine)	Synthetic	mACh-R – M2 antagonist
Oxotremorine (acetylene-linked pyrrolidine pyrrolidone)	Synthetic	mACh-R agonist (3nM)
Muscarinic Acetylcholine receptor (mACh-R) – antagonists		5.2B
Alkaloid		5.2Ba
Atropine (= d,l- Hyoscamine; Tropine (\pm)-tropate ester) (racemate of hyoscamine) (tropane); from Atropos, the Greek Fate who cut short life	<i>Atropa belladonna</i> (belladonna, deadly nightshade), <i>Datura stramonium</i> , <i>Mandragora</i> , <i>Scopolia</i> spp. (Solanaceae); Atropine studied by Richard Willstätter (Nobel Prize, Chemistry, 1915, plant pigments & chlorophyll; fled Nazis, 1938)	mACh-R antagonist ($\alpha 9$ nACh-R), SM contraction inhibition [1 nM] [anticholinergic, anti-spasmodic, antidote for organophosphate poisoning, mydriatic, suppresses salivation, gives blurred vision, vasodilatory, very toxic]; belladonna agent in poisoning of Marc Antony's soldiers (Parthian Wars) & Danish army (by Macbeth's Scottish soldiers)
Berberamine (= Berbenine) (bisbenzylisoquinoline)	<i>Berberis</i> , <i>Mahonia</i> spp. (Berberidaceae), <i>Atherosperma moschatum</i> (Monimiaceae)	mACh-R ligand [0.2] (nACh-R) [antibiotic, antitumour, spasmolytic, toxic, vasodilatory]
Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> (Annonaceae), <i>Berberis</i> , <i>Hydrastis</i> , <i>Mahonia</i> , <i>Nandina</i> (Berberidaceae), <i>Archangelica</i> (Menispermaceae), <i>Argemone</i> , <i>Chelidonium</i> , <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> , <i>Thalictrum</i> (Ranunculaceae), <i>Evodia</i> , <i>Toddalia</i> , <i>Zanthoxylum</i> (Rutaceae) spp.	mACh-R ligand (1) ($\alpha 1A$ -R, $\alpha 2A$ -R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT ₂ -R, nACh-R, MLCK, PKA, PKC) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
Caracurine V (indole)	<i>Strychnos dolichothyrsa</i> (Loganiaceae) [stem bark]	M2 mACh-R allosteric antagonist (at ~ 10nM) [muscle relaxant, NM blocker]
Caracurine V mono-N- oxide (indole)	<i>Strychnos dolichothyrsa</i> (Loganiaceae) [stem bark]	M2 mACh-R allosteric antagonist [muscle relaxant, NM blocker]
Caracurine V di-N-oxide (indole)	<i>Strychnos dolichothyrsa</i> (Loganiaceae) [stem bark]	M2 mACh-R allosteric antagonist [local anaesthetic, muscle relaxant, NM blocker, topical ophthalmic anaesthetic]
(–)-Cocaine (= Benzoylmethylecgonine; Methylbenzoylcocaine) (tropane)	<i>Erythroxylum coca</i> , <i>E. recurrens</i> , <i>E. steyermarkii</i> , <i>E.</i> spp. (Erythroxylaceae) [coca leaf]	M2 mACh-R antagonist [19] (D-TR, 5HT-TR)

(continued)

Table 5.2 (Continued)

Compound (class)	Plant (family) [part]	Receptor affected (other target) / in vivo effects/
(+)-Cocaine (= Benzoylmethylecgonine; Methylbenzoylecgonine) (tropane)	Not in coca plant – cf. (–)- Cocaine	M2 mACh-R antagonist [2]
Constrictosine (protopine isoquinoline)	<i>Aristolochia constricta</i> (Aristolochiaceae)	mACh-R antagonist [inhibits ACh- induced ileum contraction]
Cryptolepine (indole, indoloquinoline)	<i>Cryptolepis sanguinolenta</i> , <i>C. triangularis</i> (Asclepiadaceae) [root]	mACh-R antagonist (M1, M2, M3) [2–10]
5,6-Dihydro constrictosine (protopine isoquinoline)	<i>Aristolochia constricta</i> (Aristolochiaceae)	mACh-R antagonist [inhibits ACh- induced ileum contraction]
5,6-Dihydro-3,5-di-O- methylconstrictosine (protopine isoquinoline)	<i>Aristolochia constricta</i> (Aristolochiaceae)	mACh-R antagonist [inhibits ACh- induced ileum contraction]
Dihydrohimbacine (piperidine)	<i>Himantandra (Galbulimima)</i> <i>baccata</i> , <i>H. belgraveana</i> (Himantandraceae) [bark]	mACh-R antagonist [inhibits atrial & ACh-induced ileum contraction] [anti-spasmodic]
Dihydrohimbandravine (piperidine)	<i>Himantandra (Galbulimima)</i> <i>baccata</i> , <i>H. belgraveana</i> (Himantandraceae) [bark]	mACh-R antagonist [inhibits atrial & ACh-induced ileum contraction] [anti-spasmodic]
Dihydrohimbeline (piperidine)	<i>Himantandra (Galbulimima)</i> <i>baccata</i> , <i>H. belgraveana</i> (Himantandraceae) [bark]	mACh-R antagonist [inhibits atrial & ACh-induced ileum contraction] [anti-spasmodic]
3,5-Di-O-methyl- constrictosine (isoquinoline)	<i>Aristolochia constricta</i> (Aristolochiaceae)	mACh-R antagonist [inhibits ACh- induced ileum contraction]
Ebeinone (steroidal)	<i>Fritillaria imperialis</i> (Liliaceae)	mACh-R antagonist – M2 & M3 [carbachol antagonist – atrium [7 nM; 81 nM], ileum [931 nM], trachea [547 nM]
Himbacine (piperidine)	<i>Himantandra (Galbulimima)</i> <i>baccata</i> , <i>H. belgraveana</i> (Himantandraceae) [bark]	mACh-R antagonist [inhibits ACh- induced ileum contraction] [anti-spasmodic]
Himbandravine (piperidine)	<i>Himantandra (Galbulimima)</i> <i>baccata</i> , <i>H. belgraveana</i> (Himantandraceae) [bark]	mACh-R antagonist [inhibits ACh- induced ileum contraction] [anti-spasmodic]
Himbeline (piperidine)	<i>Himantandra (Galbulimima)</i> <i>baccata</i> , <i>H. belgraveana</i> (Himantandraceae) [bark]	mACh-R antagonist [inhibits ACh- induced ileum contraction] [anti-spasmodic]
Hyoscyne (= 6,7- Epoxytropine tropate; Scopolamine) (tropane)	<i>Anthocercis viscosa</i> , <i>A. fasciculata</i> , <i>Datura metel</i> , <i>D. innoxia</i> [Datura potion for S. Am. Indian sacrificial victim pre-sacrifice stupor], <i>Duboisia myoporoides</i> , <i>Hyoscyamus</i> <i>niger</i> (henbane), <i>Methysticodendron</i> <i>amesianum</i> , <i>Scopolia carniolica</i> (Solanaceae)	mACh-R antagonist [amnesic, anticholinergic, anti-spasmodic formation sickness; Hyoscyne investigational “truth drug”]
Hyoscamine (= Daturine; Duboisine; 3 α - Tropanyl S-(–)-tropate) (Atropine is the racemate) (tropane)	<i>Atropa belladonna</i> (belladonna, deadly nightshade), <i>Datura</i> <i>stramonium</i> , <i>Duboisia myoporoides</i> , <i>Hyoscyamus niger</i> (henbane), <i>H. muticus</i> (Solanaceae)	mACh-R antagonist [anticholinergic, antiemetic, anti-spasmodic, antisecretory for saliva, perspiration & gastric secretion, mydriatic, toxic]

(continued)

Table 5.2 (Continued)

Compound (class)	Plant (family) part/	Receptor affected (other target) / in vivo effects/
Imperialine (cervane steroid)	<i>Petilium eduardi</i> , <i>P. raddeana</i> (Liliaceae)	M1-M4 mAChR antagonist – M1 [130 nM], M2 [20–63 nM; 2], M3 [0.2–1], M4 [130 nM] [SM relaxant]
Liriodenine (= Spermatheridine) (benzylisoquinoline)	<i>Annona</i> , <i>Guatteria</i> spp., <i>Fissistigma glaucescens</i> (Annonaceae), <i>Liriodendron</i> <i>tulipifera</i> , <i>Magnolia obovata</i> (Magnoliaceae)	mACh-R antagonist (SM M2+M3) [2 μ M] [antimuscarinic, antifungal, cytotoxic, blocks tracheal contraction [1 μ M] cytotoxic]
[Lolitrein B] (indole)	<i>Acremonium lolii</i> -infected <i>Lolium perenne</i> (perennial rye grass)	mACh-R agonist [from Paxilline; livestock uncoordination, staggering; tremorgen]
Methuenine (acylindole)	<i>Pterotaberna inconspicua</i> (Apocynaceae)	mACh-R non-competitive antagonist [inhibits ACh-induced guinea pig ileum contraction (8)]
3-O-Methyl- constrictosine (protopine isoquinoline)	<i>Aristolochia constricta</i> (Aristolochiaceae)	mACh-R antagonist [inhibits ACh- induced ileum contraction]
N-Methylhimbandravine (piperidine)	<i>Himantandra</i> (<i>Galbulimima</i>) <i>baccata</i> , <i>H. belgraveana</i> (Himantandraceae) [bark]	mACh-R antagonist [inhibits ACh- induced ileum contraction] [anti-spasmodic]
[Methylscopolamine (= Hyoscine methyl bromide)] (tropane alkaloid derivative)	Semi-synthetic from Scopolamine (= Hyoscine)	mACh-R antagonist (M1–M4) [25 pM] [anticholinergic, antiulcerative]
Norhyoscamine (= Pseudohyoscamine; Solandrine; 1-Tropic acid 3 α -nortropanyl ester) (tropane)	<i>Datura</i> spp., <i>Hyoscamus muticus</i> (Egyptian henbane) (Solanaceae)	mACh-R antagonist
Palmatine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Jateorrhiza palmata</i> (Menispermaceae), <i>Berberis</i> , <i>Mahonia</i> (Berberidaceae), <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> (Ranunculaceae) spp.	mACh-R ligand (4) (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, 5HT2-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]
[Paxilline] (indole)	<i>Acremonium lolii</i> -infected <i>Lolium perenne</i> (perennial rye grass)	Precursor of mACh-R agonist & tremorgen Lolitrein B (IP ₃ -R)
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Argemone</i> , <i>Bocconia</i> , <i>Chelidonium</i> , <i>Corydalis</i> , <i>Dicentra</i> , <i>Eschscholtzia</i> , <i>Glaucium</i> , <i>Macleaya</i> , <i>Papaver</i> , <i>Sanguinaria</i> (Papaveraceae), <i>Fumaria</i> (Fumariaceae), <i>Zanthoxylum</i> (Rutaceae), <i>Pteridophyllum</i> (Sapindaceae) spp.	mACh-R ligand (2) (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT2-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]
Tetrahydrocoptisine (benzophenanthridine)	<i>Chelidonium majus</i> , <i>Corydalis</i> spp. (Papaveraceae) [tuber]	mACh-R ligand [0.7]
(-)-Tetrandine (= Phaeanthine) (bisbenzylisoquinoline)	<i>Stephania tetrandra</i> (Menispermaceae) [root]	mACh-R ligand [73 nM] [apoptotic]

(continued)

Table 5.2 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other target) / in vivo effects
Usambarensine (tertiary amine)	<i>Strychnos usambarensis</i> [root bark] (Loganiaceae)	mACh-R antagonist [arrow poison, antimuscarinic, atropine-like, spasmolytic, toxic]
Terpene		5.2Bt
Ginsenoside Rg3 (triterpene saponin)	<i>Panax ginseng</i> [ginseng root] (Araliaceae)	mACh-R antagonist (H-R) (at 1–100) [antitumour]
Swertiamarin (= Erythrocentaurin glucoside; Swertiamaroside) (seco-iridoid glucoside)	<i>Centaurium</i> , <i>Gentiana</i> spp., <i>Swertia japonica</i> (Gentianaceae)	mACh-R antagonist [anticholinergic, stomachic; aglycone bitter]
Other		5.2Bo
D-Sorbitol (sugar alcohol)	<i>Schefflera bodinieri</i> (Araliaceae), <i>Cocos nucifera</i> (Arecaceae), <i>Althaea officinalis</i> (Malvaceae), <i>Plantago major</i> (Plantaginaceae)	mACh-R ligand (3) [1]
Non-plant reference		5.2Bn
[Dextimide] (piperidine tertiary amine)	Synthetic	mACh-R antagonist [anticholinergic, anti-Parkinsonian]
[Dimethocaine] (aryl tertiary amine)	Synthetic	M1 & M2 mACh-R antagonist [antimuscarinic, local anaesthetic]
[4-Diphenylacetoxy-N- methylpiperidine (= 4- DAMP)] (piperidine)	Synthetic SM selective mAChR M3 antagonist	mACh-R antagonist – SM selective M3 antagonist [2 nM] [cytotoxic]
[Gallamine] (aryl tetraalkyl ammonium)	Synthetic	mACh-R antagonist (M2 selective at 2) ($\alpha 9$ nACh-R) [skeletal muscle relaxant]
[Lidocaine] (aryl tertiary amine)	Synthetic	M1 & M2 mACh-R antagonist (V- gated Na ⁺) (204, 326) [allergenic, local anaesthetic, antiarrhythmic]
[Mepenzolate] (aryl piperidine quaternary amine)	Synthetic	mACh-R antagonist (at 0.01–10) [anticholinergic]
[Methacholine (= Acetyl 2-methylcholine)] (alkyl quaternary amine)	Synthetic	M2 (cardiac) mACh-R agonist [cholinergic (antidote: Atropine)]
[Methoctramine] (aryl amine)	Synthetic	mACh-R antagonist (cardioselective M2 antagonist) [89 nM] [antimuscarinic, antifungal, cytotoxic]
[N-Methylatropine] (tropane)	Semi-synthetic	mACh-R antagonist – M1, M2, M3
[MT-7 (= Muscarinic toxin 7)] (polypeptide)	<i>Dendroaspis angusticeps</i> (green mamba snake venom)	M1 mACh-R non-competitive antagonist (at 1–30 nM)
[Norcocaine] (tropane)	Synthetic	M1 & M2 mACh-R antagonist [antimuscarinic, local anaesthetic]
[Pirenzepine] (piperazine benzodiazepine tertiary amine)	Synthetic	mACh-R antagonist (M1 selective at 7 nM; M1 & M3 at 3) [anticholinergic, anti-ulcerative, gastric secretion inhibitor]

(continued)

Table 5.2 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other target) / in vivo effects
[Procaine] (aryl amine)	Synthetic	M1 & M2 mACh-R antagonist [antimuscarinic, local anaesthetic]
[3-Quinuclidinol benzilate ester (piperidine)	Synthetic	mACh-R antagonist [0.2 nM] (M2 selective) [atropine-like, chemical warfare incapacitant]
[Tiotropium] (tropanium thienyl quaternary amine)	Synthetic	mACh-R antagonist (M1, M2, M3) [potent, long-lasting antimuscarinic bronchodilator esp. for chronic obstructive airways disease]

Table 5.3 Adrenergic receptors

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
α1-Adrenergic receptor (α1A-R)		5.3A
Alkaloid		5.3Aa
Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> (Annonaceae), <i>Berberis</i> , <i>Hydrastis</i> , <i>Mahonia</i> , <i>Nandina</i> (Berberidaceae), <i>Archangelica</i> (Menispermaceae), <i>Argemone</i> , <i>Chelidonium</i> , <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> , <i>Thalictrum</i> (Ranunculaceae), <i>Evodia</i> , <i>Zanthoxylum</i> (Rutaceae) spp.	α 1A-R antagonist (3) (α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
Brucine (= 10,11- Dimethoxystrychnine) (indole)	<i>Strychnos aculeata</i> , <i>S. ignatii</i> , <i>S. nox vomica</i> (Loganiaceae) [bark, seed, wood]	α 1A-R antagonist – rat vas deferens Prazosin displacement (3) (mACh-R) [CNS stimulant]
<i>l</i> -Crebanine (Tetrahydroisoquinoline)	<i>Stephania succifera</i> (Menispermaceae)	α 1A-R antagonist (α 2A-R)
Dehydroevodiamine (indole)	<i>Evodia rutaecarpa</i> (Rutaceae)	α 1A-R antagonist (4) (AChE) [anti-amnesic, vasodilatory]
<i>d</i> -Dicentrine (aporphine isoquinoline)	<i>Dicentra pusilla</i> , <i>D. spp.</i> (Fumariaceae), <i>Lindera megaphylla</i> (Lauraceae), <i>Hordeum vulgare</i> (Poaceae)	α 1A-R antagonist (1–6 nM) [SM relaxant, \uparrow cAMP, PAI]
Dihydrocorynantheine (indole)	<i>Uncaria tomentosa</i> (Pedaliaceae), <i>Corynanthe pachyceras</i> , <i>Pausinystalia</i> <i>johimbe</i> (Rubiaceae) [bark]	α 1A-R antagonist (α 2A-R) (0.4) [leishmanicidal]
Dihydropapaverine (benzoisoquinoline)	Semi-synthetic	α 1A-R antagonist (18) (L-type Ca ²⁺ CH)
(–)-Discretamine (tetrahydroprotoberberine isoquinoline)	<i>Fissistigma glaucescens</i> , <i>Guatteria</i> <i>discolor</i> (Annonaceae)	α 1A-R antagonist (25–63 nM) (α 2A-R, 5HT-R)
Harmaline (= 3,4- Dihydroharmine; Harmidine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria</i> <i>caapi</i> , <i>Banisteriopsis caapi</i> (Malpighiaceae), <i>Peganum harmala</i> (Zygophyllaceae)	α 1A-R antagonist [~30] (I2-R, MAO-A)

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part/	Receptor affected (other targets) in vivo effects/
Harmalol (= Demethylharmaline) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteriopsis caapi</i> (Malpighiaceae), <i>Peganum harmala</i> (Zygophyllaceae) [seed]	α 1A-R antagonist [36]
Harman (= 1-Methyl- β -carboline) (β -carboline, indole)	<i>Passiflora edulis</i> , <i>P. incarnata</i> (Passifloraceae), <i>Singickia rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> , <i>Zygophyllum fabago</i> (Zygophyllaceae)	α 1A-R antagonist (BZ-R, DNA, 5HT ₂ -R, L-type Ca ²⁺ CH) [convulsant, cytotoxic]
Harmine (= Banisterine; Leucoharmine; Telepathine; Yageine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> (Zygophyllaceae)	α 1A-R antagonist [31] (5HT-R, MAO-A, L-type Ca ²⁺ CH) [CNS stimulant, hallucinogen ; Gestapo use as "truth drug"]
Ibogaine (= 12-Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> (iboga), <i>Voacanga thouarsii</i> (Apocynaceae); iboga W. African stimulant & aphrodisiac	α 1A-R ligand (7) (AD-R, mACh-R, D-R, D-TR, 5HT-R, NE-TR, NMDA-Glu-R, O-R) [anti-addictive, anticonvulsant, hallucinogenic]
Isocorydine (= Artabotrine; Luteanine) (aporphine isoquinoline)	<i>Annona</i> , <i>Artabotrys</i> , <i>Asimina</i> , (Annonaceae), <i>Mahonia</i> (Berberiaceae), <i>Corydalis</i> , <i>Glaucium</i> , <i>Papaver</i> spp. (Papaveraceae)	α 1A-R antagonist [cataleptic, sedative, toxic]
Isothebaine (= 1-Hydroxy-2,11-dimethoxyaporphine) (aporphine isoquinoline)	<i>Papaver bracteatum</i> , <i>P. orientale</i> , <i>P. pseudo-orientale</i> (Papaveraceae)	α 1A-R antagonist [AI, analgesic, respiratory & cardiac depressant]
Laudanosine (= Laudanine methyl ether) (benzylisoquinoline)	<i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [opium exudate]	α 1A-R antagonist (6; 12) (GABAA-R, L-Ca ²⁺ CH, O-R) [analgesic, convulsive, hypotensive, tetanic, toxic, antinociceptive]
Liriodenine (= Spermatheridine) (benzylisoquinoline)	<i>Annona cherimolia</i> (Annonaceae), <i>Liriodendron tulipifera</i> , <i>Magnolia obovata</i> (Magnoliaceae)	α 1A-R antagonist (at 0.1–100) (L-Ca ²⁺ CH) [vasodilator]
[Lysergamide (= 9,10-Didehydro-6-methylergoline-8 β -carboxamide); Ergine; Lysergic acid amide] (ergoline); in ergot [dried sclerotia of fungus <i>Claviceps purpurea</i> parasitic on rye]	<i>Ipomoea argyrophylla</i> , <i>I. tricolor</i> , <i>Rivea corumbosa</i> (Convolvulaceae) [drug ololiqui], <i>Stipa robusta</i> , <i>S. vaseyi</i> (sleepy grass) (Poaceae); <i>Festuca arundinacea</i> (tall fescue) (Poaceae) infected with fungus <i>Acremonium coenophialum</i>	α 1A-R partial agonist & antagonist (inhibits Phenylephrine-induced vasoconstriction) (at 10) (α 2A-R, 5HT ₂ -R); precursor for synthesis of LSD [depressant, hallucinogenic]
Norreticuline (benzylisoquinoline)	<i>Berberis wilsoniae</i> (Berberidaceae), <i>Erythrina crista-galli</i> (Fabaceae)	α 1A-R ligand (26) (α 2A-R, β A-R, 5HT ₂ -R) [hair growth accelerant]
Norushinsunine (aporphine isoquinoline)	<i>Annona cherimolia</i> (Annonaceae)	α 1A-R antagonist (at 0.1–100) (L-Ca ²⁺ CH) [vasodilator]

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Ocoteine (aporphine isoquinoline)	<i>Cassytha filiformis</i> (Lauraceae)	α 1A-R antagonist
Palmitine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Berberis</i> , <i>Mahonia</i> spp. (Berberidaceae), <i>Jateorrhiza palmata</i> (Menispermaceae), <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> (Ranunculaceae) spp.	α 1A-R ligand (6) (α 2A-R, AChE, ATPase, BChE, ChAT, diamine oxidase, 5HT ₂ -R, mACh-R, nACh-R, PK) [antibacterial, AI]
Papaverine (benzoisoquinoline)	<i>Papaver bracteatum</i> , <i>P. serpentina</i> , <i>P. somniferum</i> (opium poppy) (Papaveraceae)	α 1A-R antagonist (prazosin competition) (4; 39) (L-type Ca ²⁺ channel, PDE)
(+)-Reticuline (= Coclanoline) (benzylisoquinoline)	<i>Annona glabra</i> , <i>A.</i> spp. (Annonaceae), <i>Cryptocarya odorata</i> (Lauraceae), <i>Papaver somniferum</i> (opium poppy latex), <i>P.</i> spp. (Papaveraceae)	α 1A-R ligand (22) (α 2A-R, β A-R, 5HT-R) [hair growth accelerant]
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> (Papaveraceae), <i>Sanguinaria canadensis</i> , <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	α 1A-R ligand (34) (α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]
<i>l</i> -Stephanine (tetrahydroisoquinoline)	<i>Stephania japonica</i> (Menispermaceae)	α 1A-R antagonist
<i>l</i> -Stepholidine (tetrahydroisoquinoline)	<i>Annona cherimola</i> (Annonaceae), <i>Pachygone ovata</i> , <i>Stephania glabra</i> (Menispermaceae)	α 1A-R antagonist (α 2A-R)
<i>l</i> -Tetrahydrocoptisine (tetrahydroisoquinoline)	<i>Corydalis thysiflora</i> , <i>C. turtchaninowii</i> , <i>Chelidonium majus</i> (Papaveraceae)	α 1A-R antagonist (α 2A-R)
<i>l</i> -Tetrahydropalmitine (tetrahydroisoquinoline)	<i>Stephania glabra</i> (Menispermaceae) <i>Corydalis</i> spp., <i>Papaver bracteatum</i> (Papaveraceae) [rhizome]	α 1A-R antagonist (α 2A-R)
[Tetrahydropapaverine] (tetrahydro- benzoisoquinoline)	Semi-synthetic	α 1A-R antagonist (8) (DHP- binding & L-type Ca ²⁺ channel blocker)
[Tetrahydropapaveroline] (tetrahydro- benzoisoquinoline)	Metabolic product of Dopamine	α 1A-R antagonist (18) (β 1A-R, DHP-binding & L-type Ca ²⁺ channel blocker)
Xylopinine (aporphine)	<i>Annona</i> spp., <i>Guatteria scadens</i> , <i>Xylophia discreta</i> , <i>X. papuana</i> (Annonaceae)	α 1A-R antagonist
Xylopinine (aporphine)	<i>Xylophia discreta</i> , <i>X. buxifolia</i> (Annonaceae), <i>Duguetia</i> spp. (Menispermaceae)	α A-R antagonist
(+)-Yohimbine (= A phrodine; Corynine; Hydroergotocin; Quebrachine) (indole)	<i>Catharanthus lanceus</i> , <i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia yohimbe</i> (Rubiaceae) [yohimbe bark]	α 1A-R antagonist (0.7) (α 2A- R, D-R, 5HT-R)[antidepressant, aphrodisiac, mydriatic, toxic]

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
β -Yohimbine (= 17- β -OH anomer of Yohimbine) (indole)	<i>Catharanthus lanceus</i> , <i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia yohimbe</i> (Rubiaceae) [yohimbe bark]	α 1A-R antagonist (1) (α 2A-R, 5HT-R)
Phenolic		5.3Ap
Dopamine (= 4-(2-Aminoethyl)-benzene-1,2-diol; 3-Hydroxy-tyramine) (catecholamine phenolic)	<i>Carnegiae gigantea</i> , <i>Lophophora williamsii</i> (mescal button) (Cactaceae), <i>Cytisus scoparius</i> (Fabaceae), <i>Musa paradisiaca</i> (banana peel) (Musaceae), <i>Hernandium alipes</i> (Nyctaginaceae)	α A-R agonist (β A-R, D-R) [dopaminergic NT, increases cardiac output, reduced in Parkinsonism, sympathomimetic]
Geraniin (ellagitannin)	<i>Acer</i> (Aceraceae), <i>Spondias pinnata</i> (Anacardiaceae), <i>Cercidiphyllum</i> (Cercidiphyllaceae), <i>Coriaria</i> (Coriariaceae), <i>Geranium</i> , <i>Erythroxylum</i> (Erythroxylaceae), <i>Euphorbia</i> , <i>Mallotus</i> (Euphorbiaceae), <i>Fuchsia</i> (Onagraceae) spp.	α 1A-R ligand (>10) (α 2-A R, D1-R, 5HT1-R, O-R)[inhibits Epinephrine-induced adipocyte lipolysis, increases ACTH-induced adipocyte lipolysis]
Octopamine (= <i>p</i> -Hydroxyphenylethanolamine) (phenolic amine)	<i>Coryphantha macromeris</i> (Cactaceae), <i>Cyperus papyrus</i> , <i>C. rotundus</i> (Cyperaceae), <i>Citrus reticulata</i> , <i>C. sinensis</i> , <i>C. spp.</i> (Rutaceae), <i>Capsicum frutescens</i> (Solanaceae)	Insect α -A-R-like octopamine-R
Procyanidin B3 (= Catechin (4 α →8) catechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae)	α 1A-R ligand (>10) (β A-R, D1-R, D2-R, 5HT1-R, O-R)
Procyanidin B4 (catechin (4 α →8)epicatechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae), <i>Rubus idaeus</i> (Rosaceae)	α 1A-R ligand (~10) (α 2A-R, β A-R, D2-R, 5HT1-R, H1-R) [anti-ulcerative]
Tellimagrandin I (= 4,5-Hexahydroxydiphenoyl 2,3-digalloylglucose) (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Quercus</i> (Fagaceae), <i>Syzygium</i> , <i>Feijoa</i> , <i>Psidium</i> , <i>Eucalyptus</i> (Myrtaceae), <i>Fuchsia</i> (Onagraceae), <i>Geum</i> , <i>Rosa</i> , <i>Tellima</i> (Rosaceae), <i>Stachyurus</i> (Syachyuraceae), <i>Camellia</i> (Theaceae)	α 1A-R ligand (>10) (ATP-K ⁺ CH, α 2A-R, D2-R, O-R) [inhibits Epinephrine-induced adipocyte lipolysis]
Other		5.3Ao
Synephrine acetoneide (aryl amine)	<i>Casimiroa edulis</i> (Rutaceae) [seed]	α A-R agonist (β A-R) [hypertensive]
Non-plant reference		5.3An
[(-)-Indoloquinolizidine] (indole)	Synthetic	α 1A-R antagonist (α 2A-R) [0.2] [Clonidine antagonism]
[Methoxamine (= 2,5-Dimethoxynorephedrine)] (aryl amine)	Synthetic cf. Ephedrine	α 1A-R agonist [antihypotensive]
[Phenylephrine (= 3-(<i>N</i> -Methylaminoethanol)-phenol)] (phenolic amine)	Synthetic	α 1A-R agonist (α 2A-R) [decongestant, hypertensive, mydriatic, vasoconstrictor]

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
[Phentolamine] (aryl imidazoline tertiary amine)	Synthetic	α 1A-R blocker [31 nM] (α 2A-R)
[Prazosin] (furan piperazine quinazoline)	Synthetic	α 1A-R blocker (MT3-R antagonist) [antihypertensive]
[Thaligrisine] (bisbenzyltetrahydroisoquinoline)	Semi-synthetic	α 1A-R antagonist [48 nM] (L-Ca ²⁺ CH) [vascular SM relaxant]
α2-Adrenergic receptor (α2A-R)		5.3B
Alkaloid		5.3Ba
Agmatine (= (4-Aminobutyl) guanidine; 1-Amino-4-guanidinobutane) (aminoalkyl guanidine)	<i>Glycine max</i> , <i>Lathyrus sativa</i> (Fabaceae), <i>Hordeum vulgare</i> (Gramineae), <i>Sesamum indicum</i> (Pedaliaceae); animals, bacteria	α 2A-R agonist (I1-R, I2-R, NMDA-Glu-R, NOS) [hypotensive; \uparrow gastric acid secretion \rightarrow ulceration]
Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> (Annonaceae), <i>Berberis</i> , <i>Hydrastis</i> , <i>Mahonia</i> , <i>Nandina</i> (Berberidaceae), <i>Archangelica</i> (Menispermaceae), <i>Argemone</i> , <i>Chelidonium</i> , <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> , <i>Thalictrum</i> (Ranunculaceae), <i>Evodia</i> , <i>Toddalia</i> , <i>Zanthoxylum</i> (Rutaceae) spp.	α 2A-R antagonist (0.5) (α 1A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA, 5HT2-R, mACh-R, nACh-R, MLCK, PKA, PKC, RT) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
l-Crebanine (Tetrahydroisoquinoline)	<i>Stephania succifera</i> (Menispermaceae)	α 2A-R antagonist (α 1A-R)
Dihydrocorynantheine (indole)	<i>Corynanthe pachyceras</i> (Rubiaceae) [bark]	α 2A-R antagonist (α 1A-R) [blocks methoxamine-induced vas deferens contraction (0.4); Clonidine antagonism; leishmanicidal]
(-)-Discretamine (tetrahydroprotoberberine isoquinoline)	<i>Fissistigma glaucescens</i> , <i>Guatteria discolor</i> (Annonaceae)	α 2A-R antagonist (α 1A-R, 5HT-R)
Harmaline (= 3,4-Dihydroharmine; Harmidine) (dihydro β -carboline, indole)	<i>Banisteria caapi</i> , <i>Banisteriopsis caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae) [seed]	α 2A-R antagonist (>10) agonist (α 2A-R, BZ-R, 5HT-R, NMDA-Glu-R) [hallucinogenic, anti-Parkinson's]
Lysergamide (= 9,10-Didehydro-6-methylergoline-8 β -carboxamide); Ergine; Lysergic acid amide (ergoline); in Ergot	<i>Argyria</i> spp., <i>Ipomoea argyrophylla</i> , <i>I. tricolor</i> , <i>Rivea corumbosa</i> (Convolvulaceae) [drug ololiuqui], <i>Stipa robusta</i> , <i>S. vaseyi</i> (sleepy grass) (Poaceae); <i>Festuca arundinacea</i> (tall fescue) (Poaceae) infected with fungus <i>Acremonium coenophialum</i>	α 2A-R partial agonist & antagonist (inhibits agonist BHT-920-induced vasoconstriction) (at 10) (α 2A-R, 5HT2-R); precursor for synthesis of LSD [depressant, hallucinogenic]
Norharman (β -carboline, indole)	<i>Cichorium intybus</i> (Asteraceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae) [seed]	α 2A-R antagonist (w.r.t. Epinephrine) (human platelet) (>10) (5HT-R)

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Norreticuline (benzylisoquinoline)	<i>Berberis wilsoniae</i> (Berberidaceae), <i>Erythrina crista-galli</i> (Fabaceae)	α 2A-R ligand (10) (α 1A-R, β A-R, 5HT-R) [hair growth accelerant]
Palmatine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Berberis</i> , <i>Mahonia</i> spp. (Berberidaceae), <i>Jateorrhiza palmata</i> (Menispermaceae), <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> (Ranunculaceae)	α 2A-R ligand (1) (α 1A-R, AChE, ATPase, BChE, ChAT, diamine oxidase, DNA, 5HT2- R, mACh-R, nACh-R, PK) [antibacterial, AI]
Rauwolfscine (= Isoyohimbine; α -Yohimbine) (indole)	<i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia yohimbe</i> (Rubiaceae) [yohimbe bark]	α 2A-R antagonist [2–10 nM] (5HT1A-R, I1-R, I2-R)
(+)-Reticuline (= Coclanoline) (benzylisoquinoline)	<i>Annona glabra</i> , <i>A.</i> spp. (Annonaceae), <i>Cryptocarya odorata</i> (Lauraceae), <i>Papaver somniferum</i> (opium poppy latex), <i>P.</i> spp. (Papaveraceae),	α 2A-R ligand (5) (α 1A-R, β A- R, 5HT-R) [hair growth accelerant]
(–)-Salsolinol (tetrahydroisoquinoline)	<i>Annona reticulata</i> (Annonaceae), <i>Musa paradisiaca</i> (banana) (Musaceae) [fruit], <i>Theobroma cacao</i> (cocoa, chocolate) (Sterculiaceae) [seed]	α 2A-R antagonist (1; >10) (β A-R, D2-R, D3-R) [inhibits cAMP formation, β -endorphin release & ACTH release (pituitary)]
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> (Papaveraceae), <i>Sanguinaria canadensis</i> , <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Peridophyllum</i> spp. (Sapindaceae)	α 2A-R ligand (6) (α 1A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT2-R, mACh-R, nACh-R, MLCK, PKA, PKC, RT) [antibacterial, AI]
<i>l</i> -Stepholidine (tetrahydroisoquinoline)	<i>Annona cherimola</i> (Annonaceae), <i>Pachygone ovata</i> , <i>Stephania glabra</i> (Menispermaceae)	α 2A-R antagonist (α 1A-R)
<i>l</i> -Tetrahydrocoptisine (Tetrahydroisoquinoline)	<i>Corydalis thysiflora</i> , <i>C. turtschaninovi</i> , <i>Chelidonium majus</i> (Papaveraceae)	α 2A-R antagonist (α 1A-R)
[1,2,3,4-Tetrahydro- isoquinoline] (tetrahydroisoquinoline)	Semi-synthetic	α 2A-R antagonist (w.r.t. Epinephrine) (platelet) (10)
[1,2,3,4- Tetrahydronorharman] (tetrahydro β -carboline, indole)	Semi-synthetic	α 2A-R antagonist (w.r.t. Epinephrine) (human platelet) (10)
<i>l</i> -Tetrahydropalmatine (tetrahydroisoquinoline)	<i>Stephania glabra</i> (Menispermaceae), <i>Corydalis</i> spp., <i>Papaver bracteatum</i> (Papaveraceae) [rhizome]	α 2A-R antagonist (α 1A-R)
[(<i>S</i>)-(–)-Tetrahydro- papaveroline] (tetrahydroisoquinoline)	Metabolite of Dopamine	α 2A-R ligand (brain, Clonidine binding site) (0.7)
[(<i>R</i>)-(+)–Tetrahydro- papaveroline] (tetrahydroisoquinoline)	Metabolite of Dopamine	α 2A-R (brain, Clonidine binding site) (50)

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
[Thaligrisine] (bisbenzyltetrahydro- isoquinoline)	Semi-synthetic	α 2A-R antagonist [48 nM] (Prazosin displacement) [inhibits SM contraction]
Yohimbine (= Aphrodine; Corynine; Hydroergotocin; Quebrachine) (indole)	<i>Catharanthus lanceus</i> , <i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia yohimbe</i> (yohimbe) (Rubiaceae) [bark]	α 2A-R antagonist [1–10 nM] (α 1A-R, 5HT-R) [antidepressant, aphrodisiac, mydriatic, toxic]
β -Yohimbine (indole)	<i>Catharanthus lanceus</i> , <i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia yohimbe</i> (Rubiaceae) [yohimbe bark]	α 2A-R antagonist (1) (α 1A-R, 5HT-R) [Clonidine antagonism]
Phenolic		5.3Bp
Davidiin (= 1,5 Hexahydroxydiphenoyl 2,3,4-trigalloylglucose) (ellagitannin)	<i>Quercus</i> sp. (Fagaceae)	α 2A-R ligand (~10) (β A-R, D2-R, 5HT2-R, O-R)
(–)-Epiafzelechin (flavan-3-ol)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial], <i>Camellia sinensis</i> (Theaceae) [leaf]	α 2A-R (ATP K ⁺ CH, β A-R, COX-1, D2-R, 5HT1A-R, O-R) [AI with Carrageenin-induced paw oedema]
Geraniin (ellagitannin)	<i>Acer</i> (Aceraceae), <i>Cercidiphyllum</i> (Cercidiphyllaceae), <i>Coriaria</i> (Coriariaceae), <i>Geranium</i> , <i>Erythroxylum</i> (Erythroxylaceae), <i>Euphorbia</i> , <i>Mallotus</i> (Euphorbiaceae), <i>Fuchsia</i> (Onagraceae) spp.	α 2A-R ligand (~10) (α 1A-R, D1-R, 5HT1-R, O-R) [inhibits Epinephrine-induced adipocyte lipolysis, increases ACTH- induced adipocyte lipolysis]
1-Norepinephrine (= 1-Noradrenaline) (catecholamine)	<i>Abuzia julibrissin</i> , <i>Mimosa pudica</i> , <i>Phaseolus multiflorus</i> , <i>Pisum sativum</i> , <i>Samanea saman</i> (Fabaceae), <i>Musa sapientum</i> (Musaceae), <i>Portulaca oleraceae</i> (Portulacaceae), <i>Solanum tuberosum</i> (Solanaceae)	α 2A-R agonist [6–25 nM] (β A-R) [vasoconstrictive, hypertensive, sympathomimetic hormone]
Pedunculagin (= 2,3 Hexahydroxydiphenoyl 4,5 hexahydroxydiphenoyl glucose) (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Quercus</i> (Fagaceae), <i>Potentilla</i> , <i>Rubus</i> (Rosaceae), <i>Stachyurus</i> (Stachyuraceae), <i>Camellia</i> (Theaceae) spp.	α 2A-R ligand (~10) (ATP-K ⁺ CH, β A-R, D1-R, O-R) [inhibits Epinephrine-induced adipocyte lipolysis]
β -1,2,3,4,6-Penta-O-galloyl- D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark], <i>Geranium thumbergii</i> (Geraniaceae), <i>Paeonia lactiflora</i> (Paeoniaceae)	α 2A-R ligand (~10) (ATP-K ⁺ CH, D1-R, D2-R, O-R)
Procyanidin B4 (catechin (4 α →8) epicatechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae), <i>Rubus idaeus</i> (Rosaceae)	α 2A-R ligand (<10) (α 1A-R, β A-R, D2-R, 5HT1-R, H1-R) [anti-ulcerative]
Rugosin D (ellagitannin)	<i>Filipendula ulmaria</i> , <i>Rosa rugosa</i> (Rosaceae) [petal]	α 2A-R ligand (<10) (β A-R, D1-R, H1-R, O-R) [antitumour]

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Tellimagrandin I (= 4,5-Hexahydroxydiphenoyl 2,3-digalloylglucose) (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Quercus</i> (Fagaceae), <i>Syzygium</i> , <i>Feijoa</i> , <i>Psidium</i> , <i>Eucalyptus</i> (Myrtaceae), <i>Fuchsia</i> (Onagraceae), <i>Geum</i> , <i>Rosa</i> , <i>Tellima</i> (Rosaceae), <i>Stachyurus</i> (Stachyuraceae), <i>Camellia</i> (Theaceae) spp.	α 2A-R ligand (>10) (α 1A-R, D2-R, GPT, O-R, SU-R) [inhibits Epinephrine-induced adipocyte lipolysis]
β -1,2,4,6-Tetra-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark]	α 2A-R ligand (<10) (ATP-K ⁺ CH, β A-R, D2-R, O-R)
β -1,2,6-Tri-O-galloyl-D-glucose (gallotannin)	<i>Phyllanthus emblica</i> [fruit] (Euphorbiaceae), <i>Quercus</i> spp. (Fagaceae) [bark]	α 2A-R ligand (>10) (β A-R, D1-R, 5HT2-R, O-R)
Tyramine (= 4-Hydroxyphenylalanine) (phenolic)	<i>Lophophora williamsii</i> , <i>Trichocereus pachanoi</i> (Cactaceae), <i>Hordeum vulgare</i> , <i>Lolium multiflorum</i> (Poaceae), <i>Citrus</i> spp. (Rutaceae), <i>Viscum album</i> (Viscaceae)	Insect α 2A-R-like tyramine-R agonist (\downarrow AC) (D-TR ligand) [indirect adrenergic]
Terpene		5.3Bt
Dalsaxin (triterpene glycoside)	<i>Dalbergia saxatilis</i> (Fabaceae) [root]	α 2A-R agonist [stimulates uterine contraction]
Withaferin A (triterpene)	<i>Acanthus arborescens</i> , <i>Withania somnifera</i> (Indian ginseng), <i>W.</i> spp. (Solanaceae) [root]	α 2A-R antagonist [blocks Clonidine ileum effect; immunosuppressive]
Withanoside VI (triterpene glycoside)	<i>Withania somnifera</i> (Indian ginseng) (Solanaceae) [root]	α 2A-R antagonist [blocks Clonidine ileum effect]
Non-plant reference		5.3Bn
[Clonidine (= 2-[[2,6-Dichlorophenyl]imino]-2-imidazoline)] (aryl imidazoline)	Synthetic	α 2A-R agonist [2–6 nM] [antihypertensive]
[Epinephrine (= Adrenaline; <i>l</i> -Methylaminoethanol-catechol)] (catecholamine)	Animals (e.g. <i>ex</i> adrenal medulla)	α A-R agonist [2–11 nM] (β A-R, I1-R, I2-R) [vasoconstrictor, cardiostimulant, sympathomimetic hormone]
[(-)-Indoloquinolizidine] (indole)	Synthetic	α 2A-R antagonist (α 1A-R) (0.2) [Clonidine antagonism]
[Mirtazepine] (pyrazinopyridobenzazepine)	Synthetic analogue of Mianserin	α 2A-R antagonist (5HT2-R, 5HT3-R) [antidepressant]
[Phenylephrine (= 3-(<i>N</i> -Methylaminoethanol)-phenol)] (phenolic amine)	Synthetic	α 2A-R agonist [0.3] (α 1A-R) [decongestant, hypertensive, mydriatic, vasoconstrictor]
[Phentolamine] (aryl imidazoline tertiary amine)	Synthetic	α 2A-R agonist [2–78 nM] (α 1A-R)
[Prazosin] (furan piperazine quinazoline)	Synthetic	α 2A-R blocker [0.2] (α 1A-R) [antihypertensive]

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
β-Adrenergic receptor (βA-R)		5.3C
Alkaloid		5.3Ca
Higenamine (= Demethylcoclaurine racemate) (bisbenzylisoquinoline)	<i>Annona squamosa</i> (Annonaceae), <i>Nelumbo nucifera</i> (Nelumbonaceae), <i>Aconitum japonicum</i> (Ranunculaceae)	βA-R agonist [cardiac stimulant]
Isocorydine (= Artabotrine; Luteanine) (aporphine isoquinoline alkaloid)	<i>Annona squamosa</i> , <i>Artabotrys</i> , <i>Asimina triloba</i> (Annonaceae), <i>Mahonia</i> (Berberidaceae), <i>Phoebe</i> (Lauraceae), <i>Corydalis</i> , <i>Glaucium</i> , <i>Papaver</i> (Papaveraceae), <i>Isopyrum</i> (Ranunculaceae)	βA-R antagonist [anti- adrenergic, sedative, toxic]
Norreticuline (benzylisoquinoline)	<i>Berberis wilsoniae</i> (Berberidaceae), <i>Erythrina crista-galli</i> (Fabaceae)	βA-R ligand (6) (α1A-R, α2A-R, 5HT-R) [hair growth accelerant]
Oxyacanthine (bisbenzylisoquinoline alkaloid)	<i>Berberis vulgaris</i> , <i>Mahonia acanthifolia</i> , <i>M. aquifolium</i> (Berberidaceae); Magnoliaceae, Menispermaceae, Ranunculaceae	βA-R antagonist
(+)-Reticuline (= Coclanoline) (benzylisoquinoline)	<i>Annona glabra</i> , <i>A. spp.</i> (Annonaceae), <i>Cryptocarya odorata</i> (Lauraceae), <i>Papaver somniferum</i> (Papaveraceae),	βA-R ligand (7) (α1A-R, α2A-R, 5HT-R) [hair growth accelerant]
(-)-Salsolinol (isoquinoline)	<i>Annona reticulata</i> (Annonaceae), <i>Musa paradisiaca</i> (banana) (Musaceae) [fruit], <i>Theobroma cacao</i> (cocoa) (Sterculiaceae)	β1A-R ligand (Dihydroalprenolol binding site) (40)
[Tetrahydropapaveroline] (tetrahydroisoquinoline)	Metabolic product of Dopamine	β1A-R ligand (0.3) (α2A-R, L- type Ca ²⁺ CH)
Phenolic		5.3Cp
Davidiin (= 1,5 Hexahydroxydiphenoyl 2,3,4-trigalloylglucose) (ellagitannin)	<i>Quercus</i> sp. (Fagaceae)	βA-R ligand (~10) (α2A-R, D2-R, 5HT2-R, O-R)
Dopamine (= 4-(2- Aminoethyl)benzene-1,2- diol; 3-Hydroxytyramine) (catecholamine phenolic)	<i>Lophophora williamsii</i> (mescal button) (Cactaceae), <i>Cytisus scoparius</i> (Fabaceae), <i>Musa paradisiaca</i> (Musaceae), <i>Hermidium alipes</i> (Nyctaginaceae)	βA-R agonist (αA-R, D-R) [dopaminergic NT, increases cardiac output, reduced in Parkinsonism, sympathomimetic]
β-2,4-Di-O-galloyl-glucose (gallotannin)	<i>Croton lechleri</i> (Euphorbiaceae)	β-A R ligand (>10) (D1-R, D2-R, 5HT1-R, O-R)
(-)-Epiatzelechin (flavan-3-ol)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial], <i>Camellia sinensis</i> (Theaceae) [leaf]	βA-R ligand (<10) (ATP K ⁺ CH, α1A-R, COX-1, 5HT1A- R, O-R) [AI with Carrageenin- induced paw oedema]
(-)-Epicatechin (= (2R,3R)- 5,7,3',4'- Tetrahydroxyflavan-3-ol) (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), <i>Pterocarpus spp.</i> (Fabaceae) [bark], <i>Podocarpus nagi</i> (Podocarpaceae), <i>Crataegus monogyna</i> (Rosaceae)	βA-R ligand (<10) (AD-R, D2-R, PKA) [antibacterial, AI, anti-oxidant]

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
(-)-Epigallocatechin-3-gallate (flavan-3-ol, gallotannin)	<i>Camellia sinensis</i> (Theaceae), <i>Davidsonia pruriens</i> (Davidsoniaceae), <i>Hamamelis virginiana</i> (Hamamelidaceae)	β A-R ligand (>10) (D1-R, D2-R, O-R, PKC) [AI, blocks COX-2 & iNOS induction]
Gallocatechin (gallotannin)	<i>Eugenia uniflora</i> (Myrtaceae)	β A-R ligand (>10) (DNAP)
1-Norepinephrine (= 1-Noradrenaline) (catecholamine)	<i>Musa sapientum</i> (Musaceae), <i>Albizia julibrissin</i> , <i>Mimosa pudica</i> , <i>Phaseolus multiflorus</i> , <i>Pisum sativum</i> , <i>Samanea saman</i> (Fabaceae), <i>Portulaca oleraceae</i> (Portulacaceae), <i>Solanum tuberosum</i> (Solanaceae)	β A-R agonist (α 2A-R) [vasoconstrictive, hypertensive, sympathomimetic hormone]
Pedunculagin (= 2,3 Hexahydroxydiphenoyl 4,5 hexahydroxyldiphenoyl glucose) (ellagitannin)	<i>Casuarina stricta</i> (Casuarinaceae), <i>Quercus</i> sp. (Fagaceae), <i>Potentilla</i> sp., <i>Rubus</i> spp. (Rosaceae), <i>Stachyurus praecox</i> (Stachyuraceae), <i>Camellia japonica</i> (Theaceae)	β A-R ligand (<10) (α 2A-R, D1-R, GPT, SU-R, O-R) [inhibits Epinephrine-induced adipocyte lipolysis]
Procyanidin B3 (= Catechin (4 α →8) catechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae)	β A-R ligand (>10) (α 1A-R, D1-R, D2-R, 5HT1-R, O-R)
Procyanidin B4 (= Catechin (4 α →8) epicatechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae), <i>Rubus idaeus</i> (Rosaceae)	β A-R ligand (>10) (α 1A-R, α 2A-R, , D2-R, 5HT1-R, H1-R) [anti-ulcerative]
Rugosin D (ellagitannin)	<i>Filipendula ulmaria</i> , <i>Rosa rugosa</i> [petal] (Rosaceae)	β A-R ligand (~10) (α 2A-R, D1-R, H1-R, O-R) [antitumour]
Tannin (polyphenol)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [bract]	β A-R inhibition [contributes to cotton-induced byssinosis , bronchoconstriction]
β -1,2,4,6-Tetra- <i>O</i> -galloyl- β -D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark]	β A-R ligand (>10) (α 2A-R, D2-R, O-R, SU-R)
β -1,2,6-Tri- <i>O</i> -galloyl- β -D-glucose (gallotannin)	<i>Phyllanthus emblica</i> (Euphorbiaceae), <i>Quercus</i> spp. (Fagaceae) [bark]	β A-R ligand (<10) (α 2A-R, D1-R, 5HT2-R, O-R)
β -1,3,6-Tri- <i>O</i> -galloyl- β -D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark]	β A-R ligand (<10) (D2-R, O-R ligand)
Other		5.3Co
D-Cathine (= 2-Amino-1-hydroxy-1-phenylpropane; Katine; ψ -Norephedrine; Nor- ψ -ephedrine; Norpseudoephedrine; Pseudonorepinephrine) (phenylpropanoid)	<i>Catha edulis</i> (khat), <i>Maytenus krukovi</i> (Celastraceae), <i>Ephedra</i> spp. (Ephedraceae) [leaf]; khat (qat) – Arabian, Yemeni & E. African stimulatory tea beverage or masticatory	β A-R agonist [anorexic, CNS stimulant, euphoriant]
D-Cathinone (= (<i>S</i>)-2-Amino-1-phenyl-1-propanone) (phenylpropanoid)	<i>Catha edulis</i> (khat), <i>Maytenus krukovi</i> (Celastraceae) [leaf]	β A-R agonist (D-TR, 5HT-TR) [anorexic, CNS stimulant, euphoriant]
1-Ephedrine (= 1 <i>R</i> , 2 <i>S</i>)-1-Phenyl-1-hydroxy-2-methylaminopropane) (phenylpropanoid amino alcohol)	<i>Catha edulis</i> (khat) (Celastraceae), <i>Ephedra equisetina</i> , <i>E. gerardiana</i> , <i>E. sinica</i> , <i>E. spp.</i> (Ephedraceae), <i>Taxus baccata</i> (Taxaceae)	β A-R agonist (α A-R) [bronchodilator, hypertensive, respiratory stimulant, sympathomimetic, vasoconstrictive]

(continued)

Table 5.3 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
<i>N</i> -Formylnorephedrine (phenylpropanoid)	<i>Catha edulis</i> (khat) [leaf]	β A-R agonist [anorexic, CNS stimulant, euphoriant]
D-Pseudoephedrine (= D-isomer of ephedrine) (phenylpropanoid amino alcohol)	<i>Ephedra equisetina</i> , <i>E. gerardiana</i> , <i>E. sinica</i> , <i>E. spp.</i> (Ephedraceae)	β A-R agonist (α A-R) [bronchodilator, hypertensive, respiratory stimulant, sympathomimetic, vasoconstrictive]
Synephrine acetoneide (aryl amine)	<i>Casimiroa edulis</i> (Rutaceae) [seed]	β A-R agonist (α A-R) [hypertensive]
Non-plant reference		5.3Cn
[Epinephrine (= Adrenaline; <i>l</i> -Methylaminoethanol-catechol)] (catecholamine)	Animals (e.g. adrenals); cardiac action – Otto Loewi (Germany, Nobel Prize, 1936, chemical transmission)	β A-R agonist (α A-R agonist) [vasoconstrictor, cardiostimulant]
[Pindolol] (indolamine)	Synthetic	β A-R antagonist (5HT-R) [vasodilator]
[Propranolol (= 1-(Isopropylamino)-3-(1-naphthoxy)-2-propanol)] (naphthalenyloxypropanol imine)	Synthetic; Sir James Black (UK, Nobel Prize, Medicine, 1988, β-blocker & anti-histamine drug development)	β A-R antagonist [0.2nM] [anti-anginal, antihypertensive, antiarrhythmic, β -blocker]

Table 5.4 Dopamine receptors

Hormone compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Dopamine receptor (D1-R, D2-R)	Arvid Carlsson (Sweden, D & 5HT signalling), Paul Greengard (USA, D signalling) & Eric Kandel (Austria/USA, 5HT & memory) (Nobel Prize, Physiology/Medicine, 2000)	5.4
Alkaloid		5.4a
(<i>S,R</i>)-Antioquine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (>100), D2-R antagonist (3)
[Apomorphine] (aporphine isoquinoline)	Derived synthetically from Morphine (morphinan isoquinoline alkaloid from <i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [aerial])	Dopamine D-R agonist (CDPK, MLCK, PKA, PKC) [anti-Parkinson's]
(<i>R,S</i>)-Borbamunine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (1), D2-R antagonist (0.3)
[Bromocryptine (= 2-Bromoergocryptine)] (indole)	Semi-synthetic from Ergocryptine	D2-R agonist (53 nM) [2 nM] (\oplus D-REL) [anti-Parkinsonian, inhibits prolactin secretion]

(continued)

Table 5.4 (Continued)

Hormone compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
[Chanoclavine] (indole)	From hydrolysis of ergot (<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals)	D2-R agonist
(<i>S,R</i>)- <i>O</i> , <i>O</i> - Dimethylgrisabine (Bisbenzylisoquinoline)	<i>Phycanthus vietnamensis</i> (Annonaceae)	D1-R antagonist (6), D2-R antagonist (1)
(<i>S,R</i>)-Dimethyl- pseudoxandrine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (22), D2-R antagonist (4)
Ergine (= Lysergic acid amide; Lysergamide) (indole)	<i>Argyrea spp.</i> , <i>Ipomoea argyrophylla</i> , <i>I. tricolor</i> , <i>I. violacea</i> , <i>Rivea uricata</i> (Convolvulaceae); from hydrolysis of ergot (<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals)	D2-R agonist (53 nM) [0.7] (α 1A-R, α 2A-R, 5HT-R) [depressant, hallucinogenic]
[Ergocornine] (indole)	<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals e.g. <i>Secale</i> (rye); ergot-induced hallucinations possibly inspired apocalyptic paintings of Hieronymus Bosch	D2-R agonist [ergotism (hallucinogenic , convulsant), haemostatic, inhibits Prolactin release, vasoconstrictor]
[Ergocristine] (indole)	<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals e.g. <i>Secale</i> (rye); ergot-induced hallucination = St Anthony's fire, addressed by Mandrake root extract	D2-R agonist (\oplus D-REL) [ergotism (hallucinogen , convulsant), haemostatic, inhibits Prolactin release, vasoconstrictor]
[α -Ergocryptine (= Ergokryptine)] (indole)	<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals e.g. <i>Secale</i> (rye); Salem witch-killing hysteria coincided with ergot outbreak; ergotism gives "devil possession" symptoms; some 40,000–100,000 "witches" (75% female) tortured & murdered in ergot-prone regions of W. Europe	D2-R agonist (153 nM) [2 nM] (\oplus D-REL) [anti-Parkinson's, ergotism (hallucinogenic , convulsant), haemostatic, inhibits Prolactin release, vasoconstrictor]
[Ergonovine] (indole)	<i>Claviceps purpurea</i> , <i>C. paspali</i> (ergot fungus) on cereals e.g. <i>Secale</i> sp. (rye) & <i>Acremonium</i> -infected <i>Stipa robusta</i> (sleepy grass) (Poaceae); cattle & horse stupor after eating infected grass	D2-R agonist (83 nM) [0.4] (5HT2-R) [ergotism (hallucinogenic , convulsant), haemostatic, inhibits Prolactin release, oxytocic, vasoconstrictor]
[Ergotamine] (indole)	<i>Claviceps purpurea</i> , <i>C. paspali</i> (ergot fungus) on cereals e.g. <i>Secale</i> sp. (rye) (Poaceae); ergot studied by Sir Henry Dale (UK, Nobel Prize, Medicine, 1936, chemical neurotransmission)	D2-R agonist (1 nM) [6 nM] [anti-migraine, ergotism (hallucinogen, convulsant), haemostatic, inhibits Prolactin release, vasoconstrictor]
[Ergovaline] (indole)	<i>Claviceps purpurea</i> , <i>C. paspali</i> (ergot fungus) on grasses & cereals e.g. <i>Secale</i> sp. (rye), <i>Festuca arundinacea</i> (tall fescue) (Poaceae)	D2-R agonist (6 nM) [7 nM] [ergotism (hallucinogenic , convulsant), haemostatic, inhibits Prolactin release, vasoconstrictor]

(continued)

Table 5.4 (Continued)

Hormone compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
(<i>R,S</i>)-Homoaromoline (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (15), D2-R antagonist (66)
Ibogaine (= 12- Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> , <i>Voacanga thouarsii</i> (Apocynaceae)	D1-R ligand (>10), D2-R ligand (>10), D1-R ligand (>10) (AD-R, mACh-R, D-TR, 5HT-TR, NMDA- Glu-R, O-R) [anti-addictive, anticonvulsant, hallucinogenic]
(<i>S,R</i>)-Isotetrandine (Bisbenzylisoquinoline) [Lergotril] (indole)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark] <i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals e.g. <i>Secale</i> sp. (rye) (Poaceae)	D1-R antagonist (33), D2-R antagonist (0.7) D2-R agonist [ergotism (hallucinogenic , convulsant), inhibits Prolactin release, vasoconstrictor]
[LSD (= D-Lysergic acid diethylamide; Lysergide; <i>N,N</i> -Diethyl-D- Lysergamide)] (ergoline indole)	Semi-synthetic from Lysergamide by Albert Hofmann (Swiss chemist, 1943); use advocated by Timothy Leary (US psychologist, sacked from Harvard, imprisoned) – “turn on, tune in, drop out” (from 1960s)	D1-R ligand [27 nM], D2 ligand [6 nM], D1 agonist (cAMP increase) [30 nM] (5HT1-R, 5HT2-R) [hallucinogenic]
Noribogaine (= 12- Hydroxyibogamine) (indole)	Metabolite of Ibogaine; hallucinogenic	D1-R ligand (>10), D2-R ligand (>10), D1-R ligand (>10) (D-TR, 5HT-TR, O-R) [anti-addictive, anticonvulsant]
Nuciferine (aporphine isoquinoline) principle of Egyptian and Mayan narcotic (psychodysleptic) for priestly ecstasies	<i>Nelumbo nucifera</i> , <i>Nymphaea caerulea</i> (Egyptian blue lotus), <i>N. ampla</i> water lily) (Nymphaeaceae) [flower] – Egyptian blue lotus sacred, source of creation, depicted in social & sexual scenes; Odysseus (Ulysses) & Land of the Lotus Eaters	D-R antagonist (Glu-R antagonist) (Mayan [anti-spasmodic, antiviral, neuroleptic]; blue lotus emblem of Nefertem, God of Perfumes; in wine gives “tranquil euphoria”)
(<i>R,S</i>)-Obaberine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (39), D2-R antagonist (28)
(<i>S,S</i>)-Oxandrine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (11), D2-R antagonist (3)
Pseudoprotopine (protoberberine isoquinoline)	<i>Thalictrum delavayi</i> (Ranunculaceae) [root]	D1-R ligand (<100)
(-)-Salsolinol (= 1-Methyl- 6,7-dihydroxy-1,2,3,4- tetrahydro-isoquinoline) (tetrahydroisoquinoline); Salsolinol main psychoactive in cocoa & linked to chocolate craving	<i>Annona reticulata</i> (Annonaceae), <i>Musa paradisiaca</i> (banana) (Musaceae) [fruit], <i>Theobroma cacao</i> (cocoa) (Sterculiaceae) [seed]; Salsolinol linked to chocolate addiction & ROS-based neurotoxicity in Parkinson’s & alcoholism; West African cocoa production “chocolate slavery” – child slave 2002 price US\$30	D2-R, D3-R agonist [0.5] (α 2A-R, β 1A-R, NADH- CoQ R) [antagonist w.r.t. Apomorphine, dopaminergic, inhibits cAMP formation, β -endorphin release & ACTH release (pituitary)]

(continued)

Table 5.4 (Continued)

Hormone compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
(S)-Secoantioquine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (>30), D2-R antagonist (10)
(S)-Secobuberine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (>30), D2-R antagonist (>30)
(S)-Secolucidine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D1-R antagonist (>100), D2-R antagonist (82)
Songorine (= Bullatine G; Napellonine) (diterpene alkaloid)	<i>Aconitum karakolicum</i> , <i>A. monticola</i> , <i>A. soongaricum</i> (Ranunculaceae)	D2-R agonist (at 1–100); [convulsant, hypotensive, toxic]
[1,2,3,4-Tetrahydro- isoquinoline] (tetrahydroisoquinoline)	Metabolite of Dopamine	D-R antagonist [dopamine antagonist w.r.t. Apomorphine]
(R,S)-Thaligrisine (Bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae)	D1-R antagonist (6), D2-R antagonist (27 nM)
(+)-Yohimbine (= Aphrodine; Corynine; Hydroergotocin; Quebrachine) (indole)	<i>Catharanthus lanceus</i> , <i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia yohimbe</i> [yohimbe bark] (Rubiaceae)	D-R antagonist (α 1A-R, α 2A-R, 5HT-R) [antidepressant, aphrodisiac , mydriatic, toxic]
Phenolic		5.4p
Catechin 3-O-gallate (gallotannin)	Widespread	D1-R ligand (<10), D2-Rx ligand (>10) (AD1-R, D1-R, 5HT1-R, O-R)
Davidiin (= 1,5- Hexahydroxydiphenoyl 2,3,4-trigalloylglucose) (ellagitannin)	<i>Quercus</i> sp. (Fagaceae)	D2-R ligand (~10) (α 2A-R, β A-R, 5HT2-R, O-R)
β -2,4-Di-O-galloyl-glucose (gallotannin)	<i>Croton lechleri</i> (Euphorbiaceae)	D1-R ligand (>10) (β A-R, D2-R, 5HT1-R, O-R)
Dopamine (= 4-(2- Aminoethyl)-benzene-1,2- diol; 3-Hydroxytyramine) (catecholamine phenolic)	<i>Carnegiea gigantea</i> (giant cactus), <i>Lophophora williamsii</i> (mescal button) (Cactaceae), <i>Cytisus scoparius</i> (broom) (Fabaceae), <i>Musa cavendishii</i> , <i>M. paradisiaca</i> (banana peel), <i>M. sapientum</i> (Musaceae), <i>Hermidium alipes</i> (Nyctaginaceae); animal NT	D-R agonist – D1-R [106 nM; 2], D2-R agonist [370 nM] (α A-R, β A-R, COUP- TF) [dopaminergic NT, increases cardiac output, reduced in Parkinsonism , sympathomimetic]
(–)-Epiafzelechin (flavan-3-ol)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial], <i>Camellia sinensis</i> (Theaceae)	D2-R ligand (>10) (ATP K ⁺ CH, α 1-A R, α 2A-R, β A-R, D2-R, COX-1, 5HT1A-R, O-R) [AI with carrageenin-induced paw oedema]
(–)-Epicatechin (= (2R,3R)-5,7,3',4'- Tetrahydroxyflavan-3-ol) (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), <i>Pterocarpus</i> spp. (Fabaceae) [bark], <i>Podocarpus nagi</i> (Podocarpaceae), <i>Crataegus monogyna</i> (Rosaceae), <i>Camellia sinensis</i> (Theaceae)	D2-R ligand (~10) (AD-R, β A-R, PKA) [antibacterial, AI, anti-oxidant]
(–)-Epigallocatechin (gallotannin)	Widespread [bark, leaf]; <i>Camellia sinensis</i> (Theaceae)	D2-R ligand (~10) (5HT1-R)

(continued)

Table 5.4 (Continued)

Hormone compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
(-)-Epigallocatechin-3-gallate (flavan-3-ol, gallotannin)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (Theaceae)	D1-R ligand (~10), D2-R ligand (>10) (β A-R, O-R, PKC, TOPII) [AI, blocks COX-2 & iNOS induction]
Geraniin (ellagitannin)	<i>Acer</i> (Aceraceae), <i>Cercidiphyllum</i> (Cercidiphyllaceae), <i>Coriaria</i> (Coriariaceae), <i>Geranium</i> , <i>Erythroxylum coca</i> (Erythroxylaceae), <i>Euphorbia</i> , <i>Mallotus</i> (Euphorbiaceae), <i>Fuchsia</i> (Onagraceae) spp.	D1-R ligand (<10) (α 1A-R, α 2A-R, 5HT1-R, O-R) [inhibits Epinephrine-induced adipocyte lipolysis]
Hyperforin (phloroglucinol)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae)	D2-R agonist (Steroid X-R) [inhibits prolactin release]
Pedunculagin (= 2,3-Hexahydroxydiphenoyl 4,5-hexahydroxydiphenoyl glucose) (ellagitannin)	<i>Casuarina stricta</i> (Casuarinaceae), <i>Quercus</i> sp. (Fagaceae), <i>Potentilla</i> sp., <i>Rubus</i> spp. (Rosaceae), <i>Stachyurus praecox</i> (Stachyuraceae), <i>Camellia japonica</i> (Theaceae)	D1-R ligand (>10) (α 2A-R, β A-R, GPT, SU-R, O-R) [inhibits Epinephrine-induced adipocyte lipolysis]
β -1,2,3,4,6-Penta-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark], <i>Geranium thunbergii</i> (Geraniaceae), <i>Paonia lactiflora</i> (Paeoniaceae)	D1-R ligand (~10), D2-R ligand (~10) (α 2A-R, D2-R, O-R, SU-R)
Procyanidin B3 (= Catechin (4 α →8) catechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae)	D1-R ligand (>10), D2-R ligand (>10) (α 1A-R, β A-R, 5HT1-R, O-R)
Procyanidin B4 (= Catechin (4 α →8) epicatechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae), <i>Rubus idaeus</i> (Rosaceae)	D2-R ligand (~10) (α 1A-R, α 2A-R, β A-R, 5HT1-R, H1-R) [anti-ulcerative]
Rugosin D (ellagitannin)	<i>Filipendula ulmaria</i> , <i>Rosa rugosa</i> (Rosaceae) [petal]	D1-R ligand (~10) (α 2A-R, β A-R, H1-R, O-R) [antitumour]
Tellimagrandin I (= 4,5-Hexahydroxydiphenoyl-2,3-digalloylglucose) (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Quercus</i> (Fagaceae), <i>Syzygium</i> , <i>Feijoa</i> , <i>Psidium a Eucalyptus</i> (Myrtaceae), <i>Fuchsia</i> (Onagraceae), <i>Geum</i> , <i>Rosa.</i> , <i>Tellima</i> (Rosaceae), <i>Stachyurus</i> (Stachyuraceae), <i>Camellia</i> (Theaceae) spp.	D2-R ligand (>10) (α 1A-R, α 2A-R, GPT, O-R, SU-R) [inhibits Epinephrine-induced adipocyte lipolysis]
β -1,2,4,6-Tetra-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark]	D2-R ligand (<10) (α 2A-R, β A-R, O-R, SU-R)
β -1,2,6-Tri-O-galloyl-D-glucose (gallotannin)	<i>Phyllanthus emblica</i> (Euphorbiaceae) <i>Quercus</i> spp. (Fagaceae) [bark]	D1-R ligand (>10) (α 2A-R, β A-R, 5HT2-R, O-R)
β -1,3,6-Tri-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark]	D2-R (~10) (β A-R, O-R ligand)
Terpene		5.4t
Bodirin A (triterpene)	<i>Schefflera bodinieri</i> (Araliaceae)	D2-R ligand (2) [0.6]
6 β ,7 β -Diacetoxy-13-hydroxy-labda-8,14-diene (diterpene)	<i>Vitex agnus-castus</i> (Verbenaceae) [fruit]	D2-R antagonist
Rotun-difuran (diterpene)	<i>Vitex agnus-castus</i> (Verbenaceae) [fruit]	D2-R antagonist

(continued)

Table 5.4 (Continued)

Hormone compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
α -Santalol (sesquiterpene)	<i>Santalum album</i> (sandalwood) (Santalaceae) [wood oil]	D2-R antagonist (5HT2A-R) [antipsychotic, perfume smell]
Non-plant reference		5.4n
[Chlorpromazine (= 3- Chloro-10-(3- dimethylaminopropyl) phenothiazine) (phenothiazine)	Synthetic	D1-R antagonist, D2-R antagonist [0.9 nM] [antiemetic, antipsychotic, tranquillizer]
[Domperidone] (piperidine benzimidazole)	Synthetic	D2-R antagonist [anti-emetic, controls migraine-associated nausea & vomiting; does not cross BBB]
[Haloperidol] (fluorobenzoyl hydroxypiperidino chlorobenzene)	Synthetic	D2-R antagonist (V-Ca ²⁺ CH) [antidyskinetic, antipsychotic]
[Metoclopramide] (benzamide)	Synthetic	D2-R antagonist [controls migraine-associated nausea & vomiting]
[Spiperone] (aryl triazaspirodecane)	Synthetic	D2-R antagonist [0.2 nM] [antipsychotic]
[Sulpiride] (pyrrolidinyl aminosulphonyl benzamide)	Synthetic	D2-R antagonist (20 nM; 0.3) [antipsychotic, antidepressant, antiemetic]

Table 5.5 Metabotropic GABA(B)-, glutamate- and serotonin-receptors

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
γ-Aminobutyric acid (GABA) metabotropic B receptor R (GABAB-R)		5.5A
γ -Aminobutyric acid (= 4-Aminobutyric acid; GABA) (amino acid)	<i>Phoenix dactylifera</i> (Areaceae), <i>Phaseolus</i> spp., <i>Pisum</i> spp., <i>Vicia</i> spp. (Fabaceae) [seed], <i>Rehmannia glutinosa</i> (Scrophulariaceae), <i>Valeriana officinalis</i> (valerian) (Valerianaceae)	GABAB-R agonist (GABAA-R, GABAB-R) [antihypertensive, neurotoxic]
[Gabapentin (= 1- (Aminomethyl)- cyclohexaneacetic acid)] (alicyclic amine carboxylic acid)	Synthetic	GABAB-R agonist (\rightarrow blocks V-Ca ²⁺ CH) [anticonvulsant]

(continued)

Table 5.5 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Metabotropic Glutamate receptor (mGlu-R) (mGlu(1-8)-R)		5.5B
Alkaloid		5.5Ba
[Ibotenic acid (= α - Amino-3-hydroxy-5- isoxazoleacetic)] (isoxazole amino acid)	<i>Amanita muscaria</i> , <i>A. pantheria</i> (mushroom) (Agaricaceae); precursor of Muscimol	mGlu-R (Class I & II) agonist – Class I: 1a (10–60), 5a (2–10); Class II: 2 (35–250), 3 (10–15); Class III: 4a (100–1000), 6 (>300) (non-NMDA-Glu-R (K-R)) [insecticidal, narcosis- potentiating, neurotoxic]
Quisqualic acid (= (<i>S</i>)- α - Amino-3,5-dioxo-1,2,4- oxadiazolidine-2- propionic acid) (oxadiazolidine amino acid)	<i>Quisqualis chinensis</i> , <i>Q. indica</i> (Combretaceae) [seed]	mGlu-R (Class I) agonist – Class I: 1a [27 nM] (0.2–3), 5a [81 nM] (30–300); Class II: 2 (>1000), 3 (40); Class III: 4a (100–1000), 6 (>300) (non- NMDA-Glu-R (K-R) agonist) [anthelmintic, excitatory]
Phenolic		5.5Bp
3,5-Dihydroxyphenyl- glycine (aryl amino acid)	<i>Euphorbia helioscopia</i> (Euphorbiaceae)	mGlu-R (Class I) agonist – 1a (7), 5a (2)
3-Hydroxyphenylglycine (aryl amino acid)	<i>Euphorbia helioscopia</i> (Euphorbiaceae)	mGlu-R (Class I) agonist – 1a (68–100), 5a (14–35)
Terpene		5.5Bt
Jatrophone (jatrophone diterpene)	<i>Jatropha elliptica</i> , <i>J. gossypifolia</i> (Euphorbiaceae)	Glu-R (DNA) [antitumour, anti-nociceptive, molluscicide]
Other		5.5Bo
1-Glutamate (= (+)- α - Amino-1-glutaric acid) (α -amino acid)	All organisms; <i>Arachis hypogaea</i> , <i>Ceratonia siliqua</i> , <i>Lupinus alba</i> , <i>Glycine max</i> , <i>Phaseolus vulgaris</i> (Fabaceae), <i>Brassica chinensis</i> , <i>Sinapis alba</i> (Brassicaceae)	mGlu-R (Class I, II & III) agonist – Class I: 1a (9–13), 5a (3–10); Class II: 2 (4–20), 3 (4–5); Class III: 4a (3–20), 6 (16), 7 (1000), 8 (80 nM) (NMDA-Glu-R, non-NMDA-Glu-R)
[L-Cysteic acid (C-SO ₃ H)] (amino acid)	Oxidation product of L-Cysteine (C-SH)	mGlu-R Class I (1a, 5a) agonist (NMDA-Glu-R) [excitotoxic, stimulates IP ₃ formation]
[L-Cysteine sulfenic acid (C-SO ₂ H)] (amino acid)	Oxidation product of Cysteine	mGlu-R Class I (1a) agonist (NMDA-Glu-R) [excitotoxic, stimulates IP ₃ formation]
[L-Homocysteine sulphinic acid (HC-SO ₂ H)] (amino acid)	Oxidation product of L-Homocysteine (HC-SH)	mGlu-R Class I (1a) partial agonist (300), 5a (NMDA- Glu-R) [excitotoxic, stimulates IP ₃ formation]
β -N-Methylamino-1- alanine (= BMAA) (amino acid)	<i>Cycas circinalis</i> (Cycadaceae); causes amyotrophic lateral sclerosis- Parkinsonian dementia (ALS-PD) of Guam	mGlu-R Class I agonist – 1a (480) (NMDA-Glu-R)

(continued)

Table 5.5 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Receptor affected (other targets) in vivo effects </i>
Non-plant reference		5.5Bn
[1 <i>S</i> , 3 <i>R</i> -1-Amino-1, 3-cyclopentane-dicarboxylate (= 1 <i>S</i> ,3 <i>R</i> -ACPD)] (cyclic aliphatic)	Synthetic	mGlu-R (Class I & II) agonist – Class I: 1a (10–80), 5a (5–7); Class II: 2 (18), 3 (8); Class III: 4a (>300), 6 (300)
[1 <i>S</i> , 3 <i>S</i> -1-Amino-1, 3-cyclopentane-dicarboxylate (= 1 <i>S</i> ,3 <i>R</i> -ACPD)] (cyclic aliphatic)	Synthetic	mGlu-R (Class II & III) agonist – Class I: 1a (>300), 5a (>300); Class II: 2 (13), 3 (30); Class III: 4a (50)
[1-Amino-phosphonobutyrate (= L-AP4)] (amino acid)	Synthetic	mGlu-R (Class III) agonist – Class III: 4a (0.4–0.9), 6 (0.9), 7 (160–500), 8 (0.4)
[(2 <i>S</i> ,1' <i>S</i> ,2' <i>S</i>)-2-(Carboxycyclopropyl)-glycine (= L-CCG-I)] (cyclic aliphatic amino acid)	Synthetic	mGlu-R (Class II > I & III) agonist – Class I: 1a (50); Class II: 2 (0.3–0.4), 3 (1); Class III: 4a (9–50)
[(<i>S</i>)-4-Carboxy-3-hydroxyphenylglycine (= (<i>S</i>)-4C3HPG)] (aryl amino acid)	Synthetic; cf. 3,5-Dihydroxyphenylglycine & 3-Hydroxyphenylglycine	mGlu-R (Class I) antagonist – Class I: 1a (10–40)
[(<i>S</i>)-4-Carboxyphenylglycine (= (<i>S</i>)-4CPG)] (aryl amino acid)	Synthetic; cf. 3,5-Dihydroxyphenylglycine & 3-Hydroxyphenylglycine	mGlu-R (Class I) antagonist – Class I: 1a (15–65), 5a (>500)
[2 <i>S</i> ,1' <i>S</i> ,2' <i>S</i> ,3' <i>R</i>)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine (= PCCG-IV)] (cyclic aliphatic amino acid)	Synthetic	mGlu-R (Class II) antagonist Class II: 2 (8)
[(2 <i>S</i> ,1' <i>R</i> ,2' <i>R</i> ,3' <i>R</i>)-2-(2,3-Dicarboxycyclopropyl)-glycine (= DCG-IV)] (cyclic aliphatic amino acid)	Synthetic	mGlu-R (Class II) agonist – Class II: 2 (0.3), 3 (0.2); Class III: 4a (>1000)
[7-Hydroxyimino-cyclopropan[b]chromen-1a-carboxylic acid ethyl ester] (chromene)	Synthetic	mGlu-R (Class I) non-competitive antagonist – Class I: 1b (7)
[α -Methyl-4-carboxyphenylglycine (= MCPG)] (aryl amino acid)	Synthetic; cf. 3,5-Dihydroxyphenylglycine & 3-Hydroxyphenylglycine	mGlu-R (Class I & II) antagonist – Class I: 1a (40–200), 5a (>200); Class II: 2 (100–1000), 3 (>1000)
[2-Methyl-6-(phenylethenyl)-pyridine (= MPEP)] (pyridine)	Synthetic	mGlu-R (Class I) antagonist – 5-specific (36 nM)
[L-Serine- <i>O</i> -phosphate (= L-SOP)] (phosphoamino acid)	Synthetic	mGlu-R (Class III) agonist – Class III: 4a (2–5), 6 (3), 7 (>160)

(continued)

Table 5.5 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
γ-Hydroxybutyric acid receptor (GHB-R) [γ-Hydroxybutyric acid] (alkyl carboxylic acid)	Metabolite of GABA; GHB aciduria from succinic semialdehyde dehydrogenase deficiency; drug of abuse (body builders, “date rape”, “raving”)	5.5C GHB-R [GPCR, decreases cAMP; ↓ alcohol & opiate dependence & narcolepsy]
5-Hydroxytryptamine (Serotonin) metabotropic R (5-HT1-R, 5HT1A-R, 5HT2-R)	Arvid Carlsson (Sweden, D & 5HT signalling), Paul Greengard (USA, D signalling) & Eric Kandel (Austria/USA, 5HT & memory) (Nobel Prize, Physiology/Medicine, 2000)	5.5D
Alkaloid		5.5Da
(-)-Annonaine (= Anonaine) (aporphine isoquinoline)	<i>Annona muricata</i> , <i>A. reticulata</i> (Annonaceae) [fruit, leaf], <i>Nelumbo nucifera</i> (Nymphaeaceae)	5HT1A-R ligand (Rauwolscine displacement) (3), agonist (decreased cAMP) (<10) [antimicrobial, insecticidal]
Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> (Annonaceae), <i>Berberis</i> , <i>Hydrastis</i> , <i>Mahonia</i> , <i>Nandina</i> (Berberidaceae), <i>Archangelica</i> (Menispermaceae), <i>Argemone</i> , <i>Chelidonium</i> , <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> , <i>Thalictrum</i> (Ranunculaceae), <i>Evodia</i> , <i>Toddalia</i> , <i>Zanthoxylum</i> (Rutaceae) spp.	5HT2-R ligand (2) (α1A-R, α2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
Asimilobine (isoquinoline)	<i>Annona muricata</i> , <i>A. spp.</i> , <i>Asimina triloba</i> , <i>Guatteria scadens</i> (Annonaceae) [fruit, leaf]	5HT1A-R ligand (Rauwolscine displacement) (5), agonist (decreased cAMP) (<10)
[Baeocystin] (indole)	<i>Psilocybe semilanceata</i> , <i>P. spp.</i> (magic mushrooms) (Strophariaceae)	5HT2A-R agonist [hallucinogenic]
Bufotenine (= <i>N,N</i> -Dimethylserotonin; 5-Hydroxy- <i>N,N</i> -dimethyltryptamine) (indole)	<i>Anadenanthera colubrina</i> , <i>Mucuna pruriens</i> , <i>Piptadenia peregrina</i> , <i>P. macrocarpa</i> (Fabaceae) [leaf, seed], <i>Arundo donax</i> (reed) (Poaceae) [flower]	5HT2A-R, 5HT2C-R agonist [hallucinogenic] , hypertensive, pupil dilation]
Confusameline (furoquinoline)	<i>Evodia merrillii</i> , <i>Melicope confusa</i> (Rutaceae) [leaf]	5HT-R antagonist (PAI)
Corynantheine (indole)	<i>Corynanthe pachyceras</i> [bark], <i>Pausinystalia johimbe</i> , <i>Uncaria sinensis</i> (Rubiaceae)	5HT-R ligand (brain), partial agonist (ileum) [anti-Leishmania]
Dihydrocorynantheine (indole)	<i>Corynanthe pachyceras</i> [bark], <i>Pausinystalia johimbe</i> , <i>Uncaria sinensis</i> , <i>U. tomentosa</i> (Rubiaceae)	5HT-R ligand (brain), partial agonist (ileum) (α1A-R, α2A-R) [leishmanicidal]
[Dihydroergotamine] (ergotaman alkaloid)	Semi-synthetic from Ergotamine	5HT1-R agonist (αA-R blocker) [anti-migraine as vasoconstrictor, selective venoconstrictive]

(continued)

Table 5.5 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
<i>N,N</i> -Dimethyltryptamine (= 3-(2-Dimethyl- aminoethyl)-indole; DMT) (indole)	<i>Prestonia amazonica</i> (Annonaceae), <i>Acacia senegal</i> (gum arabic) (Fabaceae), <i>Arundo donax</i> , <i>Phalaris</i> spp. (Poaceae), <i>Mucuna pruriens</i> , <i>Mimosa hostilis</i> , <i>Piptadenia peregrina</i> (Fabaceae), <i>Viola</i> sp. (Myristicaceae)	5HT-R agonist [hallucinogen, hypertensive, psychotomimetic, pupillary dilation]; hallucinogenic Virola & Mimosa potions by S. American Indians; Phalaris stagers contributor
(-)-Discretamine (tetrahydroproto- berberine isoquinoline) [Ergonovine] (indole)	<i>Fissistigma glaucescens</i> , <i>Guatteria discolor</i> (Annonaceae)	5HT-R antagonist (0.1) (α 1A-R, α 2A-R)
[Ergotamine] (ergotaman indole)	<i>Claviceps purpurea</i> , <i>C. paspali</i> (ergot fungus) on cereals e.g. <i>Secale</i> sp. (rye) & <i>Acremonium</i> -infected <i>Stipa robusta</i> (sleepy grass) (Poaceae); cattle & horse stupor after eating infected grass In ergot [dried sclerotia of fungus <i>Claviceps purpurea</i> (Hypocreaceae) parasitic on <i>Secale cornutum</i> (rye) (Poaceae)]	5HT2-R ligand (D2-R agonist) [ergotism (hallucinogenic, convulsant, haemostatic, inhibits Prolactin release, oxytocic, vasoconstrictor] 5HT1A-R (including 5HT1A autoR) agonist [anti-migraine as vasoconstrictor; hallucinogenic (e.g. see paintings of Hieronymus Bosch)]
Evodiamine (indole)	<i>Araliopsis tabouensis</i> (Araliaceae), <i>Evodia rutaecarpa</i> (Rutaceae)	5HT-R antagonist [diaphoretic, diuretic, vasodilatory]
Geisoshizine methyl ether (indole)	<i>Corynanthe pachyceras</i> [bark], <i>Uncaria sinensis</i> (Rubiaceae)	5HT-R ligand (brain), partial agonist (ileum) (α 2-R antagonist)
Gramine (= 3- Dimethyl- aminomethyl)-indole; Donaxine) (indole)	<i>Acer saccharinum</i> (Aceraceae), <i>Lupinus</i> spp. (Fabaceae), <i>Arundo donax</i> , <i>Hordeum vulgare</i> (barley), <i>Phalaris arundinaceae</i> , <i>Triticum aestivum</i> (Poaceae)	5HT-R antagonist [antifeedant, neuroactive]; contributes to sheep Phalaris stagers
Harmaline (= 3,4- Dihydroharmine; Harmidine) (dihydro β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> , <i>Banisteriopsis caapi</i> (Malpighiaceae), <i>Peganum harmala</i> (Zygophyllaceae)	5HT-R agonist (α 2A-R, BZ-R, NMDA-Glu-R) [hallucinogenic, anti-Parkinson's]
Harman (= 1-Methyl- β - carboline) (β -carboline, indole)	<i>Passiflora edulis</i> , <i>P. incarnata</i> (Passifloraceae), <i>Singickia rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> , <i>Zygophyllum fabago</i> (Zygophyllaceae)	5HT2-R ligand (α 1A-R, BZ-R, DNA, L-type Ca^{2+} CH) [convulsant, cytotoxic]
Harmine (= Banisterine; Leucoharmine; Telepathine; Yageine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> (Zygophyllaceae)	5HT-R agonist (α 1A-R, MAO-A, L-type Ca^{2+} CH) [CNS stimulant, hallucinogenic; Gestapo use as "truth drug"]
Hordenine (indole)	<i>Tamarindus indica</i> (Fabaceae), <i>Phalaris</i> spp., <i>Zea mays</i> (corn) (Poaceae), <i>Citrus sinensis</i> (Rutaceae)	5HT-R agonist [antifeedant; causes sheep "Phalaris stagers"]

(continued)

Table 5.5 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
8-Hydroxylysergic acid amide (ergoline indole)	<i>Stipa robusta</i> (sleepy grass) (Poaceae) infected with <i>Acremonium</i> ; cattle & horse stupor after eating infected grass	5HT-R ligand [psychotropic, sedative]
Ibogaine (= 12-Methoxyibogamine) (indole)	<i>Tabernaeanthe iboga</i> , <i>Voacanga thouarsii</i> (Apocynaceae)	5HT-TR – 5HT1a-R, 5HT2-R ligand (α 1A-R, AD-R, mACh-R, D-R, D-TR, NMDA-Glu-R, O-R) [anti-addictive, anticonvulsant, hallucinogenic]
Isolysergic acid amide (ergoline indole)	<i>Stipa robusta</i> (sleepy grass) & <i>Festuca arundinacea</i> (tall fescue) (Poaceae) infected with <i>Acremonium</i> ; cattle & horse stupor after eating infected grass	5HT-R ligand [psychotropic, sedative]
Kokusaginine (= 6, 7-Dimethoxydictamnine) (furoquinoline)	<i>Acronychia laurifolia</i> , <i>Casimiroa edulis</i> , <i>Evodia merrillii</i> , <i>Haplophyllum</i> , <i>Melicope</i> , <i>Orixa</i> spp., <i>Ruta graveolens</i> (Rutaceae)	5HT-R antagonist (PAI) [mutagenic, phototoxic antifungal, psychotropic]
[LSD (= D-Lysergic acid diethylamide; Lysergide; <i>N,N</i> -Diethyl-D-Lysergamide)] (ergoline indole)	Semi-synthetic from Lysergamide <i>ex ergot</i> ; synthesized by Albert Hofmann (Swiss chemist, 1943); use advocated by Timothy Leary (US psychologist, 1960s)	5HT1-R, 5HT2A-R, 5HT2C agonist – 5HT1A-R [4nM], 5HT2-R [1, 4, 5nM] (D-R) [hallucinogenic], dangerous drug of abuse
[Lysergamide (= 9,10-Didehydro-6-methylergoline-8 β -carboxamide); Ergine; Lysergic acid amide] (ergoline indole); in ergot	<i>Ipomoea argyrophylla</i> , <i>I. tricolor</i> , <i>Rivea corumbosa</i> (Convolvulaceae) [drug ololiuqui]; <i>Festuca arundinacea</i> (tall fescue) & <i>Stipa robusta</i> (sleepy grass) (Poaceae) infected with fungus <i>Acremonium coenophialum</i> (sleepy livestock)	5HT2-R partial agonist (vasoconstrictive) (at 1–10) & antagonist (abolishes 5HT-induced vasoconstriction) (at 0.1) (α 1A-R, α 2A-R, D2-R); precursor for synthesis of LSD [depressant, hallucinogen]
[Lysergic acid] (ergoline)	From hydrolysis of Lysergamide from ergot; synthesis (1954) by Robert Burns Woodward (USA, chemist, Nobel Prize 1965)	5HT2-R partial agonist [depressant, hallucinogenic]
5-Methoxy- <i>N,N</i> -dimethyltryptamine (= <i>O</i> -Methylbufotenine) (indole)	<i>Justicia pectoralis</i> (Acanthaceae), <i>Desmodium pulchellum</i> (Fabaceae), <i>Phalaris arundinacea</i> , <i>P. tuberosa</i> (Poaceae), <i>Virola</i> sp. (Myristicaceae) [resin]; <i>Bufo alvarius</i> (Sonoran desert toad) (psychoactive toad)	5HT-R agonist [hallucinogenic , hypertensive, sheep Phalaris stagers , Virola snuff component, psychotomimetic, toxic]
5-Methoxy- <i>N</i> -methylcarboline (pyrido- <i>N</i> -methylated) (carboline, pyridoindole)	<i>Phalaris</i> spp. (Poaceae)	5HT-R agonist [<i>Phalaris</i> stagers contributor, toxic]
5-Methoxy- <i>N</i> -methyltryptamine (indole)	<i>Phalaris arundinacea</i> , <i>P. tuberosa</i> (Poaceae)	5HT-R agonist [<i>Phalaris</i> stagers, psychotomimetic, toxic]

(continued)

Table 5.5 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
5-Methoxytryptamine (indole)	<i>Cinchona ledgeriana</i> (Rubiaceae); metabolite of Melatonin	5HT ₂ -R agonist
Nantenine (= <i>O</i> - Methyl domesticine) (aporphine isoquinoline)	<i>Nandina domestica</i> (bamboo) (Berberidaceae) [fruit]	5HT-R antagonist [inhibits 5HT-induced aorta contraction]
Norharman (β -carboline, indole)	<i>Cichorium intybus</i> (Asteraceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae) [seed]	5HT-R agonist (α 2A-R)
Nornuciferine (isoquinoline)	<i>Annona glabra</i> , <i>A. muricata</i> (Annonaceae) [fruit, leaf], <i>Nelumbo nucifera</i> (Nymphaeaceae)	5HT _{1A} -R ligand (Rauwolscine displacement) (9), agonist (decreased cAMP) (<10)
Norreticuline (benzylisoquinoline)	<i>Berberis wilsoniae</i> (Berberidaceae), <i>Erythrina crista-galli</i> (Fabaceae)	5HT-R ligand (10) (α 1A-R, α 2A-R, β A-R) [hair growth accelerant]
(<i>S,R</i>)-Pseudoxandrine (bisbenzylisoquinoline)	<i>Pseudoxandra esclerocarpa</i> (Annonaceae) [bark]	D ₁ -R antagonist (19), D ₂ -R antagonist (16)
Palmatine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Berberis</i> , <i>Mahonia</i> spp. (Berberidaceae), <i>Jateorrhiza palmata</i> (Menispermaceae), <i>Corydalis</i> spp. (Papaveraceae), <i>Coptis</i> spp. (Ranunculaceae)	5HT ₂ -R ligand (3) (α 1A-R, α 2A-R, AChE, ATPase, BChE, ChAT, diamine oxidase, mACh-R, nACh-R, PK) [antibacterial, AI]
[Psilocin (= Psilocyn)] (indole)	<i>Psilocybe mexicana</i> (Teonanacatl, Mexican sacred mushroom), <i>Psilocybe</i> spp. (magic mushrooms) (Strophariaceae); by Albert Hofmann (Swiss chemist)	5HT _{2A} -R, 5HT _{2C} -R agonist [hallucinogenic , oxidized to blue pigment]
[Psilocybin (= Indocybin; 6- Phosphopsilocin)] (indole)	<i>Psilocybe mexicana</i> (Teonanacatl, Mexican sacred mushroom), <i>Psilocybe</i> spp. (magic mushrooms) (Strophariaceae); by Albert Hofmann (Swiss chemist)	5HT _{2A} -R, 5HT _{2C} -R agonist [hallucinogenic , oxidized to blue pigment]; use advocated by Timothy Leary (US psychologist, sacked from Harvard, imprisoned)
Rauwolscine (= α -Yohimbine) (indole)	<i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia yohimbe</i> (Rubiaceae) [yohimbe bark]	5HT _{1A} -R agonist (α 2A-R)
(+)-Reticuline (= <i>Coclanoline</i>) (benzylisoquinoline)	<i>Annona glabra</i> , <i>A. spp.</i> (Annonaceae), <i>Cryptocarya odorata</i> (Lauraceae), <i>Papaver somniferum</i> (opium poppy latex), <i>P. spp.</i> (Papaveraceae)	5HT-R ligand (10) (α 1A-R, α 2A-R, β A-R) [hair growth accelerant]
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Fumaria officinalis</i> (Fumariaceae), <i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> , <i>Sanguinaria Canadensis</i> (Papaveraceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	5HT ₂ -R ligand (92) (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]

(continued)

Table 5.5 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Serotonin (= 5-Hydroxytryptamine; 5HT) (indole)	<i>Ananas comosus</i> (pineapple) (Bromeliaceae), <i>Juglans regia</i> (Juglandaceae), <i>Mucuna pruriens</i> (Fabaceae), <i>Musa sapientum</i> (Musaceae), <i>Phalaris</i> spp. (Poaceae), <i>Lycopersicon esculentum</i> (Solanaceae), <i>Theobroma cacao</i> (Sterculiaceae), <i>Urtica dioica</i> (Urticaceae)	5HT(1-7)-R agonist: 5HT1-R [3 nM], 5HT2A-R (50 nM), 5HT2c-R (16 nM) (5HT3-R) [CNS stimulatory NT, inhibits Insulin secretion]
Skimmianine (= 7, 8- Dimethoxydictamine; β -Fagarine) (furoquinoline)	<i>Evodia merrillii</i> , <i>Ruta graveolens</i> , <i>Skimmia arborescens</i> , <i>S. japonica</i> ; <i>Dictamnus</i> , <i>Esenbeckia</i> , <i>Fagara</i> , <i>Glycosmis</i> , <i>Haplophyllum</i> , <i>Murraya</i> , <i>Zanthoxylum</i> spp. (Rutaceae)	5HT-R antagonist (DNA, PAI) [anticonvulsant, mutagenic, photomutagenic, phototoxic]
Tryptamine (= 3-(2- Aminoethyl) indole) (indole)	Widespread; from Tryptophan decarboxylation; <i>Mucuna pruriens</i> , <i>Prosopis juliflora</i> (mesquite) (Fabaceae), <i>Lycopersicon esculentum</i> (Solanaceae)	Precursor of Indole-3-acetic acid (IAA, auxin) & hallucinogen Dimethyltryptamine
1-Tryptophan (= α - Aminoindole-3- propionic acid) (indole amino acid)	In all organisms; 5HT (Serotonin) precursor; <i>Helianthus annuus</i> (Asteraceae), <i>Phaseolus vulgaris</i> (Fabaceae), <i>Oenothera biennis</i> (Onagraceae) [seed]	Precursor of 5HT (Serotonin); unlike 5HT can cross blood- brain barrier [for depression, treatment of aggression]
(+)-Yohimbine (= Aphrodine; Corynine; Hydroergotocin; Quebrachine) (indole)	<i>Catharanthus lanceus</i> , <i>Rauwolfia</i> <i>serpentina</i> (Apocynaceae), <i>Paustynstalia yohimbe</i> [yohimbe bark] (Rubiaceae)	5HT-R (α 1A-R, α 2A-R) [blocking Methoxamine- induced vas deferens contraction [0.2]; antidepressant, aphrodisiac, mydriatic, toxic]
Phenolic		5.5Dp
(+)-Catechin (= Catechinic acid; Catechuic acid; (+)- Cyanidanol; (2 <i>R</i> ,3 <i>S</i>)- 5,7,3',4'-Tetrahydroxy- flavan-3-ol) (flavan-3-ol)	Widespread; <i>Gossypium</i> spp. (Malvaceae), <i>Agrimonia eupatoria</i> , <i>Crataegus laevigata</i> (Rosaceae), <i>Salix</i> <i>caprea</i> (willow) (Salicaceae) [flower]	5HT1A-R ligand (>10) (AD-R, β A-R, COX-1, COX-2, R, MLCK, PKA) [antioxidant]
Catechin 3- <i>O</i> -gallate (gallotannin)	Widespread [bark, leaf]	5HT1-R ligand (~10) (AD1-R, D1-R, D2-R, O-R)
Davidiin (= 1,5 Hexahydroxydiphenol 2,3,4-trigalloylglucose) (ellagitannin)	<i>Quercus</i> sp. (Fagaceae)	5HT2-R ligand (>10) (α 2A-R, β A-R, D2-R, O-R)
β -2,4-Di- <i>O</i> -galloyl- glucose (gallotannin)	<i>Croton lechleri</i> (Euphorbiaceae)	5HT1-R ligand (~10) (β A-R, D1-R, D2-R, O-R)
(-)-Epigallocatechin (gallotannin)	Widespread [leaf, bark]; <i>Gossypium</i> spp. (Malvaceae), <i>Camellia sinensis</i> (Theaceae)	5HT1-R ligand (~10) (D2-R)

(continued)

Table 5.5 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
(-)-Epiafzelechin (flavan-3-ol)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial], <i>Camellia sinensis</i> (Theaceae)	5HT1A-R ligand (>10) (ATP K ⁺ CH, α1A-R, βA-R, D2-R, COX-1, O-R) [AI with carrageenin-induced paw oedema]
Geraniin (ellagitannin)	<i>Acer</i> (Aceraceae), <i>Cercidiphyllum</i> (Cercidiphyllaceae), <i>Coriaria</i> <i>japonica</i> (Coriariaceae), <i>Geranium</i> , <i>Erythroxylum</i> (Erythroxylaceae), <i>Euphorbia</i> , <i>Mallotus japonicus</i> (Euphorbiaceae), <i>Fuchsia</i> (Onagraceae) spp.	5HT1-R ligand (~10) (α1A-R, α2A-R, D1-R, H1-R, O-R) [inhibits Epinephrine-induced adipocyte lipolysis, increases ACTH-induced adipocyte lipolysis]
γ-Mangostin (prenyl xanthone)	<i>Garcinia mangostana</i> (mangosteen fruit hull) (Guttiferae)	5HT2A-R antagonist (Piperone displacement) (4nM) (CDPK, MLCK, PKA) [5HT-induced aorta contraction inhibition (0.3), PAI]
Mescaline (= Mezcaline; 3,4,5- Trimethoxy- phenethylamine) (phenylethylamine)	<i>Lophophora williamsii</i> (peyote , mescal buttons = cactus flower), <i>Trichocereus pachanoi</i> (cactus) [flesh for S. Am. Indian cimora hallucinogenic potion] (Cactaceae)	5HT2A-R agonist [CNS depressant, hallucinogenic , psychotomimetic]
N-Methylmescaline (= N-Methylmezcaline; N-Methyl-3,4,5- trimethoxy- phenethylamine) (phenylethylamine)	<i>Lophophora williamsii</i> (peyote , mescal buttons = flowering heads of cactus) (Cactaceae), <i>Alhagi</i> <i>pseudoalbagi</i> (Fabaceae)	5HT2A-R agonist [CNS depressant, hallucinogenic , psychotomimetic cf. Mescaline]
Procyanidin B2 (= Epicatechin (4β→8) epicatechin) (procyanidin dimer)	<i>Malus</i> sp. (apple), <i>Prunus</i> sp. (cherry) (Rosaceae) [fruit]	5HT1-R ligand (<10), 5HT1A-R ligand (~10) (5HT1A-R)
Procyanidin B3 (= Catechin (4α→8) catechin (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae)	5HT1 R ligand (<10) (α1A-R, β A-R, D1-R, D2-R, O-R)
Procyanidin B4 (= Catechin (4α→8) epicatechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae), <i>Rubus idaeus</i> (Rosaceae)	5HT1 R ligand (<10) (α1A-R, α2A-R, βA-R, D2-R, H1-R) [anti-ulcerative]
β-1,2,6-Tri-O-galloyl-D- glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark], <i>Phyllanthus emblica</i> (Euphorbiaceae)	5HT2-R ligand (>10) (α2A-R, βA-R, D1-R, O-R)
Terpene		5.5Dt
Aescin (= Escin) (triterpene saponin)	<i>Panax quinquefolius</i> (Araliaceae), <i>Aesculus hippocastanum</i> (horse chestnut) (Hippocastanaceae)	5HT-R antagonist (HIS-R) [for oedema, chronic venous insufficiency & haemorrhoids]
Aescin Ib (= Escin Ib) (triterpene saponin)	<i>Panax quinquefolius</i> (Araliaceae), <i>Aesculus hippocastanum</i> (horse chestnut) (Hippocastanaceae)	5HT-R antagonist – 5HT2-R (HIS-R) [for oedema, chronic venous insufficiency & haemorrhoids; ↑ GI transit]

(continued)

Table 5.5 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Parthenolide (germacranolide sesquiterpene lactone)	<i>Ambrosia</i> spp., <i>Arctotis</i> spp., <i>Chrysanthemum parthenium</i> , <i>Tanacetum parthenium</i> (feverfew) (Asteraceae), <i>Michelia</i> spp. (Magnoliaceae)	5HT-R non-competitive antagonist (antagonizes serotonergic d-Fenfluramine) (IKK β) [AI, antibacterial, antifungal, antitumour, anti-migraine, cytotoxic]
α -Santalol (sesquiterpene)	<i>Apium graveolens</i> (celery) (Apiaceae), <i>Santalum album</i> (sandalwood) (Santalaceae) [wood oil]	5HT2A-R antagonist (D2-R) [antipsychotic, perfume smell]
Stigmasterol glucoside (sterol glycoside)	<i>Ammi visnaga</i> (Apiaceae), <i>Schefflera bodinieri</i> (Araliaceae) [leaf, root] <i>Syzygium aromaticum</i> (Myrtaceae)	5HT2-R ligand (4) [2] (L-Ca ²⁺ CH)
Other		5.5Do
α -L-Rha-(1 \rightarrow 4)-O- β -D-Glc-(1 \rightarrow 6)- β -D-Glc (trisaccharide)	<i>Schefflera bodinieri</i> (Araliaceae) [leaf, root]	5HT2-R ligand (8) [3]
Non-plant reference		5.5Dn
[Cispromide] (benzamide)	Synthetic	5HT4-R agonist [antiemetic for migraine]
[β -Hydroxy-dipropyl-amino tetralin] (benzocyclohexane)	Synthetic	5HT1A-R antagonist [3nM]
[Ketanserin] (piperidinylquinazoline)	Synthetic	5HT2-R antagonist [3nM]
[Methysergide] (indole)	Semi-synthetic	5HT1-R agonist; 5HT2-R antagonist [anti-migraine]
[Mianserin] (dibenzopyrazino-azepine)	Synthetic	5HT2-R antagonist (5HT3-R antagonist) [antidepressant]
[Mirtazepine] (pyrazinopyrido-benzazepine)	Synthetic	5HT2-R antagonist (5HT3-R, α 2A-R) [antidepressant]
[Pindolol] (indolamine)	Synthetic	5HT-R antagonist (β -A R) [vasodilator]
[Spiperone] (aryl triazaspirodecane)	Synthetic	5HT2-R antagonist (D2-R) [antipsychotic]
[Sumatriptan] (indole sulphonamide)	Synthetic	5HT1B/D-R agonist [antimigraine]

Table 5.6 Opiate receptors

Compound (class)	Plant (family) part	Receptor inhibited / activated (other targets) in vivo effects
Alkaloid		5.6a
Akuammidine	<i>Aspidosperma quebracho-blanco</i> , <i>Picalima nitida</i> (Apocynaceae) (indole) [seed]	O-R ligand (μ) [0.6], (δ) [2], (κ) [9] [opioid agonist: Naloxone antagonized MVD relaxation]

(continued)

Table 5.6 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Akuammicine (indole)	<i>Aspidosperma quebracho-blanco</i> , <i>Catharanthus roseus</i> , <i>Picralima nitida</i> (Apocynaceae) [seed]	O-R ligand (κ) [0.2] [opioid agonist (Naloxone antagonized GPI relaxation), partial agonist (mouse & rabbit VD relaxation)]
Akuammine (indolomonoterpene)	<i>Catharanthus roseus</i> , <i>Picralima nitida</i> (Apocynaceae) [seed]	μ O-R ligand [0.5], κ O-R ligand [opioid antagonist against DAMGO on MVD relaxation]
(+)-Allomatrine (quinolizidine)	<i>Sophora</i> spp. (Fabaceae)	O-R agonist (κ O-R) [anti- nociceptive]
(-)-Apparicine (indole)	<i>Aspidosperma dasycarpon</i> , <i>Tabernaemontana pachysiphon</i> (Apocynaceae) [leaf]	O-R ligand (agonist) [3] (A ₁ AD-R) [analeptic, analgesic (mouse abdominal relaxant), antiviral]
Codeine (= 3-O- Methylmorphine) (morphinan isoquinoline)	<i>Argemone mexicana</i> , <i>Eschscholzia californicum</i> , <i>Papaver bracteatum</i> , <i>P. somniferum</i> (opium poppy) (Papaveraceae) [latex]	O-R agonist [analgesic, anti- tussive, narcotic , spasmolytic]
Coronaridine (= Carbo- methoxyibogamine) (indole)	<i>Tabernaemontana coronaria</i> , <i>Tabernanthe iboga</i> (Apocynaceae)	μ O-R [2], δ O-R ligand [8], κ O-R ligand [4] (V-gated Na ⁺ channel) [cytotoxic, diuretic, oestrogenic]
[O-Desmethylibogaine (= 12-Hydroxy- ibogamine)] (indole)	Metabolite of Ibogaine	κ O-R ligand (5HT-TR, NMDA- Glu-R, V-D-TR, V-MA-TR, σ 2-R)
[Dihydroakuammine] (indolomonoterpene)	Semi-synthetic from Akuammine	μ O-R ligand, κ O-R ligand
Dihydrocodeine (morphinan isoquinoline)	Semi-synthetic from Codeine & Neopine	O-R agonist [analgesic, antitussive, narcotic]
<i>cis</i> -8,10-Di-N- Propyllobelidol hydrochloride dehydrate (piperidine)	<i>Siphocampylus verticillatus</i> (Campanulaceae) antinociceptive]	O-R agonist [Naloxone-reversed opiate analgesic effects] [analgesic, (piperidine) antinociceptive]
[(-)-Eseroline] (indole)	Metabolite of Physostigmine	O-R ligand (opiate agonist & thence inhibits AC per G α i) [analgesic, narcotic (\approx Morphine), neurotoxic]
[(+)-Eseroline] (indole)	Metabolite of Physostigmine	O-R ligand (antagonist)
[Heroin (= Morphine diacetate] (morphinan isoquinoline)	Semi-synthetic from Morphine; globally 9 million heroin users out of 180 million illicit drug users	O-R agonist (μ O-R, δ O-R) [antinociceptive, narcotic , opiate agonist]
Ibogaine (= 12- Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> (iboga), <i>Voacanga thouarsii</i> (Apocynaceae); iboga West African stimulant & aphrodisiac	κ O-R ligand (25) [2], μ O-R [4], δ O-R [>100] (AD-R, mACh-R, D-R, D-TR, 5HT-TR, NMDA-Glu-R, V-D-TR, V-MA-TR, V-gated Na ⁺ channel, σ) [anti-addictive, anti- convulsant, CNS activity, hallucinogenic]

(continued)

Table 5.6 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
Ibogamine (indole)	<i>Tabernanthe iboga</i> (iboga) (Apocynaceae)	O-R ligand – κ O-R [3], μ O-R [>100], δ O-R [>100] (V-gated Na ⁺ channel, σ) [brachycardiac activity, cytotoxic, hypotensive]
Laudanosine (= Laudanine methyl ether) (benzylisoquinoline)	<i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [opium exudate]; metabolite of synthetic NM relaxant atracurium besylate	O-R ligand (agonist) – μ 1O-R [3], μ 2O-R [13], δ O-R [6], κ 1O-R [21], κ 3O-R [24] (GABA-R) [analgesic, convulsive, epileptogenic, hypotensive, tetanic, toxic, Naloxonazine-antagonized (μ 1O-R) antinociceptive]
(+)-Matrine (= Lupanindine) (quinolizidine)	<i>Euchresta horsfieldii</i> , <i>Goebelia pachycarpa</i> , <i>Sophora angustifolia</i> , <i>S. spp.</i> , <i>Vexibia pachycarpa</i> (Fabaceae)	O-R agonist (μ O-R, κ O-R) [antinociceptive]
Mitragynine pseudoindoxyl (corynantheidine indole alkaloid)	<i>Mitragyna speciosa</i> (Rubicaceae) [leaf]	O-R agonist (μ O-R, δ O-R) [GPI relaxation, antagonized by Naloxone & μ O-R antagonist Naloxonazine; MVD relaxation antagonized by δ O-R antagonist Naltrindole; analgesic, antitussive, CNS depressant, narcotic]
Morphine (= Morphia) (morphinan isoquinoline); isolated from opium by F.W.A. Sertümer (Germany); Heinrich Otto Wieland (Germany, Nobel Prize, Chemistry, 1927, bile acids); Sir Robert Robinson (UK, Nobel Prize, 1947, Chemistry, alkaloids); named after Morpheus, god of dreams; China Opium Wars (1839–1842, 1856–1860) & subsequent Tai Ping rebellion & associated famine (1850–1864, 20–100 million deaths)	<i>Argemone mexicana</i> , <i>Eschscholzia californicum</i> , <i>Papaver bracteatum</i> , <i>P. somniferum</i> (opium poppy) (Papaveraceae) [latex; opium (laudanum = opium tincture) users – Hector Berlioz (inspired <i>Symphonie Fantastique</i>), Elizabeth Barrett Browning, Samuel Taylor Coleridge, (inspired poem <i>Kubla Khan</i>), reputed agent in attempted suicide of Napoleon Bonaparte (12 April 1814) & suicide of Robert Clive, Helen of Troy, Sherlock Holmes, Modest Mussorgsky, Florence Nightingale, Edgar Allen Poe, Thomas de Quincey (<i>Confessions of an English Opium-eater</i>); illegal opium industry worth US\$400 billion pa	O-R agonist – μ O-R [2 nM], δ O-R [1], κ O-R [0.1] [inhibition of Forskolin-stimulated cAMP production via μ O-R [26 nM], δ O-R [3], κ O-R [2]; addictive, analgesic, antitussive, sedative, spasmolytic, toxic]; Hermann Göring, WW2 Luftwaffe C-in-C, morphine addict (1925); laudanum (opium) used by Mrs Robinson in alleged murder of Bertie Robinson, allegedly plagiarized & cuckolded by Sir Arthur Conan Doyle (<i>The Hound of the Baskervilles</i>); eighteenth- to nineteenth-century opium trade by East India Company, opium from Bengal to China for tea (& thence 1769/1770 Bengal Famine, China Opium Wars, China Tai Ping rebellion)

(continued)

Table 5.6 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
α -Narcotine (phthalideisoquinoline); Sir Robert Robinson (UK, Nobel Prize, 1947, Chemistry, alkaloids)	<i>Brassica oleraceae</i> (Brassicaceae), <i>Papaver somniferum</i> (opium poppy) (Papaveraceae) [latex], <i>Lycopersicon esculentum</i> (Solanaceae)	O-R agonist [antitussive]
Neopine (= β -Codeine) (morphinan isoquinoline)	<i>Papaver somniferum</i> (opium poppy), <i>P. bracteatum</i> (Papaveraceae) [latex]	O-R agonist [analgesic, spasmodic]
Noribogaine (= 12- Hydroxyibogamine) (indole)	Metabolite of Ibogaine	κ O-R ligand (4), μ O-R (0.2) (D-R, D-TR, 5HT-TR, NMDA-Glu-R) [anti-addictive, anticonvulsant, CNS activity, hallucinogen]
[Oripavine (= Di-O- Demethylthebaine)] (morphinan isoquinoline)	Generated via cytochrome P450 after ingestion of Thebaine	O-R agonist (μ , κ , δ)
Pericine (indole)	<i>Picralima nitida</i> (Apocynaceae) [cell culture]	O-R agonist
Salsolinol (isoquinoline)	<i>Annona reticulata</i> (Annonaceae), <i>Musa paradisiaca</i> (banana) (Musaceae) [banana peel], <i>Theobroma cacao</i> (cocoa) (Sterculiaceae) [seed, cocoa]	O-R agonist [62] (Dopamine R antagonist) [Naloxone-blocked antinociceptive (rat, i.v. \approx Enkephalins)]
Tabernanthine (= 13- Methoxyibogamine) (indole)	<i>Conopharyngia</i> (<i>Tabernaemontana</i>) spp., <i>Stemmadenia</i> spp., <i>Tabernanthe</i> <i>iboga</i> (Apocynaceae)	O-R ligand – δ O-R [3], κ O-R [0.2], μ O-R (>100) (CBZ-R, V-gated Na ⁺ channel, σ) [CNS activity]
Tetrahydropapaveroline (tetrahydroisoquinoline)	Metabolite of Dopamine	O-R agonist [20] (D-TR) [Naloxone-blocked antinociceptive (i.v. \approx Enkephalins)]
(–)-Thebaine (= Paramorphine) (morphinan)	<i>Papaver bracteatum</i> , <i>P. serpentina</i> , <i>P. somniferum</i> (opium poppy) (Papaveraceae) [flower]	μ O-R ligand, δ O-R ligand [1] [antinociceptive]
[(+)-Thebaine (= isomer of (–)-Thebaine)] (morphinan)	Semi-synthetic enantiomer of (–)- Thebaine	μ O-R ligand (agonist) [3], δ O-R ligand [antinociceptive]
Tubotaiwine (alkaloid)	<i>Tabernaemontana pachysiphon</i> , <i>Tabernanthe iboga</i> (Apocynaceae) [leaf]	O-R ligand [2] (A ₁ AD-R)
Phenolic		5.6p
Catechin 3-O-gallate (gallotannin)	Widespread	O-R ligand (<10) (AD1-R, D1-R, D2-R, 5HT1-R)
Davidiin (= 1,5 Hexahydroxydiphenoyl 2,3,4-trigalloylglucose) (ellagitannin)	<i>Quercus</i> sp. (Fagaceae) [bark]	O-R ligand (<10) (α 2A-R, β A-R, D2-R, 5HT2-R)
7,9':7',9-Diepoxylicnan (lignan phenolic)	<i>Valeriana officinalis</i> (valerian) (Valerianaceae) [root]	μ O-R (5HT1A-R, GABAA-R, benzodiazepine R)
β -2,4-Di-O-galloyl- glucose (gallotannin)	<i>Croton lechleri</i> (Euphorbiaceae)	O-R ligand (<10) (β A-R, D1-R, D2-R, 5HT1-R)

(continued)

Table 5.6 (Continued)

Compound (class)	Plant (family) part/	Receptor affected (other targets) in vivo effects/
(-)-Epiarfelechin (flavan-3-ol)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial], <i>Camellia sinensis</i> (Theaceae)	O-R ligand (>10) (ATP K ⁺ CH, α 1A-R, α 2A-R, β A-R, COX-1, D2-R, 5HT1A-R) [AI with Carrageenin-induced paw oedema]
(-)-Epigallocatechin-3-gallate (flavan-3-ol, gallotannin)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (Theaceae)	O-R ligand (~10) (β A-R, D1-R, D2-R, PKC) [AI, blocks COX-2 & iNOS induction]
Geraniin (ellagitannin)	<i>Acer</i> (Aceraceae), <i>Cercidiphyllum</i> (Cercidiphyllaceae), <i>Coriaria</i> (Coriariaceae), <i>Geranium</i> , <i>Erythroxylum</i> (Erythroxylaceae), <i>Euphorbia</i> , <i>Mallotus</i> (Euphorbiaceae), <i>Fuchsia</i> (Onagraceae) spp.	O-R ligand (>10) (α 1A-R, α 2A-R, D1-R, 5HT1-R) [inhibits Epinephrine-induced adipocyte lipolysis, increases ACTH-induced adipocyte lipolysis]
Hypericin (= Hypericum red) (bianthraquinone)	<i>Hypericum perforatum</i> (St John's wort), <i>H.</i> spp. (Hypericaceae)	σ O-R ligand (antagonist ?) [antidepressant, anti-retroviral, photosensitising, ovine photogenic hypericism]
Pedunculagin (= 2,3-Hexahydroxydiphenoyl 4,5-hexahydroxyldiphenoyl glucose) (ellagitannin)	<i>Casuarina stricta</i> (Casuarinaceae), <i>Quercus</i> sp. (Fagaceae), <i>Potentilla</i> sp., <i>Rubus</i> spp. (Rosaceae), <i>Stachyurus praecox</i> (Stachyuraceae), <i>Camellia japonica</i> (Theaceae)	O-R ligand (~10) (α 2A-R, β A-R, D1-R, GPT, SU-R) [inhibits Epinephrine-induced adipocyte lipolysis]
Procyanidin B3 (= Catechin (4 α \rightarrow 8) catechin) (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae)	O-R ligand (>10) (α 1A-R, β A-R, D1-R, D2-R, 5HT1-R)
Rugosin D (ellagitannin)	<i>Filipendula ulmaria</i> , <i>Rosa rugosa</i> [petal] (Rosaceae)	O-R ligand (>10) (α 2A-R, β A-R, D1-R, H1-R) [antitumour]
Tellimagrandin I (= 4,5-Hexahydroxydiphenoyl 2,3-digalloylglucose) (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Quercus</i> (Fagaceae), <i>Syzygium</i> , <i>Feijoa</i> , <i>Psidium</i> , <i>Eucalyptus</i> (Myrtaceae), <i>Fuchsia</i> (Onagraceae), <i>Geum</i> , <i>Rosa</i> , <i>Tellima</i> (Rosaceae), <i>Stachyurus</i> (Stachyuraceae), <i>Camellia</i> (Theaceae) spp.	O-R ligand (~10) (α 1A-R, α 2A-R, D2-R, SU-R) [inhibits Epinephrine-induced adipocyte lipolysis]
β -1,2,3,4,6-Penta-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark], <i>Geranium thunbergii</i> (Geraniaceae), <i>Paeonia lactiflora</i> (Paeoniaceae)	O-R ligand (<10) (α 2A-R, D1-R, D2-R, SU-R)
β -1,2,4,6-Tetra-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark]	O-R ligand (~10) (α 2A-R, β A-R, D2-R, SU-R)
β -1,2,6-Tri-O-galloyl-D-glucose (gallotannin)	<i>Phyllanthus emblica</i> (Euphorbiaceae), <i>Quercus</i> spp. (Fagaceae) [bark]	O-R ligand (~10) (α 2A-R, β A-R, D1-R, 5HT2-R, RT)

(continued)

Table 5.6 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
β -1,3,6-Tri- <i>O</i> -galloyl- D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark]	O-R ligand (<10) (β A-R, D2-R)
Terpene		5.6t
Ginsenoside R(c) (triterpene saponin)	<i>Panax ginseng</i> (ginseng), <i>Panax</i> spp. (Araliaceae) [root]	O-R ligand (antagonist?) [tonic, blocks β -Endorphin-induced antinociception]
24-Methylene- cycloartenol (phytosterol triterpene)	<i>Oenothera biennis</i> (Onagraceae), <i>Epidendrum mosenii</i> (Orchidaceae); Cycloartenol widespread	[Naloxone-reversed antinociceptive (formalin-induced pain)]
4 α ,7 α ,7 α - Nepetalactone (iridoid monoterpene lactone)	<i>Mentha pulegium</i> , <i>Nepeta caesarea</i> , <i>N. cataria</i> (catnip) (Lamiaceae) [leaf oil]	O-R (agonist) [analgesic (mouse tail flick, antagonized by antagonist Naloxone); isomer mixture repels insects & excites Felidae (cats)]
Pholidotin (triterpene)	<i>Epidendrum mosenii</i> (Orchidaceae)	[Inhibits acetic acid-induced pain]
α -Santolol (sesquiterpene)	<i>Santalum album</i> (Santalaceae) [wood oil]	δ O-R antagonist (D2-R, 5HT2A-R) [antipsychotic, perfume constituent]
Other		5.6o
α -Gliadin (43–49) (peptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour gluten fraction]	O-R ligand (peripheral lymphocyte, Naloxone & Enkephalin inhibit binding) [0.02]
GYPMYPLPR (= Oryzatensin) (peptide)	<i>Oryza sativa</i> (rice) (Poaceae) [seed]	O-R antagonist (μ O-R) [37] [opioid (ileum contraction, muscarinic cholinergic) (at 0.5)]
GYYP (= Gluten exorphin A4) (peptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour]	O-R agonist (δ O-R) (4) [opioid (δ O-R, MVD) (70)]
GYYPPT (= Gluten exorphin A5) (peptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour]	O-R agonist (rat O-R δ) (2) [opioid (δ O-R, MVD) (60)]
GYYPPTS (peptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour]	O-R agonist (O-R δ) (50) [opioid (δ O-R, MVD) (72)]
Lipopolysaccharide, of wheat (= LPSw) (lipopolysaccharide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour]	Induces β -Endorphin [analgesic (at 10 ng/mouse); O-R antago- nist Naloxone blocks effect]
SYYP (peptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour]	O-R agonist (O-R δ) (6) [opioid (δ O-R, MVD) (200)]
YGGW (= Gluten exorphin B4) (peptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour]	O-R agonist (μ O-R) (0.2) (δ O-R) (0.2) [opioid (μ O-R, GPI) (2), (δ O-R, MVD) (3)]
YGGFL (= [Leu]enkephalin) (peptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour]	O-R agonist (μ O-R) (40 nM) (rat δ O-R) (3 nM) [opioid (μ O-R, GPI) (40 nM), (δ O-R, MVD) (4 nM)]
YGGWL (= Gluten exorphin B5) (peptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed, flour]	O-R agonist (μ O-R) (0.05) (δ O-R) (5 nM) [opioid (μ O-R, GPI) (50 nM), (δ O-R, MVD) (20 nM)]

(continued)

Table 5.6 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Receptor affected (other targets) in vivo effects </i>
Non-plant reference		5.6n
[Dihydrocodeine (=Paracodin)] (morphinan isoquinoline)	Semi-synthetic from Codeine	O-R agonist [analgesic, antitussive, narcotic]; Hermann Göring, euphoric WW2 Luftwaffe C-in-C, on Dihydrocodeine (1937–1945)
[Dihydroetorphine] (morphinan isoquinoline)	Semi-synthetic from Morphine	O-R agonist – μ [0.5 nM], δ [2 nM], κ [0.6 nM] [inhibition of Forskolin-stimulated cAMP production via μ O-R [0.04 nM], δ O-R [0.9 nM], κ O-R [4 nM]; analgesic, antinociceptive]
[Dynorphin A] (peptide)	Endogenous animal opiate	κ O-R agonist [analgesic, endogenous anti-convulsant]
[Endomorphin-1 (=YPWF)] (peptide)	Endogenous animal opiate	μ O-R agonist [analgesic, antinociceptive, endothelial NO release-mediated vasodilatory]
[Endomorphin-2 (=YPWFF)] (peptide)	Endogenous animal opiate	μ O-R agonist [analgesic, antinociceptive, endothelial NO release-mediated vasodilatory]
[β -Endorphin (= YGGFMTSFKSQIPLV TLFKNAIKKNAYKKGE)] (oligopeptide)	Endogenous animal opiate	O-R agonist [analgesic, narcotic]
[Met-Enkephalin (= YGGFFM)] (hexapeptide)	Endogenous animal opiate	O-R agonist [analgesic, narcotic]
[Leu-Enkephalin (= YGGFL)] (hexapeptide)	Endogenous animal opiate	O-R agonist [analgesic, narcotic]
[Etorphine] (morphinan isoquinoline)	Semi-synthetic from Morphine	O-R agonist – μ [\sim 1 nM], δ [\sim 1 nM], κ [\sim 1 nM] [analgesic, antinociceptive]
[Methadone (= 6-Dimethylamino-4,4-diphenyl-3-heptanone)] (aryl tertiary amine)	Synthetic	O-R agonist (NMDA-Glu-R) [analgesic, narcotic]
[Naloxonazine] (morphinan isoquinoline)	Synthetic (cf. Morphine)	μ O-R antagonist [inhibits opiate antinociceptive & SM relaxation effects]
[Naloxone] (morphinan isoquinoline)	Synthetic (cf. Morphine)	Non-selective O-R antagonist (μ , κ , δ) [1 nM] [anorectic i.e. inhibits food & water intake (κ); administered for Heroin overdose]
[Naltrexone] (morphinan isoquinoline)	Synthetic (cf. Morphine)	O-R antagonist ($\mu > \kappa$, δ)

(continued)

Table 5.6 (Continued)

Compound (class)	Plant (family) part	Receptor affected (other targets) in vivo effects
[Naltrindole] (morphinan isoquinoline)	Synthetic (cf. Morphine)	δ O-R antagonist [0.1–0.3 nM], μ O-R, κ O-R & ε O-R antagonist [0.1–0.3] ($\delta > \mu, \kappa$) [inhibits opiate antinociceptive & SM relaxation effects]
[Nociceptin] (peptide)	Endogenous animal opiate	ORL1-R agonist

Table 5.7 Leucocyte- and inflammation-related G protein-coupled receptors

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
ADP receptor (ADP-R)		5.7A
ADP (= Adenosine-5'-diphosphate) (purine nucleotide, alkaloid)	Universal	ADP-R (P2Y1-R, P2Y12-R, P2Y13-R) agonist [induces PA & Ca ²⁺ elevation]
ATP (= Adenosine-5'-triphosphate) (purine nucleotide, alkaloid)	Universal	ADP-R antagonist [blocks ADP-induced PA & Ca ²⁺ elevation]
Ellagitannins (hydrolysable tannins)	Widespread e.g. Rugosin E	ADP-R agonists (PA)
[5'- <i>p</i> -Fluorosulphonylbenzoyl-adenosine (= FSBA)] (nucleoside)	Synthetic	Alkylates platelet ADP-R aggregin (ATP- & ADP-like alkylating agent)
Rugosin E (ellagitannin phenolic)	<i>Rosa rugosa</i> (Rosaceae)	ADP-R agonist (2) [PA (antagonized by ATP)]
Bradykinin receptor (BK-R)		5.7B
Abruquinone A (isoflavanquinone)	<i>Abrus precatorius</i> (Fabaceae)	[Inhibits BK-induced plasma extravasation; AI]
[Anchinopeptolides A, B, C & D; Cycloanchinopeptolide C] (peptide alkaloids)	<i>Anchinoe tenacior</i> (Mediterranean sponge)	B2-BK-R ligands (NPY-R, SOM-R)
[Bradykinin] (9aa, 1 kDa protein)	Animals; <i>ex</i> leucocytes	BK-R agonist [↑ capillary permeability, nociceptive-pain receptor, NO synthesis; induces SM contraction, inflammation, mast cell Histamine release]
1,7-Dihydroxy-2,3-dimethoxyxanthone (xanthone)	<i>Polygala cyparissias</i> (Polygalaceae)	[Inhibits BK-induced tracheal contraction (9)]
Norathiol (xanthone)	<i>Tripterospermum lanceolatum</i> (Gentianaceae)	[Inhibits SP-induced inflammation]

(continued)

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Table 5.7 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
Chemokine receptor (CHK-R)		5.7C
Baicalein (= 5,6,7-Trihydroxyflavone) (flavone)	<i>Scutellaria</i> spp. (Lamiaceae) [root, leaf], <i>Plantago major</i> (Plantaginaceae); glycosides in <i>Oroxylum indicum</i> (Bignoniaceae) [leaf], <i>S. galericulata</i> (Lamiaceae)	Binds IL-8 & other CKs (↓ CHK-R binding; (-)-HIV-1-CHK-R binding [blocks (CHK-R + CD4)-dependent HIV-1 entry] (BZ-R, glyoxalase I, 12-LOX) [antiallergic, anti-HIV-1, AI, diuretic]
[Caffeic acid phenethyl ester] (phenolic)	Honeybee propolis [derived from plant nectar]	[(-)-NFκB activation → ↓ IL-8 & MCP-1 expression; anticarcinogenic, AI, antimitogenic, immunomodulatory]
Capsianoside G (diterpene glycoside)	<i>Capsicum annuum</i> (sweet pepper, paprika) (Solanaceae)	Causes CD4 & CXCR4 (CHK-R) colocalization & capping → ↑ HIV-1 dual attachment & infection
Curcumin (= Diferuloylmethane; Turmeric yellow) (phenylpropanoid)	<i>Curcuma longa</i> (turmeric), <i>C. aromatica</i> , <i>C. xanthorrhiza</i> , <i>C. zedoaria</i> , <i>Zingiber officinale</i> (Zingiberaceae) [root]	(PK, RTK) [(-)-IKK → (-)-NFκB activation → ↓ IL-8 & MCP-1 expression; AI, anti-oxidant, hypoglycaemic, cytotoxic]
Ferulic acid (phenolic acid)	Widespread; <i>Ferula assafoetida</i> (Apiaceae), <i>Cimifuga</i> (Ranunculaceae), <i>Oplopanax</i> (Araliaceae), <i>Beta</i> (Chenopodiaceae), <i>Oryza</i> , <i>Phleum</i> (Poaceae), <i>Ajuga</i> , <i>Salvia</i> (Lamiaceae), <i>Periploca</i> (Periplocaceae), <i>Pinus</i> , <i>Tsuga</i> (Pinaceae) spp.	[Inhibits viral-induced IL-8 expression; antibacterial, antifungal, antihepatotoxic, antioestrogenic, antimitotic, antitumour, PAI]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Phaseolus lunatus</i> , <i>Trifolium brachycalcinum</i> , <i>T. subterraneum</i> , <i>T.</i> spp. (clover) (Fabaceae); glycosides (Fabaceae)	(AD-R, GABAA-R, HISK, lipase, PK, RTK, peroxidase, TOPII) [(-)-RTK → (-)-NFκB activation → ↓ IL-8 & MCP-1 expression; antifungal, oestrogenic]
Ginsenan S-IIA (acidic polysaccharide)	<i>Panax ginseng</i> (ginseng) (Araliaceae) [root]	[Induces monocyte IL-8 expression]
[IL-1 (= Interleukin-1)] (12–18 kDa protein)	Animal cytokine	[Infection e.g. <i>Helicobacter pylori</i> → ↑ IL-1 → ↑ IL-8 expression → e.g. inflammation, ulceration]
[IL-8 (= Interleukin-8)] (protein)	Animal chemokine	CXCR1 (CHK-R) agonist [pro-I, granule exocytosis from neutrophils, basophils & eosinophils, leucocyte attraction]

(continued)

Table 5.7 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
Isoferulic acid (phenylpropanoid phenolic acid)	<i>Helianthus annuus</i> (Asteraceae), <i>Catalpa ovata</i> (Bignoniaceae), <i>Arachis hypogaea</i> (Fabaceae), <i>Triticum aestivum</i> (Poaceae), <i>Cimicifuga racemosa</i> , <i>C. spp.</i> (Ranunculaceae) [rhizome], <i>Tamarix aphylla</i> (Tamaricaceae) [leaf]	[(-)-viral-induced IL-8 expression; AI]
Isohelenine (= Isoalantolactone) (eudesmanolide sesquiterpene lactone)	<i>Inula helenium</i> [oil of elecampane], <i>I. spp.</i> , <i>Liatris cylindrica</i> , <i>Telekia speciosa</i> (Asteraceae)	[(-)-IκBα degradation → (-)-NFκB activation → ↓ TNF-α-induced IL-8 expression; AI, antibacterial, antifungal, anthelmintic, antifeedant, vermifuge]
Parthenolide (sesquiterpene lactone)	<i>Ambrosia spp.</i> , <i>Arctotis spp.</i> , <i>Chrysanthemum parthenium</i> , <i>Tanacetum vulgare</i> (tansy), (Asteraceae), <i>Michelia champaca</i> , <i>M. lanuginosa</i> (Magnoliaceae)	[(-)-IκBα degradation → (-)-NFκB activation → ↓ IL-8 & MCP-1 expression; antibacterial, antifungal, antimigraine, antitumour, cytotoxic]
[Peptidoglycan] (peptidoglycan)	Bacterial	[TLR2 agonist → ⊕ NFκB → ↑ IL-8 expression]
Pheophorbide a (pyrrole)	<i>Psychotria acuminata</i> (Rubiaceae)	[Light-dependent inactivation of IL-8 CHK-R]
Reynosin (sesquiterpene lactone)	<i>Ambrosia confertiflora</i> , <i>Chrysanthemum parthenium</i> , <i>Saussurea lappa</i> [root; aphrodisiac], <i>Tanacetum vulgare</i> (tansy) (Asteraceae), <i>Laurus nobilis</i> (Lauraceae), <i>Magnolia grandiflora</i> (Magnoliaceae)	[(-)-LPS-induced CINC-1 expression (1)]
Sanguin H-11 (tannin)	<i>Sanguisorba officinalis</i> (Rosaceae)	[(-)-CINC-1(GRO-like CHK)-dependent neutrophil chemotaxis]
Shikonin (= 1'R-Alkannin) (naphthoquinone)	<i>Echium lycopsis</i> , <i>Lithospermum erythrorhizon</i> , <i>Onosma caucasicum</i> (Boraginaceae)	CCR1 (CHK-R) antagonist versus RANTES (3), MIP-1α (3)
[TNF-α (= Tumour Necrosis Factor-α)] (protein)	Animals; leucocyte cytokine	[TNF-α-R agonist → ⊕ NFκB → ↑ IL-8 expression]
[vCCI (= Viral Chemokine Inhibitor)] (protein)	Pox virus	CCR2 (CHK-R) competitive antagonist versus MCP-1 (βCK)
Collagen R (COLL-R) (cf. 8.3B)		5.7D
Avicine pseudocyanide (isoquinoline)	<i>Zanthoxylum integrifolium</i> (Rutaceae)	COLL-R antagonist [blocks IP ₃ -mediated ↑ Ca ²⁺]
Frangulin B (anthraquinone)	<i>Frangula alnus</i> , <i>Rhamnus formosana</i> (Rhamnaceae)	COLL-R antagonist [blocks IP ₃ -mediated ↑ Ca ²⁺]

(continued)

Table 5.7 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
[Trimucytin] (collagen-like protein)	<i>Trimeresurus mucrosquamatus</i> (snake) venom	COLL-R (glycoprotein Ia/IIa) agonist
Histamine R (HIS-R)		5.7E
Alkaloid		5.7Ea
Casimiroedine (imidazole, N-glycoside)	<i>Casimiroa edulis</i> (Rutaceae) [seed]	HIS-R (H3) agonist [hypotensive]
N,N-Dimethylhistamine (imidazole)	<i>Casimiroa edulis</i> (Rutaceae) [seed]	HIS-R (H1) agonist [hypotensive]
16-Epimethuenine (acylindole)	<i>Pterotaberna inconspicua</i> (Apocynaceae)	HIS-R antagonist [inhibits HIS-induced guinea pig ileum contraction (0.3)]
Histamine (= 5-Imidazole- ethylamine; 2-(Imidazol-4-yl) ethylamine) (imidazole); discovered by Adolph Windaus (Germany, Nobel Prize, Chemistry, 1928, sterols & Vitamin D); histamine & allergy – Sir Henry Dale (UK, Nobel Prize, Medicine, 1936, chemical neurotransmission)	<i>Opuntia ficus-indica</i> (Cactaceae), <i>Spinacia oleracea</i> (Chenopodiaceae), <i>Drosera</i> spp. (Droseraceae), <i>Senna obtusifolia</i> (Fabaceae), <i>Musa sapientum</i> (banana) (Musaceae), <i>Nepenthes</i> spp. (Nepenthaceae), <i>Sarracenia</i> sp. (Sarraceniaceae), <i>Urtica</i> <i>dioica</i> (Urticaceae); animals; decarboxylation product of Histidine	HIS-R agonist [bronchoconstrictant, inflammatory, irritant, vasodilator, promotes gastric pepsin secretion]
Methuenine (acylindole)	<i>Pterotaberna inconspicua</i> (Apocynaceae)	HIS-R antagonist [inhibits H-induced guinea pig ileum contraction (7)]
N-Methylhistamine (imidazole)	<i>Casimiroa edulis</i> (Rutaceae) [seed]	HIS-R (H1) agonist [hypotensive]
Phenolic		5.7Ep
Geraniin (ellagitannin)	<i>Acer</i> (Aceraceae), <i>Cercidiphyllum</i> (Cercidiphyllaceae), <i>Coriaria</i> (Coriariaceae) [leaf], <i>Geranium</i> , <i>Erythroxylum</i> (Erythroxylaceae), <i>Euphorbia</i> , <i>Mallotus japonicus</i> (Euphorbiaceae), <i>Fuchsia</i> (Onagraceae) spp.	H1 HIS-R ligand (>10) (α 1A-R, α 2A-R, D1-R, 5HT1-R, O-R)[inhibits Epinephrine-induced adipocyte lipolysis, increases ACTH-induced adipocyte lipolysis]
α -Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	HIS-R (Ca^{2+} ATPase, cAMP PDE, EST-R, HIV-1 PR, PK) [antibacterial, AI, anti-ulcer]
Procyanidin B4 (= Catechin (4 α →8) epicatechin (procyanidin dimer)	<i>Croton lechleri</i> (Euphorbiaceae), <i>Rubus idaeus</i> (Rosaceae)	H1 HIS-R ligand (~10) (α 1A-R, α 2A-R, β -A R, D2-R, 5HT1-R) [anti-ulcerative]
Rugosin D (ellagitannin)	<i>Filipendula ulmaria</i> , <i>Rosa</i> <i>rugosa</i> [petal] (Rosaceae)	H1 HIS-R ligand (>10) (α 2A-R, β A-R, D1-R, O-R) [antitumour]
Δ^1 -Tetrahydro-cannabinol (= Dronabinol; Δ^9 - Tetrahydrocannabinol; (-)- Δ^1 -3, 4- <i>trans</i> - Tetrahydrocannabinol (dibenzopyranol)	<i>Cannabis sativa</i> (marijuana) (Cannabaceae) [cannabis resin, marijuana leaf]	H1 HIS-R (CBI) [AI, antiemetic, hallucinogenic, psychotropic]

(continued)

Table 5.7 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
Terpene		5.7Et
Aescin (= Escin) (triterpene saponin)	<i>Panax quinquefolius</i> (Araliaceae), <i>Aesculus hippocastanum</i> (horse chestnut) (Hippocastanaceae)	HIS-R antagonist (5HT-R) [for oedema, chronic venous insufficiency & haemorrhoids]
Ginsenoside Rg3 (triterpene saponin)	<i>Panax ginseng</i> [ginseng root] (Araliaceae)	HIS-R antagonist (at 100) (mACh-R) [antitumour]
ϵ -Phytol (acyclic diterpene)	All plants; part of chlorophyll [leaf]; <i>Ocimum suave</i> (Lamiaceae), <i>Linum usitatissimum</i> (Linaceae), <i>Fucus vesiculosus</i> (kelp), <i>Jasminum officinale</i> (Oleaceae), <i>Elettaria cardamomum</i> (Zingiberaceae)	H1 HIS-R antagonist [AI, inhibits histamine-induced paw oedema]
Non-plant reference		5.7En
[Cimetidine] (imidazolyl guanidinyl thioether)	Synthetic; Sir James Black (UK, Nobel Prize, Medicine, 1988, β-blocker & anti-histamine drug development)	H2 HIS-R antagonist [antihistamine]
[Pyrilamine (= Mepyramine; <i>N</i> - <i>p</i> -Methoxybenzyl- <i>N</i> ', <i>N</i> '-dimethyl- <i>N</i> '- α -pyridylethylenediamine)] (benzyl pyridyl tertiary amine)	Synthetic	H1 HIS-R antagonist [2nM] [antihistamine]
[(<i>R</i>)- α -Methylhistamine] (methyl histamine)	Synthetic	H3 HIS-R agonist
Neurotensin receptor (NEUT-R)		5.7F
Cyclopsychoptide A (31 aa; 3kDa; 6 Cys; S-S knotted cyclotide cyclic peptide)	<i>Psychotria longipes</i> (Rubiaceae)	NEUT-R antagonist (3) (Ca ²⁺ permeability)
Ginsenoside Rg3 (triterpene glycoside saponin)	<i>Panax ginseng</i> (ginseng) (Araliaceae) [root]	[\downarrow Neurotensin-induced adrenal chromaffin cell catecholamine secretion]
<i>Solanum</i> PCI (= Potato Carboxypeptidase Inhibitor) (4kDa protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	NEUT-R antagonist (CPA) [inhibits mast cell Histamine release]
[Neurotensin] (13 aa, ~1 kDa protein)	Animals; brain & gut	NEUT-R agonist (\downarrow cAMP (0.5nM), \uparrow cGMP (1nM) [anorexigenic, autocrine growth factor for small cell lung cancer cells (SCLC cells), CNS NT, duodenum relaxation, ileum & uterine contraction, mast cell Histamine release, \downarrow gastric emptying]
[SR 48692] (non-peptide)	Synthetic	NEUT-R antagonist (15nM) (mast cell CPA) [inhibits mast cell Histamine release]

(continued)

Table 5.7 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
Platelet-activating factor receptor (PAF-R)		5.7G
Alkaloid		5.7Ga
Dauricine (bisbenzylisoquinoline alkaloid)	<i>Menispermum canadense</i> , <i>M. dauricum</i> (Menispermaceae)	PAF-R ligand [AI, anaesthetic, weak curare-like]
Ochotensimine (isoquinoline)	<i>Corydalis ochotensis</i> , <i>C. spp.</i> (Apiaceae)	PAF-R antagonist
Tetrandine (bisbenzylisoquinoline)	<i>Cissampelos pareira</i> , <i>Cyclea peltata</i> , <i>Stephania discolor</i> , <i>S. tetrandia</i> (Menispermaceae)	PAF-R ligand [AI, analgesic, antipyretic]
Phenolic		5.7Gp
Aglafoline (benzofuran)	<i>Aglaiia basiphylla</i> , <i>A. elliptifolia</i> (Meliaceae)	PAF-R antagonist (18)
[<i>trans</i> -2,5-Bis (3,4,5-Trimethoxyphenyl) tetrahydrofuran] (tetrahydrofuran lignan)	Synthetic (related synthetic lignans also variously active)	[PAI (PAF-induced) (50)] PAF-R antagonist (20 nM)
Denudatin B (lignan)	<i>Magnolia denudata</i> , <i>M. fargesii</i> (Magnoliaceae) [flower bud], <i>Piper hancei</i> , <i>P. wallichii</i> (Piperaceae)	PAF-R antagonist [PAI – PAF-induced (28)]
3',4'-Diisovalerylhellactone diester (coumarin)	<i>Peucedanum japonicum</i> (Apiaceae)	PAF-R antagonist (4) [PAI – PAF-induced (56), collagen-induced (89)]
Di- <i>O</i> -methyltetrahydrofuroguaiacin B (tetrahydrofuran lignan)	<i>Illicium floridanum</i> (Illiciaceae) [fruit, leaf]	PAF-R antagonist [AI]
Galbelgin (tetrahydrofuran lignan)	<i>Piper futukadsura</i> (Piperaceae) [stem = haifengteng]	PAF-R antagonist (5) [AI]
Galgravin (tetrahydrofuran lignan)	<i>Nectandra rigida</i> (Lauraceae), <i>Piper futukadsura</i> , <i>P. wallichii</i> (Piperaceae) [stem = haifengteng]	PAF-R antagonist (1) [AI]
Hancinone C (neolignan)	<i>Piper wallichii</i> (Piperaceae)	PAF-R antagonist [AI]
Kadsurenin B (neolignan)	<i>Piper kadsura</i> (Piperaceae)	PAF-R antagonist
Kadsurenin C (neolignan)	<i>Piper kadsura</i> (Piperaceae)	PAF-R antagonist
Kadsurenin K (bicyclo(3,2,1) octanoid neolignan)	<i>Piper kadsura</i> (Piperaceae)	PAF-R antagonist
Kadsurenin L (bicyclo(3,2,1) octanoid neolignan)	<i>Piper kadsura</i> (Piperaceae)	PAF-R antagonist
Kadsurenone (lignan)	<i>Piper futukadsura</i> , <i>P. hancei</i> , <i>P. wallichii</i> (Piperaceae) [stem = haifengteng]	PAF-R antagonist [39 nM; 58 nM] [PAI – PAF-induced (18); AI]
Kadsurin A (lignan)	<i>Piper cubeb</i> , <i>P. futukadsura</i> (Piperaceae) [stem], <i>Kadsura longipedunculata</i> (Schizandraceae)	PAF-R antagonist
Kadsurin B (lignan)	<i>Piper futukadsura</i> (Piperaceae) [stem = haifengteng], <i>Kadsura longipedunculata</i> (Schizandraceae)	PAF-R antagonist

(continued)

Table 5.7 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
Piperbetol (neolignan)	<i>Piper betle</i> (Piperaceae)	PAF-R antagonist (9) [PAI – PAF-induced (18)]
(–)-Piperenone (neolignan)	<i>Piper cubeb</i> (Piperaceae)	PAF-R antagonist
Piperol A (neolignan)	<i>Piper betle</i> (Piperaceae)	PAF-R antagonist (88) [PAI – PAF-induced (114)]
Piperol B (neolignan)	<i>Piper betle</i> (Piperaceae)	PAF-R antagonist (6) [PAI – PAF-induced (12)]
PJ-1 (khellactone)	<i>Peucedanum japonica</i> (Apiaceae)	PAF-R antagonist
Sanguin H-11 (polyphenol)	<i>Sanguisorba officinalis</i> (Rosaceae)	Blocks PAF-dependent neutrophil chemotaxis
Saucerneol (tetrahydrofuran lignan)	<i>Piper</i> sp. (Piperaceae)	PAF-R antagonist (5) [AI]
[Δ^6 -Tetrahydrocannabinol-7-oic acid] (phenolic)	Major metabolite in humans of Δ^9 -Tetrahydrocannabinol	PAF-R antagonist (COX, LOX) [antinociceptive (probably responsible for activity of parent Δ^9 -Tetrahydrocannabinol)]
Wallichinine (neolignan)	<i>Piper wallichii</i> (Piperaceae)	PAF-R antagonist [AI]
(+)-Veraguensin (tetrahydrofuran lignan)	<i>Illicium floridanum</i> (Illiaceae) [fruit, leaf], <i>Piper futukadsura</i> (Piperaceae) [stem = haifengteng]	PAF-R antagonist (1) [AI]
Yangambin (lignan)	<i>Artemisia absinthium</i> (Asteraceae) [root], <i>Ocotea duckei</i> (Lauraceae), <i>Virola elongata</i> (Myristicaceae) [toxic & hallucinogenic bark resin]	PAF-R antagonist (at 0.1–10) [inhibits PAF-induced SM contraction & vascular permeability; protective against endotoxic/septic shock]
Terpene		5.7Gt
14-Acetoxy-7 β -(3'-ethylcrotonoyloxy)-notonipetranone (= L-652,469; Tussilagone) (terpene)	<i>Tussilago farfara</i> (coltsfoot) (Asteraceae) [bud]	PAF-R antagonist [5] (L-Ca ²⁺ CH) [AI, PAI, blocks PAF- & Carageenan-induced oedema]
Bakkenolide G (sesquiterpene lactone)	<i>Petasites formosanus</i> (butterbur) (Asteraceae)	PAF-R antagonist (3) [PAI – PAF-induced (6)]
Ginkgolide A (ginkgolide diterpene)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	PAF-R antagonist [AI, antifeedant, bitter, PAI]
Ginkgolide B (= BN52021) (ginkgolide diterpene)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	PAF-R antagonist (2) [PAI – PAF-induced (5; 12); AI, anti-asthmatic, bronchodilator]
BN52023 (ginkgolide diterpene)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	PAF-R antagonist [PAI]
α -Cedrol (= Cedar camphor; Cedrol; Cypress camphor) (sesquiterpene)	<i>Biota orientalis</i> [leaf], <i>Cupressus sempervirens</i> , <i>Juniperus virginiana</i> , <i>J.</i> spp. (Cupressaceae), <i>Satureja odora</i> (Lamiaceae)	PAF-R ligand (13) [perfume]

(continued)

Table 5.7 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
Ginkgolide A (diterpene)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae)	PAF-R antagonist [AI, antifeedant, antiasthmatic, bitter, bronchodilatory]
Methylpiperbetol	<i>Piper betle</i> (Piperaceae)	PAF-R antagonist (5) [PAI – PAF-induced (11)]
Pinusolide (labdane diterpene lactone)	<i>Biota orientalis</i> [leaf] (Cupressaceae)	PAF-R ligand (0.3) [PAI – PFA-induced (5)]
Other		5.7Go
1,2-Di- <i>O</i> -palmitoyl-3- <i>O</i> -(6-sulpho- α-D-quinovopyranosyl)-glycerol (sulphonoglycolipid)	<i>Polypodium decumanum</i> (calaguala) (fern)	PAF-R antagonist (2) [inhibits PAF-induced neutrophil exocytosis; calaguala anti-psoriatic]
Non-plant reference		5.7Gn
[<i>trans</i> -2,5-Bis (3,4,5- trimethoxyphenyl) tetrahydrofuran] (tetrahydrofuran lignan)	Synthetic – cf. Veraguensin	PAF-R antagonist (20 nM) [AI]
[CIS-19] (aryl naphthylamine)	Semi-synthetic from Fagaronine from <i>Fagara zanthoxyloides</i> (Rutaceae)	PAF-R antagonist (2; 10)
[<i>all cis</i> -3,4-Dimethyl-2,5- <i>bis</i> (3,4- dimethoxyphenyl) tetrahydrofuran] (tetrahydrofuran lignan)	Synthetic – cf. Veraguensin	PAF-R antagonist (0.2) [AI]
[PAF (= 1- <i>O</i> -Alkyl-2-acetyl-sn- glyceryl-3-phosphorocholine)] (phospholipid)	Animals – endogenous ligand	PAF-R agonist [6 nM]
[Phomactin] (tricyclic furanochroman)	<i>Phoma</i> sp. (marine fungus)	PAF-R antagonist
Prostaglandin receptors (PG-Rs)		5.7H
Other		5.7Ho
9-Hydroxy-10- <i>trans</i> ,12- <i>cis</i> - octadecadienoic acid (= 9-HODE) (unsaturated FA)	<i>Glechoma hederacea</i> (ground ivy) (Lamiaceae)	PGE ₁ PG-R (platelet) (competes with PGE ₁) [22]; PGD ₂ -R (competes with PGD ₂) [12]; PGE ₁ -R & PGD ₂ -R (platelet) (partial agonist) (10–20)
Non-plant reference		5.7Hn
[Prostaglandins (e.g. PGE ₁ , PGE ₂ , PGD ₁ & PGD ₂)] (FA derivatives)	Animals; Bengt Samuelsson (Sweden), Sune Bergström (Sweden) & Sir John Vane (UK) (Nobel Prize, Medicine, 1982, PGs)	PG-R agonists
Sphingosine-1-phosphate (= S1P) receptor (S1P-R)		5.7I
Sphinganine 1-phosphate (= Dihydrosphingosine 1-phosphate) (sphingolipid)	Universal	S1P-R EDG-1 agonist [chemotaxis]

(continued)

Table 5.7 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
Sphingosine (= 1,3-Dihydroxy-2-amino-4-octadecene; 4-Sphingenine) (sphingolipid)	Universal; precursor of Sphingosine-1-phosphate (= S1P)	Phosphorylated by sphingosine kinase → Sphingosine-1-phosphate (= S1P)
Sphingosine-1-phosphate (= S1P) (sphingolipid)	Universal; likely signaller in plants & fungi as well as animals	S1P-R EDG-1 agonist (SPH-R) [chemotaxis]
Thrombin protease activated receptors (PARs)		5.7J
Baicalein (= 5,6,7-Trihydroxyflavone) (flavone)	<i>Scutellaria baicalensis</i> , <i>S. spp.</i> (Lamiaceae) [root, leaf], <i>Plantago major</i> (Plantaginaceae); glycosides in <i>S. galericulata</i> (Lamiaceae), <i>Oroxylum indicum</i> (Bignoniaceae) [leaf]	[Inhibits t-PA & PAI-1 induction by PAR agonist peptide (7)] (12-LOX, BZ-R, CK-R, glyoxalase I) [AI]
Glycine BBI-1 (8 kDa protein; 14 Cys)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	[Inhibits thrombin PAR activation] (CHY, TRY)
Glycine Kunitz PI STI (21 kDa protein)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	[Inhibits thrombin PAR activation] (TRY)
Thromboxane A2 receptor (TXA2-R)		5.7K
Cinnamophilin (= (8 <i>R</i> , 8' <i>S</i>)-4,4'-Dihydroxy-3,3'-dimethoxy-7-oxo-8,8'-neolignan) (lignan)	<i>Cinnamomum philippinense</i> (Lauraceae)	TXA2-R (0.5) (V-gated Ca ²⁺ channel) [PAI, relaxant]
[Thromboxane A2] (oxidized unsaturated fatty acid)	Animals; inflammation mediator	TXA2-R agonist [inflammation, PA, vasoconstriction]

Table 5.8 Other G protein-linked receptors

Compound (class)	Plant (family) part	Receptor interaction, (other targets) in vivo effects
ATP receptor (ATP-R)		5.8A
ATP (= Adenosine-5'-triphosphate) (purine nucleotide)	Universal	ATP-R agonist – P2Y, P2Y4 & P2Y11 ATP-Rs
[N6-Benzyladenine] (purine)	Synthetic	ATP-R agonist – P2 [mitogenic cytokinin in plants; antisenescent]
[5'- <i>p</i> -Fluorosulphonyl-benzoyl-adenosine (= FSBA)] (nucleoside)	Synthetic	Alkylates ATP-Rs (ATP- & ADP-like alkylating agent)
[Kinetin] (purine)	From DNA	ATP-R agonist – P2 [mitogenic cytokinin in plants; antisenescent]
[Suramin] (naphthalene-trisulphonic acid polycyclic)	Synthetic	ATP-R antagonist – P2

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
UTP (nucleoside triphosphate)	Universal	ATP-R agonist – P2-R agonist
<i>trans</i> -Zeatin (purine)	Widespread; plant growth regulator (cytokinin)	ATP-R agonist – P2 [mitogenic cytokinin in plants; antisenescent]
Bombesin receptor (BB-R) [Bombesin] (14aa, 2kDa protein)	Animals; endogenous Bombesin family peptide; CNS & GI tract	5.8B BB-R agonist [40pM], BB3-R agonist [anorexigenic, SCLC cancer cell autocrine growth factor; induces GI hormone release]
[Gastrin-releasing peptide (= GRP)] (3kDa protein)	Animals – endogenous Bombesin family peptide; CNS & GI tract	BB-R [40pM], GRP-R (= BB2-R) agonist [anorexigenic, Gastrin release, SCLC cancer cell autocrine growth factor]
Kuwanon G (flavone phenolic)	<i>Morus alba</i> (mulberry) (Moraceae) [root bark]	BB-R antagonist [0.5] [hypotensive]
Kuwanon H (flavone phenolic)	<i>Morus alba</i> (mulberry) (Moraceae) [root bark]	BB-R antagonist [0.3] [hypotensive]
[Neuromedin B] (protein)	Animals – endogenous Bombesin family peptide	BB-R agonist [40pM], NMB-R (= BB1-R) agonist [SCLC cancer cell autocrine growth factor]
[Somatomedin C] (protein)	Animals – endogenous Bombesin family peptide	BB-R agonist [SCLC cancer cell autocrine growth factor]
Cannabinoid R (CB1-R, CB2-R)		5.8C
Δ^1 -Tetrahydrocannabinol (= Dronabinol; Δ^9 -Tetrahydrocannabinol; (-)- Δ^1 -3,4- <i>trans</i> -Tetrahydrocannabinol (dibenzopyranol); globally 144 million cannabis users out of 180 million illicit drug users; negligible mortality compared to that from use of alcohol, tobacco, heroin & amphetamine-related drugs)	<i>Cannabis sativa</i> (marijuana , hemp) (Cannabaceae) [cannabis leaf resin (hashish), marijuana leaf extract (bhang), smoked leaf (ganja)] [incorrectly reputed intoxicant of “assassins” of Hasan-i-Sabbah (story according to Marco Polo); Arthur Rimbaud; Pierre Gautier & Charles Baudelaire, members of Club des Hachischins; Bill Clinton “did not inhale”]	CBI-R (brain) agonist (rat) [40nM] (H1-R) [inhibition of PGE1-activated AC (9nM)]; CB2-R (spleen, lymphocyte) antagonist (human) [40nM] (AND-R) [AI, anti-emetic, hallucinogenic , intoxicant, psychotropic]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
α - & β -Thujone (= α - & β -Thujan-3-one) (monoterpene)	<i>Artemisia absinthium</i> (wormwood) [leaf oil in absinthe], <i>A. dracuncululus</i> , <i>Tanacetum vulgare</i> (tansy) (Asteraceae), <i>Thuja occidentalis</i> (white cedar) (Cupressaceae) [leaf oil], <i>Salvia officinalis</i> , <i>S. triloba</i> (Lamiaceae) [neurotoxic agent of liqueur Absinthe; affected Vincent van Gogh, Henri de Toulouse-Lautrec & Charles Baudelaire]	CB1-R ligand (rat) (>10), CB2-R ligand (rat) (>10) [but inactive against Forskolin-activated AC] [anthelmintic, convulsant, hallucinogenic , intoxicant]
Non-plant reference		5.8Cn
[Anandamide (20:3, n-6)] (= Homo- γ -linolenyl ethanolamine amide) (FA ethanolamine amide)	Endogenous cannabinoid (mammal)	CB1-R (rat brain) agonist [245] [inhibition of PGE1-activated AC (109 nM)]
[Anandamide (20:4, n-6)] (= Arachidonyl ethanolamine amide) (FA ethanolamine amide)	Endogenous cannabinoid (mammal)	CB1-R (rat brain) agonist [155 nM] [inhibition of AC (101 nM)]
[Docosatetraenyl ethanolamine amide (= Anandamide (22:4, n-6)] (FA ethanolamine amide)	Endogenous cannabinoid (mammal)	CB1-R (rat brain) agonist [253 nM] [inhibition of PGE1-activated AC (117 nM)]
[N-(4-Hydroxyphenyl)-arachidonylamide (= AM4040)] (phenolic)	Synthetic (cf. Capsaicin)	Anandamide transport inhibition [14]
[Olvanil (= N-(Vanillyl)-9-oleamide] (vanilloid phenolic)	Synthetic (cf. Capsaicin)	Anandamide transport inhibition [14] (VR agonist)
Cholecystokinin receptor (CCK-R)		5.8D
<i>Arachis</i> lectin (= Peanut lectin) (lectin; CHO-binding protein)	<i>Arachis hypogaea</i> (peanut) (Fabaceae) [seed]	[\uparrow CCK release \rightarrow \uparrow pancreatic exocrine secretion via CCKA-R]
[Asperlicin] (non-peptide)	<i>Aspergillus alliaceus</i> (fungus)	CCK-R antagonist [attenuates taurocholate-induced, CCK-mediated pancreatitis]
[Cholecystokinin (= Pancreozymin)] (4kDa protein)	Animals; brain & GI tract	CCK-R agonist [anorexigenic, nociception, \uparrow pancreatic exocrine secretion, \downarrow gastric emptying]
<i>Glycine</i> lectin (= Soya bean lectin) (lectin; CHO-binding protein)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	[\uparrow CCK release \rightarrow \uparrow pancreatic exocrine secretion via CCKA-R]
Platycodin D (triterpene saponin)	<i>Platycodon grandiflorum</i> (Campanulaceae) [root]	[\uparrow Duodenal CCK release, pancreatic exocrine secretion]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
<i>Solanum</i> POT II (= Potato Protease Inhibitor II) (protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	[↑ CCK release → ↓ gastric emptying]
(+)-Yohimbine (= Aphrodine; Corynine; Hydroergotocin; Quebrachine) (indole)	<i>Catharanthus lanceus</i> , <i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia yohimbe</i> (Rubiaceae) [yohimbe bark]	[↑ CCK-like agent release] (α1A-R, α2A-R, D-R, 5HT-R) [antidepressant, aphrodisiac, mydriatic, toxic]
Cocaine- and Amphetamine-regulated transcript (CART) receptor (CART-R)		5.8E
[Amphetamine (= 1-Phenyl-2-aminopropane)] (aryl tertiary amine)	Synthetic; globally 29 million amphetamine-related drug users out of 180 million illicit drug users	Induces CART [⊕ release of catecholamines from presynaptic storage granules; anorexic, CNS stimulant]
[Cocaine- and Amphetamine-regulated transcript (CART)] (protein)	Animals; CNS	CART-R agonist [inhibits Dopamine release; anorexigenic, (-)-gastric emptying & gastric acid secretion via CRF; psychostimulant]
Cocaine (= Benzoyl-methylecgonine) (tropane)	<i>Erythroxylum coca</i> , <i>E. recurrens</i> , <i>E. steyermarkii</i> , <i>E. spp.</i> (Erythroxylaceae) [leaf]; globally 14 million cocaine users out of 180 million illicit drug users	Induces CART (NE-TR, 5HT-TR) [topical anaesthetic (ophthalmic), CNS stimulant, mydriatic, narcotic]
Corticotropin (ACTH) receptor (ACTH-R)		5.8F
[Corticotropin (= ACTH; Adrenocorticotrophic hormone)] (4kDa protein)	Animals; <i>ex</i> anterior pituitary; familial ACTH resistance from ACTH-R mutation	[Induces adrenal growth & adrenal cortex steroid hormone production]
Ginsenosides Rb1, Rb2, Rc & Rg1 (triterpene glycoside saponins)	<i>Panax ginseng</i> (ginseng) (Araliaceae) [root]	[Inhibits ACTH-induced steroidogenesis]
<i>Momordica</i> steryl glycoside (triterpene saponin)	<i>Momordica charantia</i> (Cucurbitaceae) [seed]	[Inhibits Cortisol-induced adipocyte lipolysis]
(-)-Salsolinol (tetrahydroisoquinoline alkaloid)	<i>Annona reticulata</i> (Annonaceae), <i>Musa paradisiaca</i> (banana) (Musaceae) [fruit], <i>Theobroma cacao</i> (→ cocoa, chocolate) (Sterculiaceae) [seed]	(D-R) [as D-R antagonist (0.5) inhibits ACTH release from pituitary]
Corticotropin releasing factor/ hormone receptor (CRF-R, CRH-R)		5.8G
[Corticotropin releasing hormone (= CRH)] (5kDa protein)	Animal; hypothalamus	CRF-R agonist [anorexigenic; Corticotropin (ACTH) release]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
R-(−)-Skyrin-6-O-β-glucopyranoside (bisanthraquinone glycoside)	<i>Hypericum perforatum</i> (Hypericaceae)	CRF1-R ligand
S-(+)-Skyrin-6-O-β-glucopyranoside (bisanthraquinone glycoside)	<i>Hypericum perforatum</i> (Hypericaceae)	CRF1-R ligand
Endothelin receptor (END-R)		5.8H
Myricic acid (triterpene)	<i>Myrica cerifera</i> (bayberry) (Myricaceae)	END-R [66 nM] [↓ END-induced ↑ Ca ²⁺ (11 nM)]
Myriceron caffeoyl ester (phenolic ester)	<i>Myrica cerifera</i> (bayberry) (Myricaceae)	END-R antagonist (ETA=R)
Nahocol A, A1, B, C, D1 & D2 (prenyl hydroquinones)	<i>Sargassum autumnale</i> (brown alga)	END-R antagonist
Pheophorbide a (pyrrole)	<i>Artemisia capillaris</i> (Asteraceae)	END-R antagonist – ETA-R (80 nM), ETB-R (0.2)
Resveratrol (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum grandiflorum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis</i> (Vitaceae) spp.	END-R antagonist (EST-R, F ₁ -ATPase, TYRase, p56 lck TK, soluble & membrane TK, XO)
Gastrin receptor (Gastrin-R)		5.8I
[Gastrins] (1–4 kDa proteins)	Animals; gastric mucosa	Gastrin-R [⊕ gastric secretion]
Plautanol (acrylic diterpene alcohol)	<i>Croton sublyratus</i> (Thai anti-ulcer <i>plau-noi</i>) (Euphorbiaceae)	[Releases Secretin → (−) postprandial Gastrin release; anti-ulcer]
Glucose receptor for GIP secretion (Glc-R(GIP))		5.8J
Gymnemic acid I (triperpene glycoside saponin)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	Glc-R (GIP) [Reversibly abolishes sweet taste]
Phloridzin (= Phloretin 2'-O-glucoside) (dihydrochalcone O-glycoside)	<i>Kalmia</i> , <i>Pieris</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>Malus</i> spp. (Rosaceae) [apple leaf, fruit skin], <i>Symplocos</i> spp. (Symplocaceae)	Glc-R (GIP) (Glc-TR) [bitter, feeding deterrent]
Glucagon receptor (GN-R)		5.8K
18-β-Glycyrrhetic acid (Glycyrrhetic acid; Glycyrrhetin) (triterpene saponin)	<i>Glycyrrhiza glabra</i> (licorice) (Fabaceae) [root, rhizome]	[Inhibits hepatocyte Glucagon response (TATase induction, glucose release)] (PKA, PKC) [AI, anti-ulcerogenic, anti-diuretic]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
[Glucagon] (4 kDa protein)	Animals; <i>ex</i> pancreas islets of Langerhans α cells, targets liver	GN-R agonist [antihypoglycaemic, \oplus gluconeogenesis, glycogenolysis, adipocyte lipolysis; catabolic; hyperglycaemic]
<i>Momordica</i> steryl glycoside (triterpene saponin)	<i>Momordica charantia</i> (Cucurbitaceae) [seed]	[Inhibits Glucagon-, Cortisol-, Epinephrine- & Dibutyryl cAMP-induced adipocyte lipolysis]
Imidazoline R (I-R)		
Alkaloid		
Harman (= Aribine; Loturine; 1-Methyl- β -carboline; Passiflorin) (β -carboline, indole)	<i>Phaseolus vulgaris</i> (Fabaceae) [suspension culture], <i>Passiflora edulis</i> , <i>P. incarnata</i> (Passifloraceae), <i>Singickia rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> , <i>Zygophyllum</i> <i>fabago</i> (Zygophyllaceae)	5.8L 5.8La I1-R agonist (31 nM), I2-R agonist [49nM] (DNA, MAO-A, MAO-B) [convulsant, cytotoxic, hypotensive, motor depressant]
Harmaline (= 3,4- Dihydroharmine; Harmidine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> , <i>Banisteriopsis</i> <i>caapi</i> (Malpighiaceae), <i>Peganum</i> <i>harmala</i> (Zygophyllaceae)	I2-R (MAO-A)
Rauwolfscine (= α -Yohimbine) (indole)	<i>Rauwolfia serpentina</i> (Apocynaceae), <i>Pausinystalia</i> <i>yohimbe</i> (Rubiaceae) [yohimbe bark]	I1-R, I2-R (α 2A-R, 5HT1A-R)
Tryptamine (= 3-(2- Aminoethy lindole) (indole)	<i>Cucumis sativus</i> (Cucurbitaceae), <i>Mucuna pruriens</i> , <i>Piptadenia</i> <i>peregrina</i> , <i>Prosopis juliflora</i> (Fabaceae), <i>Hordeum vulgare</i> , <i>Zea mays</i> (Poaceae), <i>Lycopersicon</i> <i>esculentum</i> , <i>Nicotiana tabacum</i> , <i>Solanum tuberosum</i> (Solanaceae)	I1-R agonist (36), I2-R agonist [27]
Other		
Agmatine (= (4- Aminobutyl) guanidine; 1- Amino-4-guanidinobutane) (aminoalkyl guanidine); Billroth II/Polya gastrectomy (surgeon Jeno Polya was my paternal grandfather) now largely obviated by antibacterials	<i>Ricinus communis</i> (Euphorbiaceae), <i>Glycine max</i> , <i>Lathyrus sativa</i> (Fabaceae), <i>Sesamum indicum</i> (Pedaliaceae), <i>Hordeum vulgare</i> (barley) (Poaceae); animals; bacteria e.g. <i>Helicobacter</i> <i>pylori</i> → Agmatine → ↑ gastric acid secretion → ulceration	5.8Lo I1-R, I2-R (α 2A-R, NMDA Glu-R, NOS) [hypotensive, inhibits morphine hyperalgesia, tolerance & withdrawal, insulin secretagogue (weak), neuroprotective]
Non-plant reference		
[Benzazoline] (anthraquinonyl-imidazoline)	Synthetic	5.8Ln I1-R ligand (α A-R) [hypertensive]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
[Clonidine (= 2-[[2,6-Chlorophenyl] imino]-2-imidazoline)] (imidazoline)	Synthetic	I1-R agonist, I2-R [58] (α A-R) [antihypertensive, sedative]
[Epinephrine (= Adrenaline; <i>l</i> -Methylamino-ethanolcatechol)] (catecholamine)	Animals (e.g. adrenals)	I1-R, I2-R (α A-R, β A-R) [vasoconstrictor, cardiostimulant, sympathomimetic hormone]
[Idazoxan]	Synthetic	I1-R (>1), I2-R [7 nM] [antidepressant]
[Pargyline (= <i>N</i> -Benzyl- <i>N</i> -methyl-2-propynylamine)] (aryl alkynyl tertiary amine)	Synthetic	I2-R ligand (MAO) [antihypertensive]
[Rilmenidine (= 2-[<i>N</i> -(Dicyclopropylmethyl) amino]-oxazoline)] (arylaminooxazoline)	Synthetic	I1-R agonist [antihypertensive]
[Tetrahydro- β -carboline] (β -carboline)	Synthetic	I1-R (10), I2-R [9 nM]
Luteinizing hormone R (LH-R)	LH releasing hormone (LH-RH = gonadotropin releasing hormone = GnRH) isolated & synthesized by Roger Guillemin (France/ USA) & Andrew Schally (Poland/USA) (Nobel Prize, Physiology/ Medicine, 1977, brain peptide hormones)	5.8M
[Luteinizing hormone (LH)] (protein)	Animals <i>ex</i> anterior pituitary	LH-R (regulates corpus luteum development & menstrual cycle)
Lithospermic acid (phenylpropanoid, caffeic acid trimer, benzofuran)	<i>Salvia miltiorhiza</i> (Lamiaceae)	LH release (from pituitary cells) (AC, AO/FRS, ProH)
α-Melanocyte stimulating-hormone (α-MSH) receptor (MC-R)		5.8N
Melatonin (= <i>N</i> -Acetyl-5-methoxytryptamine; Regulin) (indole)	<i>Chenopodia rubrum</i> (Chenopodiaceae), <i>Tanacetum parthenium</i> (<i>Chrysanthemum</i>) (feverfew) (Asteraceae); edible plant seeds; animal pineal gland; metabolized to 5-Methoxytryptamine	(MT-R) [Downstream inhibition of α -MSH-induced melanogenesis (at 10 nM); anti-amnesic, synchronizes circadian & circannual rhythms]
Non-plant reference		5.8Nn
[Adrenocorticotrophic hormone (= ACTH; Corticotropin)] (protein)	Animals <i>ex</i> anterior pituitary	MC1-R agonist
[Agouti] (protein)	Animals	MC-R antagonist – MC1-R MC4-R [stimulates feeding]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
[Agouti-related protein] (protein)	Animals	MC-R antagonist – MC1-R [at 55 nM], MC3-R, MC4-R [stimulates feeding]
[α -Melanocyte stimulating hormone (= Melanocortin; α -MSH)] (protein)	Animals; mouse hypo- or hyperpigmentation due to MSH-R mutation; Leptin- induced POMC precursor protein	MC-R (1–5) [(0.3–4 nM)] [appetite suppressant, anorexigenic]
[PT-141] (peptide)	Synthetic aphrodisiac; administered nasally for sexual dysfunction	α -MSH-R agonist [aphrodisiac]
Melatonin receptor (MT-R) Melatonin (= <i>N</i> -Acetyl-5- methoxytryptamine; Regulin) (indole); circadian rhythm control – Chernobyl, Three Mile Island & Bhopal all night work- related disasters	<i>Helianthus annuus</i> , <i>Prunus cerasus</i> , <i>Tanacetum parthenium</i> (<i>Chrysanthemum</i>) (Asteraceae), <i>Chenopodia rubrum</i> (Chenopodiaceae), <i>Hypericum perforatum</i> (Hypericaceae), <i>Musa paridasiaca</i> (Musaceae); edible plant seeds; animal pineal gland	5.8O MT-R (MT1-R and MT2-R) agonist [inhibits α - MSH-induced melanogenesis; antiamnesic, synchronizes circadian & circannual rhythms]; metabolized to 5-Methoxytryptamine
Non-plant reference [<i>N</i> -Acetyltryptamine] (indole) [Prazosin] (furan piperazine quinazoline)	Synthetic; formed during extraction of Tryptamine Synthetic	5.8On MT1-R & MT2-R partial agonist; MT3-R antagonist MT3-R antagonist (α 1-A R blocker) [antihypertensive]
Neuropeptide Y (NPY) [Neuropeptide Y] (4 kDa peptide)	Animal <i>ex</i> brain (hypothalamus), PNS & adrenal medulla; major orexigenic hormone (\uparrow feeding, \downarrow energy expenditure)	5.8P Production \downarrow by Leptin- induced anorexigenic hormones (POMC, α -MSH, CART, CRH) [orexigenic, \downarrow thermogenesis]
Oxytocin receptor (OX-R)	Vincent du Vignaud (USA, Nobel Prize, Chemistry, 1955, synthesis of Vasopressin & Oxytocin)	5.8Q
Δ^3 -Carene (= 3-Carene; (-)- Car-3-ene; Isodiprene) (monoterpene)	<i>Bupleurum gibraltarium</i> (Apiaceae) [oil], <i>Abies</i> spp., <i>Picea</i> spp., <i>Pinus longifolia</i> , <i>P. sylvestris</i> (Pinaceae) [turpentine oil], <i>Kaempferia galanga</i> (Zingiberaceae)	OX-R agonist [AI, uterine contraction]
16- α -Hydroxy- <i>ent</i> -kauran- 19-oic acid (diterpene)	<i>Montanoa hibiscifolia</i> (Asteraceae)	[Inhibits OX-induced uterine contraction (at 6–60)]
16- α -Hydroxy- <i>ent</i> -kauran- 19-oic acid methyl ester (diterpene)	<i>Montanoa hibiscifolia</i> (Asteraceae)	[Inhibits OX-induced uterine contraction (at 6–60)]
<i>Monechma</i> oxytotic principle P3 (peptide)	<i>Monechma ciliatum</i> (Acanthaceae)	OX-R agonist [uterine contraction]
[Oxytocin] (9 aa, 2 Cys, 1 kDa protein)	Animals; <i>ex</i> posterior pituitary, targets uterus, mammary tissue	OX-R agonist [stimulates uterine contraction & lactation]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
Parathyroid hormone/ parathyroid hormone- related protein receptor (PTH-R)		5.8R
Coniferin (= Abietin; Coniferoside; Coniferyl alcohol 4-O-glucoside; Laricin) (phenylpropanoid glycoside)	<i>Angelica</i> (Apiaceae), <i>Scorzonera hispanica</i> (Asteraceae), <i>Symphytum</i> (Boraginaceae), <i>Beta</i> (Chenopodiaceae), <i>Lonicera</i> (Caprifoliaceae), <i>Asparagus</i> (Liliaceae), <i>Fraxinus</i> (Oleaceae), <i>Abies</i> , <i>Larix</i> (Pinaceae), <i>Citrus</i> (Rutaceae) spp.	Digestion yields the active anti-PTH aglycone Coniferyl alcohol [lignin synthesis precursor]
Coniferyl alcohol (Phenylpropanoid phenolic)	<i>Aloe vera</i> (Aloeaceae), <i>Linum usitatissimum</i> (Linaceae) [fungus- induced phytoalexin] <i>Pinus strobus</i> (Pinaceae) [wood], <i>Vanilla mexicana</i> (Orchidaceae); glycoside Coniferin	[Inhibits PTH-induced bone resorption (at 20–200)] [antifungal; lignin synthesis precursor]
Eupaliitin 3-O-β D- galactopyranoside (flavonoid glycoside)	<i>Boerhaavia repens</i> (Nictaginaceae) [plant]	Inhibits PTH-induced bone resorption
Eupaliitin 3-O-β D- galactopyranosyl-(1→2)- β-D-glucopyranoside (flavonoid glycoside)	<i>Boerhaavia repens</i> (Nictaginaceae) [plant]	Inhibits PTH-induced bone resorption
[Priflavone (= 7- Isopropoxyisoflavone) (isoflavone)	Synthetic	[Inhibits PTH-induced bone resorption (at 20–200) (Ca ²⁺ regulator) [anti-anginal, anti-osteopenic]
8-Methyl-9'-oxopodopyrone (γ-pyrone)	<i>Gonystylus keithii</i> (Thymelaeaceae)	Inhibits PTH-induced bone resorption [osteoporosis drug potential]
8-Methyl-10'-oxopodopyrone (γ-pyrone)	<i>Gonystylus keithii</i> (Thymelaeaceae)	Inhibits PTH-induced bone resorption [osteoporosis drug potential]
9'-Oxopodopyrone (γ-pyrone)	<i>Gonystylus keithii</i> (Thymelaeaceae)	Inhibits PTH-induced bone resorption [osteoporosis drug potential]
10'-Oxopodopyrone (γ-pyrone)	<i>Gonystylus keithii</i> (Thymelaeaceae)	Inhibits PTH-induced bone resorption [osteoporosis drug potential]
[Parathyroid hormone (PTH)] (10kDa protein)	Animal; <i>ex</i> parathyroid, targets bone, endometrium, kidney & GI tract; Jansen metaphyseal chondrodysplasia from PTH-R mutation	PTH-R agonist [bone resorption, ↑ plasma Ca ²⁺]
[Parathyroid hormone-related protein (PTHrP)] (protein)	Animal; <i>ex</i> parathyroid, targets bone, endometrium, kidney & GI tract	PTH-R agonist [bone resorption, ↑ plasma Ca ²⁺]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
Vanillic acid (= 4-Hydroxy-3-methoxybenzoic acid) (phenolic acid)	<i>Coriandrum</i> , <i>Trachelospermum</i> (Apiaceae), <i>Panax ginseng</i> (Araliaceae), <i>Alnus</i> (Betulaceae), <i>Paratecoma</i> (Boraginaceae), <i>Eleagnus</i> (Eleagnaceae), <i>Erica</i> (Ericaceae), <i>Gossypium</i> (Malvaceae), <i>Melia</i> (Meliaceae), <i>Pterocarpus</i> , <i>Rosa</i> (Rosaceae), <i>Picrorhiza</i> (Scrophulariaceae) spp.	[Inhibits PTH-induced bone resorption (at 20–200)] [anthelmintic]
Vanillin (phenolic aldehyde)	Industrially from wood pulp lignin; <i>Dahlia</i> (Asteraceae), <i>Beta</i> (Chenopodiaceae), <i>Asparagus</i> (asparagus) (Liliaceae), <i>Syzygium</i> (Myrtaceae), <i>Vanilla planifolia</i> [vanilla pod], <i>Gymnadenia</i> (Orchidaceae), <i>Spiraea</i> (Rosaceae), <i>Ruta</i> (Rutaceae), <i>Solanum</i> (Solanaceae) spp.	[Inhibits PTH-induced bone resorption (at 20–200)] [antifungal, flavour]
Secretin receptor (SEC-R)		5.8S
Plautanol (acrylic diterpene alcohol)	<i>Croton sublyratus</i> (Thai anti-ulcer plant <i>plau-noi</i>) (Euphorbiaceae)	[Releases Secretin → (–) postprandial Gastrin release; anti-ulcer]
[Secretin] (27 aa, 3 kDa protein)	Animal; duodenum, jejunum	Secretin-R agonist [(–) gastrin release; ⊕ pancreatic exocrine secretion (e.g. bicarbonate)]
Sigma receptor (metabotropic) (σ-R)		5.8T
Hypericin (= Hypericum red) (bianthraquinone)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae); major herbal antidepressant	σ-R agonist (~1) [antidepressant effect overcome by Rimcazole]
Non-plant reference		5.8Tn
[Dehydroepiandrosterone] (neurosteroid)	Synthetic	σ-R agonist
[Dehydroepiandrosterone-sulfate (= DHEAS)] (neurosteroid)	Synthetic	σ-R agonist
[Haloperidol (= 1-(3- <i>p</i> -Fluorobenzoylpropyl)-4- <i>p</i> -chlorophenyl-4-hydroxypiperidine)] (aryl piperidine)	Synthetic	σ-R antagonist (D2-R, NMDA-Glu-R) [antidyskinetic (in Tourette Syndrome), antipsychotic]
[Ifenprodil] (benzylpiperidine phenol)	Synthetic	σ-R agonist [anticonvulsant, cerebral & peripheral vasodilator]
[Metazocine] (benzomorphan)	Synthetic	σ-R agonist [analgesic, antitussive, narcotic, protectant against gastric & duodenal ulcer]

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
[(+)-Pentazocine] (benzomorphan)	Synthetic	σ -R agonist [analgesic, antiamnesic, antitussive, narcotic, protectant against gastric & duodenal ulcer]
[Pregnenolone sulfate] (neurosteroid)	Synthetic	σ -R agonist
[Progesterone] (steroid)	Animals <i>ex corpus luteum</i>	σ -R antagonist [88 nM] [implantation, uterine development]
[Rimcazole] (piperazine)	Synthetic	σ -R antagonist
Somatostatin (Somatotropin release inhibiting factor) receptor (SRIF-R)		5.8U
<i>Lemna</i> SRIF-like protein (protein)	<i>Lemna gibba</i> (Lemnaceae) [leaf]	[Reactive in SRIF immunoassay]
<i>Nicotiana</i> SRIF-14-like protein (protein)	<i>Nicotiana tabacum</i> (Solanaceae) [leaf]	[Inhibits PGE ₂ -induced GH release (anterior pituitary cells)]
<i>Nicotiana</i> SRIF-28-like protein (protein)	<i>Nicotiana tabacum</i> (Solanaceae) [leaf]	[Inhibits PGE ₂ -induced GH release (anterior pituitary cells)]
Psycholeine (alkaloid)	<i>Psychotria oleoides</i> (Rubiaceae)	SRIF-R antagonist (10) [inhibits SRIF-induced inhibition of AC inhibition & GH secretion]
Quadrigemine C (alkaloid)	<i>Psychotria oleoides</i> (Rubiaceae)	SRIF-R antagonist; precursor of Psycholeine [inhibits SRIF-induced inhibition of AC inhibition & GH secretion]
[Somatostatin] (14 aa, 2 kDa, 2 Cys)	Animals	SRIF-R
<i>Spinacia</i> SRIF-14-like protein (protein)	<i>Spinacia oleracea</i> (spinach) (Chenopodiaceae) [leaf]	[Reactive only in C-terminus-specific SRIF immunoassay]
<i>Spinacia</i> SRIF-28-like protein (protein)	<i>Spinacia oleracea</i> (spinach) (Chenopodiaceae) [leaf]	[Reactive in N- & C-terminus-specific SRIF immunoassay]
Non-plant reference		5.8Un
[Anchinopeptolides A, B, C & D; Cycloanchino- peptolide C] (dimeric peptide alkaloids)	<i>Anchinoe tenacior</i> (Mediterranean sponge)	SRIF-R ligands (B ₂ -R, NY-R)
[Somatostatin-14 (= Growth hormone release inhibiting factor; GH-RIH; Somatotropin release inhibiting factor; SRIF; SRIF-14)] (14 aa; ~ 2 kDa; 2 Cys protein)	Animals – endogenous ligand	SRIF-R agonist [(–) AC, ↓ cAMP, antidiabetic, antinociceptive, inhibits GH release (anterior pituitary), inhibits insulin & glucagon release (pancreas)]

(continued)

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Table 5.8 (Continued)

Compound (class)	Plant (family) / part/	Receptor interaction (other targets) / in vivo effects/
[SRIF-28 (= Somatostatin-28; Prosomatostatin processing variant)] (28 aa; 3 kDa protein)	Animals – endogenous ligand, hypothalamus	SRIF-R agonist [(–) AC, ↓ cAMP; inhibits GH release (anterior pituitary), inhibits insulin & glucagon release (pancreas)]
Substance P receptor (SP-R)		5.8V
Abrunquione A (isoflavanquinone)	<i>Abrus precatorius</i> (Fabaceae)	[Inhibits SP-induced plasma extravasation; AI]
Capsaicin (= <i>trans</i> -8-Methyl- <i>N</i> -[[4-hydroxy-3-methoxyphenyl] methyl]-6-nonenamide; <i>trans</i> -8-Methyl- <i>N</i> -vanillyl-6-nonenamide) (vanilloid phenolic)	<i>Capsicum frutescens</i> , <i>C. annuum</i> (sweet pepper, paprika) (Solanaceae) [fruit], <i>Zingiber officinale</i> (ginger) (Zingiberaceae)	Depletes SP stores (VAN-R) [burning sensation, desensitizes sensory neurons, irritant, tachykinin release, topical analgesic]
1,7-Dihydroxy-2,3-dimethoxyxanthone (xanthone)	<i>Polygala cyparissias</i> (Polygalaceae)	[Inhibits SP-induced tracheal contraction (32)]
Ginsenosides (triterpene glycoside saponins)	<i>Panax ginseng</i> (ginseng) (Araliaceae)	[Inhibit SP-induced nociceptive response]
Mustard oil (terpenes)	<i>Sinapis alba</i> (Brassicaceae) [oil]	Releases SP [neurogenic inflammatory reactions]
Norathiol (xanthone)	<i>Tripterospermum lanceolatum</i> (Gentianaceae)	[Inhibits SP-induced inflammation]
[Substance P] (11 aa oligopeptide)	Animals; brain & intestine tachykinin	SP-R agonist [plasma extravasation, inflammation, nociception, SM contraction]
Thyrotropin-releasing hormone (TRH)		5.8W
Osthol (coumarin)	<i>Atractylodes</i> (Asteraceae), <i>Peucedanum</i> , <i>Angelica Prangos</i> (Apiaceae), <i>Flindersia</i> , <i>Citrus</i> , <i>Clausenia</i> , <i>Cneoridium</i> , <i>Haplophyllum</i> (Rutaceae) spp.	TRH-R antagonist
[Thyrotropin-releasing hormone (TRH)] (tripeptide)	Animal <i>ex</i> hypothalamus	TRH-R agonist (↑ Ca ²⁺ per IP ₃)
Vasopressin R (ADH-R, Antidiuretic hormone R) (VAS-R)		5.8X
Synthesized by Andrew Schally (Poland/USA, Nobel Prize, Physiology & Medicine with Roger Guillemin, 1977)		
Vincent du Vignaud (USA, Nobel Prize, Chemistry, 1955, synthesis of Vasopressin & Oxytocin)		
Alkaloid		5.8Xa
Chelerythrine (benzophenanthridine)	<i>Argemone</i> , <i>Bocconia</i> , <i>Chelidonium majus</i> (Papaveraceae) [root], <i>Eschscholzia</i> , <i>Glaucium</i> , <i>Sanguinaria</i> (Papaveraceae) spp., <i>Zanthoxylum americanum</i> (Rutaceae)	V1 VAS-R ligand (CaMPK, PKA, PKC, TK)

(continued)

Table 5.8 (Continued)

Compound (class)	Plant (family) part	Receptor interaction (other targets) in vivo effects
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Chelidonium majus</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Papaver somniferum</i> , <i>Sanguinaria canadensis</i> (Papaveraceae), <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	V1 VAS-R ligand (ATPase, Diamine oxidase CDPK, MLCK, PKA, PKC) [antibacterial, AI]
Terpene Khusimol (sesquiterpene alcohol)	<i>Vetiveria zizanioides</i> (Poaceae) [root]	5.8Xt V1a VAS-R ligand [50]
Non-plant reference [Vasopressin] (10 kDa; 9 aa; 2 Cys; 1 S-S; peptide)	Animals <i>ex posterior</i> pituitary; nephrogenic diabetes insipidus from V2 VAS-R mutation	5.8Xn VAS-R agonist [kidney distal tubule water reabsorption per aquaporins, vasoconstrictor]

Table 5.9 G protein-interacting plant compounds

Compound (class)	Plant (family) plant part	Target/process inhibited (other targets) in vivo effects
G protein Gα	Alfred Gilman & Martin Rodbell (USA, Nobel Prize, Physiology & Medicine, 1994)	5.9
Geraniin (ellagitannin)	<i>Acer</i> (Aceraceae), <i>Cercidiphyllum</i> (Cercidiphyllaceae), <i>Coraria</i> (Coriariaceae), <i>Erythroxyllum</i> (Erythroxyllaceae), <i>Euphorbia</i> , <i>Mallotus</i> (Euphorbiaceae), <i>Geranium</i> (Geraniaceae), <i>Fuchsia</i> (Onagraceae) spp.	G α protein-GMP-PNP binding [antinociceptive]
Ginsenoside Rf (triterpene glycoside, saponin)	<i>Panax ginseng</i> (Araliaceae)	Inhibits Ca ²⁺ channels per pertussis-sensitive G protein
Harmaline (= 3,4-Dihydro- harmine; Harmidine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> , <i>Banisteriopsis caapi</i> (Malpighiaceae), <i>Peganum harmala</i> (Zygophyllaceae)	Activates G protein (α 1A-R, I2-R, MAO-A)
Harman (= 1-Methyl- β - carboline) (β -carboline, indole)	<i>Passiflora edulis</i> , <i>P. incarnata</i> (Passifloraceae), <i>Singickia rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> , <i>Zygophyllum fabago</i> (Zygophyllaceae)	Activates G protein (α 1A-R, BZ-R, DNA, 5HT2-R, L-type Ca ²⁺ CH) [convulsant, cytotoxic]

(continued)

Table 5.9 (Continued)

Compound (class)	Plant (family) / plant part/	Target/process inhibited (other targets) / in vivo effects/
Harmine (= Banisterine; Leucoharmine; Telepathine; Yageine) (β-carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> (Zygophyllaceae)	Activates G protein (α1A-R, MAO-A, L-type Ca ²⁺ CH) [CNS stimulant, hallucinogen; Gestapo use as “truth drug”]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelerutetia henryi</i> (Sapindaceae); widespread as glycosides	Gα protein-GMP-PNP binding (LOX, PK) [AI, antinociceptive, feeding stimulant]
Rutin (= Quercetin 3-rutinoside; Rutoside) (flavonol O-glycoside)	Widespread; <i>Sophora japonica</i> (Fabaceae), <i>Fagopyrum esculentum</i> , <i>Polygonum</i> spp. (Polygonaceae), <i>Ruta graveolens</i> (Rutaceae), <i>Viola tricolor</i> (Violaceae)	Gα protein-GMP-PNP binding (5-LOX) [AI, feeding attractant, feeding deterrent, ovipositing stimulant, antiviral, antibacterial]

6 Neurotransmitter transporters and converters

6.1 Introduction

Neurons are structurally quite disparate. However a neuron typically will have a cell body, several thousand dendrites (elongated, branched processes that receive signals from other neurons) and an axon (an elongated process transmitting signals away from the cell body and which is insulated by a myelin sheath formed by the extensive winding of the plasma membranes (PMs) of accessory cells). “Incoming” axons make connections with a neuron via narrow gaps or “synapses”, the “presynaptic” end of the axon being enlarged to form a “terminal button” (“synaptic knob”). Incoming synaptic connections can be on small dendritic projections or “dendritic spines” (“axodendritic” synapses), on shafts of axons (“axo-axonal” synapses) and on cell bodies (“axosomatic” synapses). Neurons can make synaptic connections with muscle cells via “neuromuscular synapses” and with endocrine cells.

Neurons are electrically active. The transmembrane potential (Ψ_m) at any point is typically of the order of about -0.1 volt (inside with respect to outside). As described in Chapter 3, excitatory neurotransmitters (NTs) depolarize the Ψ_m (make it more positive), precipitating unidirectional transmission of this depolarization by action potentials. Inhibitory NTs have a hyperpolarizing effect (make Ψ_m more negative) and accordingly inhibit such excitation. Arrival of action potentials at synapses successively causes depolarization, Ca^{2+} entry through voltage-gated channels and thence Ca^{2+} -mediated fusion and exocytosis (external release of contents) of adenosine 5'-triphosphate (ATP)-primed synaptic vesicles containing NTs. NTs diffuse across the synapse to bind and activate “paracrine” NT receptors (on the postsynaptic membrane of the target cell) or to “autocrine” NT receptors (on the NT-releasing cell PM and thereby providing “feedback” information about NT release).

The synaptic vesicles that have emptied their contents by exocytosis at the PM are reconstituted by a process successively involving: coating of the external surface of the vesicle with a network of the protein clathrin; endocytosis (the vesicle rebudding into the cytosol); fusion of the vesicle with a large “endosome” vesicle and budding of new synaptic vesicles (“synaptosomes”). After NT uptake into synaptic vesicles the release stage of the cycle successively involves translocation of NT-loaded synaptic vesicles to the PM; protein-mediated “docking” of synaptic vesicles to the PM via synaptic vesicle synaptobrevin binding to PM syntaxin, this process being assisted by guanosine 5'-triphosphate (GTP)-rab3 (on the synaptic vesicle membrane), cytosolic SNAPs (that bind to synaptobrevin), cytosolic Munc and Sec proteins (that bind to syntaxin) and PM-located SNAP-25 (that binds to syntaxin); and finally ATP-priming of the docked synaptic vesicle to permit further Ca^{2+} -mediated fusion, exocytosis and NT release into the synapse.

It is useful at this point to simply list the variety of peptide and non-peptide compounds involved as NTs or neuromodulators (in addition to other signal transduction functions). The set of NTs and neuromodulators includes the excitatory amino acids (aspartate and glutamate), the inhibitory amino acids (glycine and γ -aminobutyric acid or GABA), other bioactive amine NTs (epinephrine, dopamine, histamine, norepinephrine and serotonin), purines (adenosine and ATP), gases (nitric oxide and carbon monoxide), a lipid (anandamide) and a large number of peptides (noting that many of these can also act elsewhere), namely: activins, angiotensin II, atrial natriuretic peptide, brain natriuretic peptide, calcitonin gene-related peptide (CGRP), cholecystokinins (CCK-4, CCK-8), corticotropin release hormone (CRH), dynorphins, endomorphins, β -endorphin, endothelins, enkephalins, galanin, gastrin, gastrin-releasing peptide, glucagon, gonadotropin release hormone (GnRH), growth hormone release hormone (GRH), inhibins, mobilin, neuropeptide Y, neurotensin, oxytocin, secretin, somatostatin, substance P and other tachykinins, thyrotropin release hormone (TRH), vasoactive intestinal peptide and vasopressin.

We have already seen how a variety of peptide and non-peptide NTs and hormones (Hs) variously act via metabotropic G protein-coupled receptors (GPCRs) or via ionotropic ligand-gated ion channels. A variety of plant-derived defensive compounds have been shown to interfere with these primary signal reception and transduction systems (Chapters 3 and 5). However other actual and potential targets for plant bioactives are the NT synthesizing and releasing mechanisms. Further, signalling has to be reversible and this requires that NTs are taken up by the releasing neuron and re-sequestered in synaptic vesicles or converted to inactive entities that do not bind to NT receptors. This chapter is concerned with plant bioactives that interfere with NT synthesis, release, re-uptake into vesicles and degradation.

6.2 Synthesis of neurotransmitters

Histamine, serotonin and the catecholamines (dopamine, epinephrine and norepinephrine) are synthesized from the aromatic amino acids histidine, tryptophan and phenylalanine, respectively. The biosynthesis of catecholamines in adrenal medulla cells and catecholamine-secreting neurons can be simply summarized as follows [the enzyme catalysing the reaction and the key additional reagents are in square brackets]: phenylalanine \rightarrow tyrosine [via liver phenylalanine hydroxylase + tetrahydrobiopterin] \rightarrow L-dopa (L-dihydroxyphenylalanine) [via tyrosine hydroxylase + tetrahydrobiopterin] \rightarrow dopamine (dihydroxyphenylethylamine) [via dopa decarboxylase + pyridoxal phosphate] \rightarrow norepinephrine (2-hydroxydopamine) [via dopamine β -hydroxylase + ascorbate] \rightarrow epinephrine (*N*-methyl norepinephrine) [via phenylethanolamine *N*-methyltransferase + S-adenosylmethionine].

Histamine is synthesized from the amino acid histidine by simple decarboxylation catalysed by histidine decarboxylase. Serotonin is synthesized primarily in platelets, the gastro-intestinal (GI) tract and the brain from the indolyl amino acid tryptophan: tryptophan \rightarrow 5-hydroxytryptophan [via tryptophan hydroxylase + tetrahydrobiopterin] \rightarrow 5-hydroxytryptamine (serotonin) [via 5-hydroxytryptophan decarboxylase].

Glutamate derives from the tricarboxylic acid (TCA) cycle intermediate α -ketoglutarate by transamination [via transaminases + pyridoxal phosphate] and GABA is thence made from α -decarboxylation of glutamate [catalysed by glutamate decarboxylase]. Cholinergic nerve ending choline acetylase catalyses the synthesis of acetylcholine from acetylcoenzyme A and choline. A variety of peptide NTs derive from processing of polypeptide pro-proteins synthesized on ribosomes. Some plant defensive compounds inhibit NT synthesis (Table 6.1).

6.3 Release of neurotransmitters from synaptic vesicles

The release of NTs into the synaptic cleft from exocytosing synaptic vesicles has been outlined above. Dopamine release is promoted by the stimulants amphetamine and tobacco-derived nicotine. The amphetamine-derived stimulants methamphetamine and 3,4-methylenedioxyamphetamine (MDMA, Ecstasy) promote dopamine and serotonin release (Table 6.2).

6.4 Re-uptake of neurotransmitters into neurons and synaptic vesicles

A major way NTs are removed from the synapse (synaptic cleft) involves energy-dependent (i.e. ultimately ATP-dependent) re-uptake into the cytosol of the releasing neuron. A major family of 12 TM α -helix transporters co-transport amine NTs with Na^+ and Cl^- . Transporters in this family include those for choline (the precursor of the NT acetylcholine), dopamine, epinephrine, GABA, norepinephrine and serotonin. The plant-derived psychoactive drug cocaine inhibits dopamine, norepinephrine and serotonin re-uptake and hence is a stimulant (Table 6.3). The synthetic prozac (fluoxetine) inhibits dopamine re-uptake and hence is excitatory and antidepressant. Transporters for glutamate couple glutamate translocation to the ATP-dependent movement of Na^+ and K^+ . Glutamate is excitotoxic and a consequence of anoxia from ischaemia is ATP depletion, inhibition of glutamate re-uptake and resultant neurotoxicity from elevated glutamate.

Uptake of amine NTs from the neuronal cytosol into synaptic vesicles is achieved by vesicular monoamine transporters (VMAT1 and VMAT2) that sequester dopamine, epinephrine, norepinephrine and serotonin. A similar vesicle transporter (VGAT) sequesters GABA and glycine and a vesicular transporter (VAcHT) sequesters acetylcholine into synaptic vesicles.

6.5 Neurotransmitter degradation

Neurotransmitters are removed by translocation into vesicles or destroyed in enzyme-catalysed reactions. Acetylcholine must be removed from the synaptic cleft to permit repolarization and relaxation. A high affinity acetylcholinesterase (AChE) (the “true” or “specific” AChE) catalyses the hydrolysis of acetylcholine to acetate and choline. A plasma AChE (pseudo-AChE or non-specific AChE) also hydrolyses acetylcholine. A variety of plant-derived substances inhibit AChE and there is considerable interest in AChE inhibitors as potential therapies for cognition enhancement and for Alzheimer’s disease. Organophosphorous compounds alkylate an active site serine on AChE and the AChE inhibition by this mechanism is the basis for the use of such compounds as insecticides (and unfortunately also as chemical warfare agents). Other synthetics with insecticidal and medical applications carbamoylate and thus inactivate AChE (Table 6.4).

Catecholamines can be variously oxidized or methylated. Extracellular epinephrine is *O*-methylated [via liver catechol-*O*-methyltransferase (COMT)] to 3-methoxyepinephrine (metanephrine) which can thence be oxidized [via monoamine oxidase (MAO)] to 3-methoxy-4-hydroxy-mandelic aldehyde and thence to 3-methoxy-4-hydroxyphenylglycol (MHPG) and 3-methoxy-4-hydroxy-mandelic acid (VMA). Similarly, extracellular norepinephrine is *O*-methylated [via liver COMT] to 3-methoxynorepinephrine (normetanephrine) which can be oxidized [via MAO] to 3-methoxy-4-hydroxy-mandelic

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aldehyde and thence to MHPG and VMA. MAO is located on the outer membrane of mitochondria and occurs as two major isozymes, namely MAO-A and MAO-B.

At adrenergic nerve terminals norepinephrine and epinephrine can be taken up, oxidized [via MAO] to 3,4-dihydroxymandelic aldehyde and thence oxidized to 3,4-dihydroxymandelic acid (DOMA) and 3,4-dihydroxyphenylglycol (DHPG). Extracellular DOMA and DHPG can then be converted via COMT to the methylated derivatives VMA and MHPG.

Dopamine (3,4-dihydroxyphenylethylamine) can similarly be oxidized [via MAO] to 3,4-dihydroxyphenylacetaldehyde which is then oxidized [via aldehyde dehydrogenase] to 3,4-dihydroxyphenylacetic acid (DOPAC); DOPAC is thence methylated [via COMT] to yield homovanillic acid (HVA). Alternatively dopamine can be methylated [via COMT] to 3-methoxytyramine which is thence oxidized [via MAO and aldehyde dehydrogenase] to yield HVA.

Serotonin (5-hydroxytryptamine) is oxidized [via MAO and aldehyde dehydrogenase] to 5-hydroxyindoleacetic acid (5-HIAA).

A minor route for histamine catabolism involves histamine conversion to imidazoleacetic acid [via diamine oxidase (histaminase)]. In the major route histamine is converted to methylhistamine [via histamine *N*-methyl transferase] which is then converted to methylimidazoleacetic acid [via MAO]. A large number of MAO inhibitors have been isolated from plants (Table 6.5).

GABA is converted to succinic semialdehyde [via GABA transaminase (GABAT) + pyridoxal phosphate] which is thence oxidized to succinic acid which is further oxidized via the TCA cycle. 4-Hydroxybenzaldehyde from *Gastrodia elata* (Orchidaceae), a plant with antiepileptic properties, is an inhibitor of GABAT, as is the synthetic antiepileptic valproic acid (2-propenylpropanoic acid) (Table 6.6).

Finally, it should be noted that peptide NTs and neuromodulators are hydrolysed by proteases. Chapter 13 deals in part with protease inhibitors from plant sources.

Table 6.1 Synthesis of neurotransmitters

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Effect/enzyme inhibited (other targets) in vivo effects </i>
Choline acetyltransferase (ChAT)		6.1A
Americanin A (neolignan)	<i>Phytolacca americana</i> (Phytolaccaceae) [seed]	[Increases ChAT in rat neuronal culture (at 10)]
Americanol A (neolignan)	<i>Phytolacca americana</i> (Phytolaccaceae) [seed]	[Increases ChAT in rat neuronal culture (at 10)]
Bicycloillicinone asarone acetal (prenylated bicyclic)	<i>Illicium tashiroi</i> (Illiciaceae) [wood]	[Increases ChAT in rat neuronal culture]
2(<i>R</i>)-12-Chloro-2,3-dihydroillicinone E (prenylated bicyclic)	<i>Illicium tashiroi</i> (Illiciaceae) [wood]	[Increases ChAT in rat neuronal culture]
Garbsellin A (polyprenylated phloroglucinol)	<i>Garcinia subelliptica</i> (Guttiferae) [wood]	[Increases ChAT in rat neuronal culture (at 10)]
Isoamericanol A (neolignan)	<i>Phytolacca americana</i> (Phytolaccaceae) [seed]	[Increases ChAT in rat neuronal culture (at 10)]

(continued)

Table 6.1 (Continued)

Compound (class)	Plant (family) part	Effect/enzyme inhibited (other targets) / in vivo effects/
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Fumaria officinalis</i> (Fumariaceae), <i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> , <i>Sanguinaria canadensis</i> , <i>Argemone</i> , <i>Bocconia</i> , <i>Eschscholzia</i> , <i>Glaucium</i> , <i>Macleaya</i> spp. (Papaveraceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	ChAT ligand (0.3) (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]
Tricycloillicinone (prenylated tricyclic)	<i>Illicium tashiroi</i> (Illiciaceae) [wood]	[Increases ChAT in rat neuronal culture]
DOPA decarboxylase (DDC) & dopamine synthesis		
Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> (Annonaceae), <i>Berberis</i> , <i>Hydrastis</i> , <i>Mahonia</i> , <i>Nandina</i> (Berberidaceae), <i>Archangelica</i> (Menispermaceae), <i>Argemone</i> , <i>Chelidonium</i> , <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> , <i>Thalictrum</i> (Ranunculaceae), <i>Evodia</i> , <i>Toddalia</i> , <i>Zanthoxylum</i> (Rutaceae) spp.	[Inhibits D synthesis (28)] (α 1A-R, α 2A-R, AChE, ATPase, BChE, ChAT, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, nACh-R, PK) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
(-)-Epigallocatechin (flavan-3-ol)	<i>Chrysophyllum cainito</i> (Sapotaceae), <i>Camellia sinensis</i> (Theaceae)	DDC
(-)-Epigallocatechin 3-gallate (flavan-3-ol gallate ester)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (Theaceae)	DDC [AI, blocks COX-2 & iNOS induction]
Palmatine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Berberis</i> , <i>Mahonia</i> (Berberidaceae), <i>Jateorrhiza palmata</i> (Menispermaceae), <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> (Ranunculaceae) spp.	[Inhibits D synthesis (22)] (α 1A-R, α 2A-R, AChE, ATPase, BChE, ChAT, diamine oxidase, 5HT ₂ -R, mACh-R, nACh-R, PK) [antibacterial, AI]
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Fumaria officinalis</i> (Fumariaceae), <i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> , <i>Sanguinaria canadensis</i> , <i>Argemone</i> , <i>Bocconia</i> , <i>Eschscholzia</i> , <i>Glaucium</i> , <i>Macleaya</i> spp. (Papaveraceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	ChAT ligand (0.3) (α 1A-R, α 2A-R, AChE, ATPase, BChE, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, nACh-R, PK) [antibacterial, AI]
Tryptophan (= α -Aminoindole-3-propionic acid) (amino acid)	In all organisms; <i>Helianthus annuus</i> (Asteraceae), <i>Phaseolus vulgaris</i> , <i>Psophocarpus tetragonolobus</i> (Fabaceae), <i>Oenothera biennis</i> (Onagraceae)	Precursor of 5HT (serotonin); unlike 5HT can cross blood-brain barrier [for depression, treatment of aggression]

(continued)

Table 6.1 (Continued)

Compound (class)	Plant (family) part	Effect/enzyme inhibited (other targets) in vivo effects/
Dopamine-β-hydroxylase (DBH)		6.1C
[Fusaric acid (= 5-Butyl-2-pyridinecarboxylic acid)] (alkylpyridine)	<i>Fusarium heterosporium</i> (fungal pathogen on corn & other Poaceae)	DBH (Tyr H)
Goitrin (= (-)-5-Vinylloxazolidine-2-thione) (oxazolidine)	Metabolite via myrosinase from Progoitrin from Brassicaceae (Cruciferae) e.g. <i>Brassica napus</i> (rape) [seed], <i>Brassica oleraceae</i> (Brussels sprouts)	DBH (↓ T3 & T4) [goitrogenic]
Hypericin (bianthraquinone)	<i>Hypericum perforatum</i> (St John's wort), <i>H. spp.</i> (Hypericaceae); major herbal antidepressant	DBH (20) [antidepressant, antiretroviral; photogenic sheep facial eczema “hypericism”]
5HT (Serotonin) synthesis		6.1D
[<i>p</i> -Chlorophenylalanine] (amino acid)	Synthetic	Tryptophan hydroxylase [↓ 5HT]
Tryptophan (= α-Aminoindole-3-propionic acid) (amino acid)	In all organisms; <i>Helianthus annuus</i> (Asteraceae), <i>Phaseolus vulgaris</i> , <i>Psophocarpus tetragonolobus</i> (Fabaceae), <i>Oenothera biennis</i> (Onagraceae)	Precursor of 5HT (serotonin); unlike 5HT can cross blood–brain barrier [for depression, treatment of aggression]
Succinic semialdehyde dehydrogenase (SSADH) & succinic semialdehyde reductase (SSAR) → GHB		6.1E
Brazilin (chalcone)	<i>Caesalpinia sappan</i> (Fabaceae) [wood]	SSAR [anticonvulsant; SSA a substrate via GABA transaminase]
Gastrodin (= <i>p</i> -Hydroxybenzylalcohol glycoside) (phenolic glycoside)	<i>Gastrodia elata</i> (Orchidaceae) [rhizome]	SSADH [potential anticonvulsant]; Gastrodin & aglycone facilitate memory
Sappanchalcone (chalcone)	<i>Caesalpinia sappan</i> (Fabaceae) [wood]	SSADH, SSAR [anticonvulsant]
Succinic semialdehyde (HOOC-CH ₂ -CH ₂ -CHO) (alkyl aldehyde carboxylic acid)	Universal; GABA metabolite via GABA transaminase	Substrate for SSADH & SSAR yielding γ-Hydroxybutyrate (GHB) (for treating narcolepsy)
Tyrosinase (TYR) (Tyr → L-DOPA → dopaquinone)		6.1F
Capsaicin (= <i>trans</i> -8-Methyl- <i>N</i> -[[4-hydroxy-3-methoxyphenyl)methyl]-6-nonenamide; <i>trans</i> -8-Methyl- <i>N</i> -vanillyl-6-nonenamide) (vanilloid phenolic)	<i>Capsicum annuum</i> (sweet pepper, paprika), <i>C. frutescens</i> (Solanaceae) [fruit], <i>Zingiber officinale</i> (Zingiberaceae); capsicum spray is used in law enforcement as a humane alternative to “deadly force” against civilians – however use against combatant soldiers is banned by the revised Geneva accords	TYR (87) (VAN-R, V-K ⁺ CH, V-Na ⁺ CH) [burning sensation, bronchoconstrictive (1), desensitizes sensory neurons, irritant, tachykinin release, topical analgesic]

(continued)

Table 6.1 (Continued)

Compound (class)	Plant (family) part	Effect / enzyme inhibited (other targets) / in vivo effects
Cuminaldehyde (monoterpene)	<i>Carum</i> , <i>Cuminum</i> , <i>Ferula</i> (Apiaceae), <i>Artemisia</i> (Asteraceae), <i>Commiphora</i> (Burseraeae), <i>Cassia</i> (Fabaceae), <i>Eucalyptus</i> (Myrtaceae) spp. [oil]	TYR [9]
Curcumin (= Diferuloylmethane; Turmeric yellow) (phenylpropanoid)	<i>Curcuma aromatica</i> , <i>C. longa</i> (turmeric), <i>C. xanthorrhiza</i> , <i>C. zedoaria</i> , <i>Zingiber officinale</i> (Zingiberaceae) [root]	TYR (47) [50] (CDPK, HIV-1-INT, IKK, PhosbK, PKA, PKC, p60 ^{c-src} TK, TYR) [AI, anti-oxidant, hypoglycaemic, cytotoxic]
Eugenol (= Allylguaiacol, Caryophyllic acid, Eugenenic acid) (phenylpropanoid)	Widespread; <i>Achillea</i> , <i>Artemisia klotschiana</i> (Asteraceae), <i>Eugenia caryophyllata</i> (= <i>Syzygium aromaticum</i>), <i>Pimentum dioica</i> , (Myrtaceae), <i>Cinnamomum</i> , <i>Sassafras</i> (Lauraceae), <i>Ocimum</i> , <i>Oreganum</i> (Lamiaceae), <i>Myristica fragrans</i> (Myristicaceae), <i>Piper</i> (Piperaceae), <i>Rosa</i> (Rosaceae) spp., <i>Camellia sinensis</i> (tea) (Theaceae)	TYR (923) (COX-1, COX-2, OD-R,) [antioxidant, AI, PAI]
Ferulaldehyde (= 4-Hydroxy-3- methoxycinnamaldehyde) (phenylpropanoid)	Widespread; per reduction of Ferulic acid	TYR (77)
Ferulic acid (= 3- <i>O</i> - methylcaffeic acid) (phenylpropanoid)	Widespread; <i>Ferula assa-foetida</i> (Apiaceae) [root sap], <i>Salvia</i> spp. (Lamiaceae)	TYR (45) [50] [AO/FRS]
2-Hydroxy-4- methoxybenzaldehyde (aryl aldehyde)	<i>Rhus vulgaris</i> [root], <i>Sclerocarya caffra</i> [bark] (Anacardiaceae), <i>Mondia whitei</i> [root] (Asclepiaceae)	TYR (30)
3-Methoxytyrosine (phenylpropanoid, amino acid)	Precursor of Ferulic acid	TYR (420)
5-[8(ζ),11(ζ),14-Penta- decatrienyl] resorcinol (phenolic)	<i>Anacardium occidentale</i> (cashew) (Anacardiaceae) [fruit]	TYR
6-[8(ζ),11(ζ),14-Penta- decatrienyl] salicylic acid (phenolic)	<i>Anacardium occidentale</i> (cashew) (Anacardiaceae) [fruit]	TYR
Yakuchinone A (= 1-(4'-Hydroxy-3'- methoxyphenyl)-7-phenyl- 3-heptanone) (phenyl propanoid, aryl heptanoid)	<i>Alpinia oxyphylla</i> (Zingiberaceae) [rhizome]	TYR (514) (COX, 5-LOX) [anti-tumour potential: \downarrow TPA- induced AP-1 activation & ODC, TNF- α & O ₂ ⁻ production]
Yakuchinone B (= 1-(4'-Hydroxy-3'- methoxyphenyl)-7- phenylhept-1-en-3-one) (phenyl propanoid, aryl heptenoid)	<i>Alpinia oxyphylla</i> , <i>A. officinarum</i> (Zingiberaceae) [rhizome]	TYR (57) [88] (ACAT, COX) [anti-tumour potential: \downarrow TPA- induced AP-1 activation & ODC, TNF- α & O ₂ ⁻ production]

(continued)

Table 6.1 (Continued)

Compound (class)	Plant (family) part	Effect/enzyme inhibited (other targets) in vivo effects
Tyrosine hydroxylase (TyrH)		6.1G
[DOPA quinone (= Dihydroxyphenylalanine quinone)] (quinone)	Generated from Dopamine by Tyrosinase or Prostaglandin H synthase	TyrH inactivation
(-)-Epigallocatechin-3-gallate (flavan-3-ol gallate ester)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (Theaceae)	Prevents neurotoxin-induced ↓ TyrH & ↓ D [AI, blocks COX-2 & iNOS induction]
[Fusaric acid (= 5-Butyl-2-pyridinecarboxylic acid)] (alkylpyridine)	<i>Fusarium heterosporium</i> (fungal pathogen on corn & other Poaceae)	TyrH (DBH)
Ginseng total saponin (glycosylated triterpenes)	<i>Panax ginseng</i> (ginseng) (Araliaceae) [root]	TyrH (~100) (D-REL)
(-)-Nicotine (pyridine pyrrolidine)	<i>Nicotiana tabacum</i> (tobacco), <i>N. spp.</i> (Solanaceae); also in <i>Asclepias syriaca</i> (Asclepiadaceae), <i>Sedum acre</i> (Crassulaceae), <i>Lycopodium spp.</i> , <i>Equisetum arvense</i> (Equisetaceae)	[TyrH induction] (nACh-R agonist) [addictive, antinociceptive, bitter, insecticide, respiratory paralytic, toxic, tranquilizer]

Table 6.2 Release of neurotransmitters from synaptic vesicles

Compound (class)	Plant (family) part	Enzyme inhibited in vivo effects
Catecholamine release (CAT-REL); Dopamine release (D-REL); Norepinephrine release (NE-REL); Serotonin release (5HT-REL)		6.2
Alkaloid		6.2a
Barakol (= 3a,4-Dihydro-3a,8-dihydroxy-2,5-dimethyl-1,4-dioxaphenalene) (polycyclic aromatic, phenolic)	<i>Cassia siamea</i> [leaf] (Fabaceae)	D-REL (no effect on D uptake) [anxiolytic]
Harman (= Aribine; Loturine; 1-Methyl-β-carboline; Passiflorin) (β-carboline, indole)	<i>Phaseolus vulgaris</i> (Fabaceae), <i>Passiflora edulis</i> , <i>P. incarnata</i> (Passifloraceae), <i>Singickia rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> , <i>Zygophyllum fabago</i> (Zygophyllaceae)	↑ D-REL, ↑ NE-REL, ↑ 5HT-REL (DNA, I1-R, I2-R, MAO) [antidepressant, co-mutagenic, convulsant, cytotoxic, genotoxic, hypotensive, motor depressant, sheep "Tribulus staggers"]; pyrolysate of Tryptophan (cooked food)

(continued)

Table 6.2 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited in vivo effects
(-)-Nicotine (pyridine pyrrolidine)	<i>Duboisia myoporoides</i> , <i>Nicotiana tabacum</i> (tobacco), <i>N.</i> spp. (Solanaceae); also in <i>Asclepias syriaca</i> (Asclepiadaceae), <i>Sedum acre</i> (Crassulaceae), <i>Lycopodium</i> spp., <i>Equisetum arvense</i> (Equisetaceae)	↑ D-REL (nACh-R agonist) [THase induction; addictive, antinociceptive, bitter, insecticide, respiratory paralytic, toxic, tranquilizer]
Phenolic D-Cathinone (= (<i>S</i>)-2-Amino-1-oxo-1-phenylpropane) (phenylpropanoid)	<i>Catha edulis</i> (khat), <i>Maytenus krukovii</i> (Celastraceae)	6.2p ↑ CAT-REL, ↑ D-REL [anorexic, CNS stimulant, euphoriant]
Terpene β-Amyrin palmitate (triterpene) Ginseng total saponin (glycosylated triterpenes) Parthenolide (sesquiterpene lactone)	<i>Lobelia inflata</i> (Campanulaceae) [leaf] <i>Panax ginseng</i> (ginseng) (Araliaceae) [root] <i>Ambrosia</i> spp., <i>Arctotis</i> spp., <i>Chrysanthemum parthenium</i> (feverfew), <i>Tanacetum vulgare</i> (tansy) [leaf surface] (Asteraceae), <i>Michelia champaca</i> , <i>M. lanuginosa</i> (Magnoliaceae)	6.2t ↑ NE-REL [antidepressant] Inhibits ↑ D-REL induced by Nicotine ↓ 5HT-REL (e.g. by amphetamine) [antibacterial, antifungal, anti-migraine agent of feverfew, anti-tumour, cytotoxic]
Other Theanine (= 5- <i>N</i> -Ethylglutamine) (amino acid)	<i>Camellia japonica</i> (Japanese green tea), <i>C. sasanqua</i> , <i>Camellia sinensis</i> (Theaceae) [leaf]	6.2o ↑ D-REL, ↑ 5HT-REL [anxiolytic, hypotensive, relaxant]
Non-plant reference [Amphetamine (= 1-Phenyl-2-aminopropane)] (aryl amine)	Synthetic; globally Amphetamine-related drugs are used by 29 million out of 180 million illicit drug users	6.2n ↑ D-REL [↑ synaptic D; anorexic, CNS stimulant]
[Methamphetamine (= Methylamphetamine; 1-Phenyl-2-methylaminopropane)] (aryl amine)	Synthetic; semi-synthetic from reduction of Ephedrine & Pseudoephedrine; taken by Adolf Hitler plus Atropine, Strychnine & Cocaine medications	↑ D-REL, ↑ 5HT-REL [↑ synaptic D & 5HT; anorexic, CNS stimulant, sympathomimetic]; WW2 Luftwaffe General Ernst Udet was on Methamphetamine & shot himself (1941)
[(+)-Methylenedioxy-methamphetamine (= Ecstasy; "E"; 3,4-Methylenedioxy-methamphetamine; MDMA; "X")] (aryl amine)	Synthetic; Ecstasy ("E") drug of abuse in disco rave scene – see <i>Glue</i> by Irvine Welsh; stimulant & hallucinogenic; ~3 million have used MDMA in the US	↑ D-REL, ↑ 5HT-REL [↑ synaptic D & 5HT; anti-dyskinetic (i.e. with Parkinson 1.-DOPA-induced dyskinesia), induces hyperactivity, CNS stimulant, neurotoxic memory impairment]

(continued)

Table 6.2 (Continued)

Compound (class)	Plant (family) part/	Enzyme inhibited / in vivo effects/
[4-Phenyltetrahydro-isoquinoline] (isoquinoline)	Synthetic	D-REL induced by Methamphetamine
[Retalin (= Methylphenidate; Methyl phenidylacetate) (piperidine arylester)]	Synthetic	↑ D-REL, ↑ 5HT-REL [CNS stimulant; ↑ synaptic D but paradoxical ADHD alleviation effect due to ↑ 5HT]

Table 6.3 Re-uptake of neurotransmitters into neurons and synaptic vesicles

Compound (class)	Plant (family) part/	Effect or enzyme/process inhibited (other targets) / in vivo effects/
Monoamine transporter (MA-TR); Dopamine transporter (D-TR); GABA transporter (GABA-TR); Vesicular monoamine transporter (VMA-TR)		6.3
Alkaloid		6.3a
Arecaidine (= Arecaine; 1,2,5,6-Tetrahydro-1-methyl-3-pyridinecarboxylic acid) (piperidine)	<i>Areca catechu</i> (betel nut) (Palmae) [seed], <i>Piper betel</i> (betel pepper) (Piperaceae)	β-Alanine-TR, GABA-TR
Cocaine (= Benzoyl-methylecgonine) (tropane); Richard Willstätter (Nobel Prize, Chemistry, 1915, plant pigments & chlorophyll; fled Nazis)	<i>Erythroxylum coca</i> , <i>E. recurrens</i> , <i>E. steyermarkii</i> , <i>E. spp.</i> (Erythroxylaceae) [leaf]; cocaine taken by Adolph Hitler (for nasal & eye problems) as well as Atropine, Methamphetamine & Strychnine; globally used by 14 million out of 180 million drug users	D-TR, NE-TR, 5HT-TR, Octopamine TR (insect) [topical anaesthetic (ophthalmic), CNS stimulant, mydriatic, narcotic, stimulant through elevation of synaptic D, NE & 5HT]
O-Desmethylibogaine (= 12-Hydroxyibogamine) (indole)	Primary metabolite of Ibogaine	V-D-TR ligand, 5HT-TR ligand (Cocaine & Paroxetine sites), V-MA-TR ligand (κO-R, NMDA-Glu-R, V-D-TR, V-MA-TR)
Guvacine (= Δ ⁹ -Tetrahydro-nicotinic acid) (piperidine)	<i>Areca catechu</i> (betel nut) (Palmae) [seed]	β-Alanine-TR, GABA-TR
Ibogaine (12-Methoxyibogamine) (indole)	<i>Tabernanthe iboga</i> (iboga), <i>Voacanga thouarsii</i> (Apocynaceae); iboga West African stimulant & aphrodisiac	D-TR (4), V-MA-TR, 5HT-TR (0.6), NE-TR (AD-R, mACh-R, D-R, NMDA-Glu-R, κO-R) [↑ synaptic 5HT; antiaddictive, anticonvulsant, CNS activity, hallucinogen, increases 5HT, inhibits morphine dependence]

(continued)

Table 6.3 (Continued)

Compound (class)	Plant (family) part	Effect or enzyme / process inhibited (other targets) in vivo effects
Noribogaine (= 12-Hydroxyibogaine) (indole)	Metabolic product of Ibogaine	D-TR (4), 5HT-TR (40 nM), [↑ synaptic 5HT; antiaddictive, anticonvulsant, CNS stimulant, hallucinogen]
Rescinnamine (= Reserpine) (indole)	<i>Rauwolfia nitida</i> , <i>R. serpentina</i> , <i>R. vomitoria</i> (Apocynaceae)	VMA-TR [antihypotensive, antipsychotic, tranquilizer]
Reserpine (indole)	<i>Catharanthus roseus</i> (Madagascar periwinkle), <i>Rauwolfia serpentina</i> (Indian snakeroot), <i>R. tetraphylla</i> (pinque-pinque, four-leaf devil pepper), <i>R. vomitoria</i> (African snakeroot), <i>Vinca minor</i> (periwinkle) (Apocynaceae)	MA-TR, VM-TR; VMAT1 (adrenal chromaffin granule), VMAT2 (brain, adrenal), L-type Ca ²⁺ CH-dependent NE release (6) (MDR-TR) [antihypertensive, antipsychotic, carcinogen, tranquilizer, neuroleptic CNS antidepressant]
[Nipecotic acid (= 3- Piperidinecarboxylic acid)] (piperidine)	Semi-synthetic from Nicotinic acid	GABA-TR
[Tetrahydropapaveroline] (isoquinoline)	Metabolite of Dopamine	D-TR (41)
Phenolic		6.3p
Adhyperforin (phloroglucinol)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae)	D-TR, 5HT-TR, NE-TR [antidepressant]
Cannabidiol (phenolic)	<i>Cannabis sativa</i> (marihuana), <i>Humulus lupulus</i> (hops) (Cannabaceae) [leaf, flower]	D-TR [~20], 5HT-R [~20], NE-TR [~20], GABA-TR [~140] (CB-R)
[7-Hydroxy-Δ ¹ - tetrahydrocannabinol] (phenolic)	Semi-synthetic	D-TR [~20], 5HT-R [~20], NE-TR [~20], GABA-TR [~140] (CB-R)
Hyperforin (phloroglucinol)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae); widely used as antidepressant herbal medicine	D-TR, 5HT-TR (by ↑ intracellular Na ⁺ as does Na ⁺ /H ⁺ exchanger monensin; weak Paroxetine binding inhibitor), NE-TR [antidepressant]
<i>Hypericum</i> extract LI 160 (= standardized preparation)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae)	Inhibits 5HT, D & NE uptake [antidepressant]
<i>Hypericum</i> extract (= St John's Wort extract) (see Adhyperforin & Hyperforin)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae); major herbal antidepressant	D-TR, 5HT-TR, NE-TR [antidepressant]
(+)- & (+/-)-Kavain (= Gonosan; Kawain) (pyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]	NE-TR - (+/-)- Kavain > (+)- Kavain
(+)-Methysticin (pyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]	NE-TR - (+/-)-Kavain > (+)- Kavain > (+)-Methysticine
Δ ¹ -Tetrahydrocannabinol (= Δ ⁹ -Tetrahydrocannabinol; Dronabinol) (phenolic)	<i>Cannabis sativa</i> (marihuana) (Cannabaceae) [leaf]	D-TR [12], 5HT-R [12-25], NE-TR [12-25], GABA-TR [140] (CB-R)

(continued)

Table 6.3 (Continued)

Compound (class)	Plant (family) part	Effect or enzyme / process inhibited (other targets) in vivo effects
Δ^6 -Tetrahydrocannabinol (phenolic)	<i>Cannabis sativa</i> (marihuana) (Cannabaceae) [leaf]	D-TR [~ 20], 5HT-R [~ 20], NE-TR [~ 20], GABA-TR [~ 140] (CB-R)
Tyramine (= 4-Hydroxy-phenylalanine) (phenolic)	<i>Lophophora williamsii</i> , <i>Trichocereus pachanoi</i> (Cactaceae), <i>Hordeum vulgare</i> , <i>Lolium multiflorum</i> (Poaceae), <i>Citrus</i> spp. (Rutaceae), <i>Viscum album</i> (Viscaceae)	D-TR ligand (insect $\alpha 2A$ -R-like TYR-R) [indirect adrenergic]
Terpene [Testosterone propionate] (sterol)	Semi-synthetic from testosterone yielding testosterone per esterases	6.3t [Increases 5-HT TR (rat brain)]
Other β -Alanine (= 3-Aminopropionic acid) (amino acid)	<i>Lunaria</i> spp. (Brassicaceae), <i>Ribes nigrum</i> (Grossulariaceae), <i>Iris tingitana</i> (Iridaceae) [seed], <i>Lycopersicon esculentum</i> (Solanaceae)	6.3o GABA-TR (GLY-R agonist)
BMAA (= β -N-Methylamino-1-alanine) (amino acid)	<i>Cycas circinalis</i> , (Cycad, sago palm), <i>C.</i> spp. (Cycadaceae) [leaf, seed]	NE uptake inhibition (at 10) (Non-NMDA-Glu-R agonist); substrate for large neutral amino acid TR (rat blood-brain barrier) (K_m 2900, competes with leucine) [excitotoxin, lathyrism (neuronal damage disease) in humans]
1-BOAA (= β -N-Oxalylamino-1-alanine) (amino acid)	<i>Lathyrus sativus</i> (Fabaceae) [seed]	NE uptake inhibition (at 10) (Non-NMDA Glu-R agonist) [excitatory, lathyrism (neuronal damage disease) in humans]
D-Cathinone (= (S)-2-Amino-1-phenyl-1-propanone) (phenylpropanoid)	<i>Catha edulis</i> (khat), <i>Maytenus krukovii</i> (Celastraceae) [leaf]	\downarrow D-TR, 5HT-TR (βA -R) [anorexic, CNS stimulant, euphoriant]
2,4-Diaminobutyric acid (diaminoalkane carboxylic acid)	<i>Acacia</i> , <i>Lathyrus</i> spp. (Fabaceae), <i>Polygonatum multiflorum</i> (Solomon's seal) (Liliaceae)	GABA-TR (OTCase) [anticonvulsant]
Methcathinone (phenylpropanoid)	<i>Catha edulis</i> (khat), <i>Maytenus krukovii</i> (Celastraceae) [leaf]	\downarrow D-TR, 5HT-TR [stimulant]
Non-plant reference compound [Amitypytline] (dibenzocycloheptadiene tertiary amine)	Synthetic	5HT-TR [antidepressant, paranoid exacerbation]
[Amphetamine (= 1-Phenyl-2-aminopropane; Benzedrine)] (aryl tertiary amine)	Synthetic; globally Amphetamine-related drugs used by 29 million out of 180 million illicit drug users	\downarrow D-TR, \downarrow 5HT-TR (\uparrow release of catecholamines from presynaptic storage granules) [anorexic, CNS stimulant]

(continued)

Table 6.3 (Continued)

Compound (class)	Plant (family) / part/	Effect or enzyme / process inhibited (other targets) / in vivo effects/
[2-(4-Bromobenzoyl)-3-methyl-4,6-dimethoxybenzofuran (= BMBD)] (xanthoxylin)	Synthetic	[Antinociceptivity reversed by 5HT synthesis inhibition by <i>p</i> -Chlorophenylalanine methyl ester]
[Citalopram] (benzodioxol fluorophenyl piperidine)	Synthetic	5HT uptake inhibitor [antidepressant]
[Dextromethorphan] (morphine analogue)	Synthetic; cough suppressant abused as the “DMX” recreational drug	D-TR (NMDA-Glu-R, σ -R agonist) [antitussive, anxiolytic, psychoactive]
[Fluoxetine (= (\pm)- <i>N</i> -Methyl- γ -[4-(trifluoromethyl)-phenoxy]-benzenepropanamine); Prozac](trifluorophenoxy phenyl tertiary amine)	Synthetic; Prozac – widely used antidepressant	5HT uptake inhibitor (nACh-R, 5HT3-R antagonist) [antidepressant, paranoid exacerbation]; antidepressant per synaptic serotonin (5HT) elevation
[Litoxetine] (aryl)	Synthetic	5HT uptake inhibitor (5HT3-R antagonist) [antidepressant, antiemetic]
[(+)-Methylenedioxy-methamphetamine (= Ecstasy; “E”; 3,4-Methylenedioxy-methamphetamine; MDMA; “X”)] (aryl amine)	Synthetic; Ecstasy (“E”) drug of abuse in disco scene – see <i>Glue</i> by Irvine Welsh; stimulant & hallucinogenic	\downarrow D-TR, 5HT-TR (\uparrow D-REL, \uparrow 5HT-REL) [\uparrow synaptic D & 5HT; anti-dyskinetic (i.e. with Parkinson L-DOPA-induced dyskinesia), induces hyperactivity, CNS stimulant, neurotoxic, memory impairment]
[Oestradiol benzoate] (sterol)	Semi-synthetic of Oestradiol yielding oestradiol per esterases	[Increases 5HT-TR (brain)]
[Paroxetine] (fluorophenyl isobenzofuran tertiary amine)	Synthetic	5HT uptake inhibitor [antidepressant]
[Rimcazole] (piperazinyl carbazole)	Synthetic	D-TR (σ -R antagonist)
[Ritalin (= Methylphenidate; Methyl phenidylacetate)] (piperidine)	Synthetic	D-TR, 5HT-TR [elevates 5HT & Dopamine, stimulant; calms children with hyperactivity-attention deficit disorder]
[Testosterone propionate] (sterol)	Semi-synthetic from testosterone yielding testosterone per esterases	[Increases 5HT-TR (brain)]
[Tetrahydropapaveroline] (isoquinoline)	Metabolite of 1-Dopa	D-TR
[Zimeldine] (aryl piridinyl amine)	Synthetic; Arvid Carlsson (Sweden, Nobel Prize, Physiology/Medicine, 2000)	5HT uptake inhibitor [antidepressant]

Table 6.4 Acetylcholinesterase

Compound (class)	Plant (family) part	Enzyme inhibited (other targets inhibited) /in vivo effects/
Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE)		6.4
Alkaloid		6.4a
Berberine(= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> (Annonaceae), <i>Berberis</i> , <i>Hydrastis</i> , <i>Mahonia</i> , <i>Nandina</i> (Berberidaceae), <i>Archangelica</i> (Menispermaceae), <i>Argemone</i> , <i>Chelidonium</i> , <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> , <i>Thalictrum</i> (Ranunculaceae), <i>Evodia</i> , <i>Toddalia</i> , <i>Zanthoxylum</i> (Rutaceae) spp.	AChE ligand (167), BChE ligand (56) ($\alpha 1A$ -R, $\alpha 2A$ -R, ATPase, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
Cassaine (diterpene alkaloid)	<i>Erythrophleum guineense</i> , <i>E. suaveolens</i> (Fabaceae) [bark]	AChE (<550) (Na ⁺ K ⁺ -ATPase) [cardiotonic, cardiotoxic, convulsant]
α -Chaconine (triterpene, steroidal alkaloid)	<i>Notholirion hyacinthinum</i> , <i>Veratrum stenophyllum</i> (Liliaceae), <i>Solanum</i> <i>tuberosum</i> , <i>S. choacoense</i> , <i>S. nigrum</i> (Solanaceae) [tuber]	BChE (at physiological postprandial (potato meal) serum levels) [teratogen, toxic]
Coumingine (alkaloid)	<i>Erythrophleum</i> sp. (Fabaceae)	AChE (<550) (Na ⁺ K ⁺ -ATPase) [cardiotonic, cardiotoxic]
Dehydroevodiamine (indole)	<i>Evodia rutaecarpa</i> (Rutaceae)	AChE (38) [antiemetic (>Tacrine (AD drug)) AChE [cholinergic]
Deoxypeganine (= Deoxyvasicine) (quinazoline quinoline)	<i>Peganum harmala</i> , <i>P. nigellastrum</i> (Zygophyllaceae)	
Faleoconitine (norditerpene alkaloid)	<i>Aconitum falconeri</i> (Ranunculaceae) [root, tuber]	AChE
Galanthamine (= Galantamine; Lycoremine; Reminyl) (galanthaman Amaryllidaceae alkaloid); clinically used for Alzheimer's disease (acetylcholine signalling- linked dementia)	<i>Galanthus woronii</i> (snowdrop) [bulb], <i>Crinum</i> , <i>Galanthus</i> , <i>Hippeastrum</i> , <i>Hymenocallis</i> , <i>Leucojum</i> , <i>Lycoris</i> , <i>Narcissus</i> , <i>Pancreatum</i> , <i>Ungernia</i> spp. (Amaryllidaceae)	AChE (nACh-R allosteric modulator) [analgesic, clinical cognitive enhancer for AD, reverses amnesia from Scopolamine, insecticide, neuroleptic]
(-)-Huperzine A (carbocyclic pyridinone)	<i>Huperzia serrata</i> (moss), <i>Lycopodium selago</i> (fir club moss) – not to be confused with non-toxic <i>L. clavatum</i> (sometimes used for a “tea”), (Lycopodiaceae)	AChE [5 nM], BChE [cholinergic – causes cramps, diarrhoea, dizziness, slurred speech, sweating, vomiting; toxic, atropine antidote]
Huperzine B (carbocyclic pyridinone)	<i>Huperzia serrata</i> (moss), <i>Lycopodium selago</i> (fir club moss) (Lycopodiaceae)	AChE [cholinergic, anti-AD]
N-(<i>p</i> -Hydroxyphenethyl) actinidine (monoterpene alkaloid)	<i>Valeriana officinalis</i> (Valerianaceae) [root]	AChE

(continued)

Table 6.4 (Continued)

Compound (class)	Plant (family) / part/	Enzyme inhibited (other targets inhibited) / in vivo effects/
(+)-Nepapakistanamine A (steroidal alkaloid)	<i>Sarcococca coriacea</i> (Buxaceae)	AChE
Palmitine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Berberis</i> , <i>Mahonia</i> spp. (Berberidaceae), <i>Jateorrhiza palmata</i> (Menispermaceae), <i>Corydalis</i> (Papaveraceae), <i>Coptis</i> (Ranunculaceae) spp.	AChE ligand (125), BChE ligand (426) (α 1A-R, α 2A-R, ATPase, CDPK, ChAT, diamine oxidase, 5HT ₂ -R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]
Papaverine (benzylisoquinoline)	<i>Rauvolfia serpentina</i> (Annonaceae), <i>Papaver bracteaetum</i> , <i>P. serpentina</i> , <i>P. somniferum</i> (opium poppy) (Papaveraceae)	AChE [antitussive, SM relaxant, spasmolytic, vasodilator]
Peganine (= Linarine; Vasicine) (quinazoline quinoline)	<i>Adhatoda vasica</i> , <i>Justicia adhtoda</i> (Acanthaceae) [leaf], <i>Lunaria</i> spp. (Cruciferae), <i>Sida cordifolia</i> (Malvaceae) [root], <i>Peganum harmala</i> (Zygophyllaceae) [leaf]	AChE [abortefacient, anthelmintic, bronchodilatory, cholinergic, hypotensive, respiratory stimulant, uterotonic]
Physostigmine (= Eserine; Physosterine; Physostol) (indole)	<i>Hippomane mancinella</i> (Euphorbiaceae), <i>Physostigma venenosum</i> (Calabar bean) (Fabaceae) [seed] (isolated 1864)	AChE, BChE (carbamoylates active site Serine) [anti-AD, esp. AD amyloid plaque- & tangle- associated ChE; mitotic, organophosphate poison antidote , parasympathetic, toxic]
Physovenine (indole)	<i>Physostigma venenosum</i> (Calabar bean) (Fabaceae) [seed]	AChE [parasympathetic, toxic]
Protopine (= Biflorine; Corydalis C; Corydinine; Fumarine; Macleyine) (benzylisoquinoline)	<i>Fumaria officinalis</i> (fumitory) (Fumariaceae), <i>Argemone mexicana</i> (prickly poppy), <i>Corydalis ternata</i> , <i>Papaver somniaferum</i> (opium poppy) (Papaveraceae)	AChE (50) [antibacterial, anti- amnesic (\approx anti-AD drug Velnacrine), sedative, SM relaxant]
Pseudoaconitine (norditerpene alkaloid)	<i>Aconitum falconeri</i> , <i>A. ferox</i> , <i>A. spicatum</i> (Ranunculaceae) [root, tuber]	AChE (nACh-R) [anticholinergic, cardiac & respiratory depressant, hypotensive, toxic]
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Chelidonium majus</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Papaver somniferum</i> , <i>Sanguinaria canadensis</i> (Papaveraceae), <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	AChE ligand (11), BChE ligand (17) (α 1A-R, α 2A-R, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA ligand, 5HT ₂ -R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]

(continued)

Table 6.4 (Continued)

Compound (class)	Plant (family) / part/	Enzyme inhibited (other targets inhibited) / in vivo effects/
α -Solanine (= Solatunine) (triterpene, steroidal alkaloid)	<i>Lycopersicon esculentum</i> (tomato), <i>Capsicum</i> spp., <i>Solanum tuberosum</i> (potato) [tuber], <i>S. nigrum</i> (woody nightshade) (Solanaceae)	BChE (at physiological postprandial (potato meal) serum levels) [causes coma, diarrhoea, hallucination, vomiting; insecticide, teratogen, toxic]
Ungiminoirine (Amaryllidaceae alkaloid)	<i>Narcissus</i> sp. (narcissus) (Amaryllidaceae)	AChE
(-)-Vaganine D (steroidal alkaloid)	<i>Sarcococca coriacea</i> (Buxaceae)	AChE
Phenolic		6.4p
Resorcinolic lipids (phenolic esters)	<i>Triticum aestivum</i> (Poaceae) [seed]	Membrane AChE (18-90)
Terpene		6.4t
1,8-Cineole (= Cajeputol; Eucalyptol) (monoterpene)	<i>Artemisia maritima</i> (Asteraceae), <i>Salvia lavandulaefolia</i> (Lamiaceae), <i>Eucalyptus globulus</i> , <i>E.</i> spp., <i>Melaleuca leucadendron</i> (Myrtaceae) [oil], <i>Alpinia</i> , <i>Curcuma</i> (Zingiberaceae)	AChE (670) [anthelmintic, antiseptic, expectorant, flavour, cockroach repellent]
α -Pinene (= 2-Pinene) (monoterpene)	<i>Juniper macrophoda</i> (Cupressaceae), <i>Mentha</i> , <i>Salvia</i> spp. (Lamiaceae), <i>Eucalyptus globulus</i> (Myrtaceae), <i>Pinus palestris</i> , <i>P. walliciana</i> , <i>P.</i> spp. (Pinaceae), <i>Citrus</i> spp. (Rutaceae)	AChE (630) [ataxic, delirium-inducing, dermatitic, irritant, perfume]
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (triterpene)	Widespread; <i>Nerium oleander</i> (Apocynaceae), <i>Vaccinium macrocarpon</i> (cranberry), <i>Arctostaphylos uva-ursi</i> (Ericaceae), <i>Organum majorana</i> , <i>Prunella vulgaris</i> , <i>Salvia</i> spp. (Lamiaceae), <i>Malus</i> sp., <i>Pyrus</i> sp. (Rosaceae) [fruit surface]	AChE [6 pM] (CDPK, DNAP, HIV-1 PR, PKA, PKC, RT, TOPI, TOPII) [AI, cytotoxic, antineoplastic]
Other		6.4o
<i>Solanum</i> CPI (= Potato Carboxypeptidase Inhibitor) (5 kDa protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	[AChE, BChE esp. AD amyloid plaque- & tangle-associated ChE (at 50–100)] (CP)
Non-plant reference		6.4n
[Aldicarb (= 2-Methyl-2- (methylthio) propionaldehyde <i>O</i> -(methylcarbamoyl) oxime] (aliphatic carbamate)	Synthetic	AChE (carbamoylates – forms carbamoyl ester with active site Serine) [acaricide, most potent market carbamate insecticide, nematocide, toxic (atropine antidote)]

(continued)

Table 6.4 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited (other targets inhibited) / in vivo effects/
[Amiloride] (pyrazine guanidine)	Synthetic	AChE, BChE (Na ⁺ /H ⁺ antiporter) [diuretic]
[Anatoxin-a(s)] (guanidine methylphosphate ester)	<i>Anabaena flos-aquae</i> (cyanobacterium, blue-green alga)	AChE (forms covalent adduct with active site Serine resistant to oxime reactivation)
[Diisopropylfluorophosphate] (organophosphate)	Synthetic insecticide	AChE (forms phosphoryl ester with active site Serine)
[Donepezil (= Aricept)] (aryl piperidine)	Synthetic	AChE [1 nM] [nootropic]
[Fasciculins] (7 kDa proteins)	<i>Dendroaspis angusticeps</i> (mamba snake) venom	AChE (at pM–nM)
[Huprine X] (quinoline)	Synthetic	AChE [26 pM] [anti-AD]
[Huprine Y] (quinoline)	Synthetic	AChE [33 pM] [anti-AD]
[Neostigmine (= 3-Dimethyl-carbamoxyphe-nyl-trimethylammonium) (quaternary amine aryl carbamate)	Synthetic – cf. Physostigmine	AChE (carbamoylates – forms carbamoyl ester with active site Serine) [cholinergic, myotic, toxic (curare antidote)]
[Parathion (= O,O-Diethyl O-p-nitrophenyl phosphorothioate)] (organophosphorothioate)	Synthetic	AChE (phosphorothiolates active site Serine) [insecticide]
[Phenserine (= (-)-N-Phenylcarbamoyl eseroline)] (phenylcarbamate)	Synthetic – cf. Physostigmine	AChE (carbamoylates – forms carbamoyl ester with active site Serine) [cognition enhancer for AD]
[Rivastigmine] (carbamate)	Synthetic – cf. Physostigmine	AChE (carbamoylates pseudoirreversibly – forms carbamoyl ester with active site Serine) [clinical cognition enhancer for AD]
[Sarin (= Isopropoxy-methylphosphoryl fluoride) (organophosphate)	Synthetic	AChE (forms phosphoryl ester with active site Serine) [chemical warfare agent]
[Soman (= Methyl-phosphonofluoridic acid 1,2,2-trimethylpropyl ester)] (organophosphate)	Synthetic	AChE (forms phosphoryl ester with active site Serine) [chemical warfare agent]
[Tacrine (= Cognex; 1,2,3,4-Tetrahydro-5-aminoacridine)] (acridine)	Synthetic	AChE [0.4 nM; 31 nM], BChE (nACh-R) [esp. AD amyloid plaque- & tangle-associated ChE; clinical cognition enhancer for AD]
[Velnacrine (= 1-Hydroxy-1,2,3,4-Tetrahydro-5-aminoacridine)] (acridine)	Synthetic; metabolite of Tacrine	AChE [cognition enhancer, nootropic, potential anti-AD]

Table 6.5 Monoamine oxidase

Compound (class)	Plant (family) part	Enzyme inhibited / in vivo effects
Monoamine oxidase (MAO)		6.5
Alkaloid		6.5a
Cinchonamine (= [3'R,4'S]-2-[2-(-Ethenyl-4-piperidinyl)-acetyl]-1H-indole-3)-ethanol (piperidinyl indole)	<i>Cinchona succirubra</i> (Rubiaceae) [cortex]	MAO (32)
Cinchonamine (= [1S,3'R,4'R]-3-(3-Ethenyl-4-piperidinyl)-1-(4-quinolinyl)-1-propanol) (piperidinyl quinoline)	<i>Cinchona succirubra</i> (Rubiaceae) [cortex]	MAO (12)
Harmaline (= 3,4-Dihydroharmine; Harmidine) (indole, carboline)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> , <i>Banisteriopsis caapi</i> (Malpighiaceae), <i>Peganum harmala</i> (Zygophyllaceae)	MAO-A (I2-R) (α 2A-R, BZ-R, DNA, NMDA-Glu-R) [ataxic, excitatory, hallucinogenic, increases cGMP, tremorigenic]
Harman (= Aribine; Loturine; 1-Methyl- β -carboline; Passiflorin) (β -carboline, indole)	<i>Phaseolus vulgaris</i> (Fabaceae) [suspension culture], <i>Passiflora edulis</i> , <i>P. incarnata</i> (Passifloraceae), <i>Singickia rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> , <i>Zygophyllum fabago</i> (Zygophyllaceae); cooked food, pyrolysate of Tryptophan	MAO-A (0.5) [5 nM], MAO-B (5) (\uparrow CAT-REL, DNA, I1-R, I2-R) [antidepressant, co-mutagenic, convulsant, cytotoxic, genotoxic, hypotensive, motor depressant, sheep "Tribulus staggers"]
Harmine (= Banisterine; Leucoharmine; Telepathine; Yageine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> (Zygophyllaceae); "pharmahuasca" (cf. S. Am. psychotropic Ayahuasca) combination of N,N-dimethyltryptamine (5HT-R agonist) + harmine (MAO inhibitor)	MAO-A [2 nM] (DNA) [CNS stimulant, hallucinogenic; WW2 Nazi Gestapo use as "truth drug"]
2-Methoxytetrahydro- β -carboline (= 2-Methoxy-tetrahydronorharman) (β -carboline, indole)	<i>Palicourea marcgravi</i> (Rubiaceae) [leaf]	MAO-A (1)
2-Methyltetrahydro- β -carboline (= 2-Methyl-tetrahydronorharman) (β -carboline, indole)	<i>Palicourea marcgravi</i> (Rubiaceae) [leaf]	MAO-A [may \uparrow toxicity of Fluoroacetate in same plant]
Norharman (= β -Carboline) (β -carboline, indole)	<i>Cichorium intybus</i> (Asteraceae), <i>Tribulus terrestris</i> (puncture vine), <i>Zygophyllum fabago</i> (Zygophyllaceae); tobacco smoke [ex <i>Nicotiana tabacum</i> [leaf] (Solanaceae)]; cooked food, pyrolysate of Tryptophan	MAO-A (weak) (BZ-R, DNA) [co-mutagenic, sheep "Tribulus staggers"]

(continued)

Table 6.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited / in vivo effects
Quinine (quinoline)	<i>Cinchona officinalis</i> , <i>C. succirubra</i> , <i>C. spp.</i> , <i>Remijia pedunculata</i> (Rubiaceae)	MAO (16) [abortefacient, antimalarial, antifibrillatory, bitter taste, cardiac depressant, stimulant]
[Tetrahydro- β -carboline (= tetrahydronorharman)] (β -carboline, indole)	Metabolite from Tryptamine	MAO-A (5), MAO-B (~50)
Tetrahydroharmine (β -carboline, indole)	<i>Banisteria caapi</i> (liana), <i>Banisteriopsis caapi</i> (ayahuasca) (Malpighiaceae) [bark]	MAO
1,2,3,4-Tetrahydro- isoquinoline 1-cyano adduct (isoquinoline)	Derived from smoking tobacco – <i>Nicotiana tabacum</i> (Solanaceae) [leaf]	MAO [~30] [tobacco smoke inhibits MAO & has protective effect against Parkinson's disease]
1,2,3,4-Tetrahydro- isoquinoline <i>N</i> -(1'- cyanoethyl), <i>N</i> -(1'- cyanopropyl) & <i>N</i> -(1'- cyanobutyl) adducts (isoquinoline)	Derived from smoking tobacco – <i>Nicotiana tabacum</i> (Solanaceae) [leaf]	MAO [~30] [tobacco smoke inhibits MAO & has protective effect against Parkinson's disease]
Tryptamine (= 3-(2- Aminoethyl) indole) (indole)	<i>Cucumis sativus</i> (cucumber) (Cucurbitaceae), <i>Mucuna pruriens</i> , <i>Piptadenia peregrina</i> , <i>Prosopis juliflora</i> (Fabaceae), <i>Hordeum vulgare</i> (barley), <i>Zea mays</i> (corn) (Poaceae) [seed], <i>Lycopersicon esculentum</i> (tomato), <i>Nicotiana tabacum</i> (tobacco), <i>Solanum melongena</i> , <i>S. tuberosum</i> (potato) (Solanaceae)	Precursor of Tetrahydro- β -carboline (I1-R, I2-R)
Phenolic		6.5p
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	<i>Apium</i> , <i>Daucus</i> (Apiaceae), <i>Mentha</i> (Lamiaceae) spp., ferns [leaf surface]; 7- apiosylglucoside (= Apiin; Apioside) in <i>Apium graveolens</i> (celery), <i>Petroselinum</i> sp. (parsley) (Apiaceae) [leaf, seed]; glucosides in <i>Cosmos bipinnatus</i> , <i>Erigeron annuus</i> (Asteraceae), <i>Amorpha fruticosa</i> (Fabaceae)	MAO-A (1; 8), MAO-B (BZ-R-like R, CDK2, EGF-RTK, MLCK, PKA, PKC, RTK (insulin-RTK, IGF- 1- RTK)) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
Chrysin (= 5,7- dihydroxyflavone) (flavone)	<i>Daucus</i> (Apiaceae), <i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (poplar) (Salicaceae) [leaf bud], <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	MAO-A (2), MAO-B (AR, PDE, ITD, histamine release) [AI, antibacterial]
Confluent acid (depside, aryl ester)	<i>Himatanthus sucuba</i> (Apocynaceae) [bark]	MAO-B (0.2) (not MAO-A)
Desmethoxyyangonin (pyrone, phenolic derivative)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome]	MAO-B [0.3]

(continued)

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Table 6.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited / in vivo effects
(+/-)-Dihydrokavain (= Dihydrokawain) (pyrone, phenolic derivative)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome]	MAO-B
(+/-)-Dihydromethysticin (pyrone, phenolic derivative)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome]	MAO-B
(-)-Epicatechin (= 2 <i>R</i> ,3 <i>R</i>)-5,7,3',4'-Tetrahydroxyflavan-3-ol) (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), <i>Pterocarpus</i> spp. (Fabaceae) [bark], <i>Podocarpus nagi</i> (Podocarpaceae), <i>Crataegus monogyna</i> (Rosaceae), <i>Camellia sinensis</i> (Theaceae)	MAO-A (> 25) (AR, PKA) [antibacterial, AI, anti-oxidant]
Isopsoralen (furocoumarin)	<i>Psoralea corylifolia</i> (Fabaceae) [seed]	MAO-A (9) [7], MAO-B (13) [11]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (grapefruit) (Rutaceae), <i>Koelreuteria henryi</i> (Sapindaceae); glycosides in Fabaceae, Hippocastanaceae	MAO-A (0.7), MAO-B (CDPK, EGF-RTK, MLCK, PKA, p56 ^{lck} TK)
(+/-)-Kavain (= Gonosan; Kawain) (pyrone, phenolic derivative)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome]; Fijian drink kava (yaqona; pronounced yangona) – excess yields local paralysis (e.g. numb lips)	MAO-B
Lemuninol A (naphthalene dimer)	<i>Diospyros</i> sp. (Ebenaceae)	MAO (12–25)
Lemuninol B (naphthalene dimer)	<i>Diospyros</i> sp. (Ebenaceae)	MAO (> 62)
Lemuninol C (naphthalene dimer)	<i>Diospyros</i> sp. (Ebenaceae)	MAO (> 60)
Malvidin 3-glucoside (anthocyanin)	<i>Malva sylvestris</i> (mallow) (Malvaceae) [flower], <i>Ligustrum vulgare</i> (Oleaceae), <i>Vitis vinifera</i> (grape) (Vitaceae)	MAO-A (> 25) [mauve colour]
3-Methyl-8-methoxy-1,4-naphthoquinone (naphthoquinone)	<i>Diospyros</i> sp. (Ebenaceae)	MAO (> 108)
2'- <i>O</i> -Methylperlatolic acid (depside, aryl ester)	<i>Himatanthus sucuuba</i> (Apocynaceae) [bark]	MAO-B (81) (not MAO-A)
<i>N</i> -Methyltyramine (phenolic amine)	<i>Palicourea marcgravii</i> (Rubiaceae) [leaf]	MAO-A (competitive substrate) [may ↑ toxicity of Fluoroacetate in same plant]
(+/-)-Methysticin (pyrone, phenolic derivative)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome]	MAO-B [1] [spasmolytic]
Myristicin (phenylpropene)	<i>Apium graveolens</i> , <i>Daucus carota</i> , <i>Levisticum scoticum</i> , <i>Pastinaca sativa</i> , <i>Petroselinum crispum</i> (Apiaceae), <i>Cinnamomum glanduliferum</i> (Lauraceae), <i>Orthodon</i> spp. (Lamiaceae), <i>Myristica fragrans</i> (Myristicaceae) [nutmeg oil]	MAO (DNA) [PAI, psychotropic]

(continued)

Table 6.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited / in vivo effects/
Pelargonidin 3,5-di- <i>O</i> -glucoside (= Pelargonin) (anthocyanin)	<i>Commiphora muhil</i> (Burseraceae), <i>Pelargonium zonale</i> (Geraniaceae), <i>Gladiolus</i> sp. (Iridaceae) [petal]	MAO-A (> 25) [red colour]
Psoralen (= Ficusin) (furocoumarin)	<i>Pastinaca sativa</i> , <i>Petroselinum crispum</i> (Apiaceae), <i>Coronilla glauca</i> , <i>Psoralea corylifolia</i> , <i>P.</i> spp. (Fabaceae) [seed], <i>Ficus carica</i> (Moraceae), <i>Phebalium argenteum</i> [oil], <i>Xanthoxylum flavum</i> [wood] (Rutaceae)	MAO-A (15) [14], MAO-B (62) [58]
<i>trans</i> -Resveratrol (= 3,5,4'-Trihydroxystilbene) (stilbene)	<i>Nothofagus</i> (Fagaceae), <i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Veratrum</i> (Liliaceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis</i> (Vitaceae) spp.; glycosides in <i>Polygonum</i> (Polygonaceae), <i>Angophora</i> , <i>Eucalyptus</i> (Myrtaceae) spp.	MAO-A (27) [47] (p56 ^{1c} k TK)
Tyramine (= 4-Hydroxyphenethylamine; Tyrosamine) (phenolic amine)	<i>Lophophora williamsi</i> , <i>Trichocereus pachanoi</i> (Cactaceae), <i>Hordeum vulgare</i> , <i>Lolium multiflorum</i> (Poaceae), <i>Palicourea maragravii</i> (Rubiaceae), <i>Citrus</i> spp. (Rutaceae), <i>Viscum album</i> (Viscaceae)	Precursor of <i>N</i> -Methyltyramine & Tetrahydro- β -carboline [sympathomimetic]
Veraphenol (stilbene)	<i>Veratrum taliense</i> [rhizome, root] (Liliaceae)	MAO-A (38) [36]
Yangonin (pyrone, phenolic derivative)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome]	MAO-B [spasmolytic]
Other		6.5o
[2-Naphthylamine] (naphthalene amine)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae) [cigarette smoke]	MAO-A [52], MAO-B [40] [carcinogen]
Non-plant reference (cf. I2-R ligands)		6.5n
[Pargyline (= <i>N</i> -Benzyl- <i>N</i> -methyl-2-propynylamine)] (aryl alkynyl tertiary amine)	Synthetic	MAO-A (I2-R ligand) [antihypertensive]
[Clorgyline] (chloroaryl alkynamine)	Synthetic	[Irreversibly inhibits MAO-A <i>in vivo</i>]
[Deprenyl] (propargylamine, aryl alkynamine)	Synthetic	MAO-B [clinical anti-AD] [anti-Parkinson]

Table 6.6 Degradation of other neurotransmitters

Compound (class)	Plant (family) part	Effect/enzyme inhibited (other targets) / in vivo effects/
GABA breakdown, GABA transaminase (GABAT)		6.6A
4-Hydroxybenzaldehyde (= 4-Formylphenol) (phenolic aldehyde)	Widespread; <i>Pterocarpus marsupium</i> (Fabaceae), <i>Gastrodia elata</i> (Orchidaceae), <i>Plocama pendula</i> (Rubiaceae)	GABAT (cf. Valproic acid) [anticonvulsant, antiepileptic]
Valerenic acid (sesquiterpene)	<i>Valeriana officinalis</i> (valerian) (Valerianaceae) [root]	[Inhibits GABA breakdown]
[Valproic acid (= 2- Propenylpropanoic acid)] (aliphatic carboxylic acid)	Synthetic	GABAT [antiepileptic, increases brain GABA]
Glutamate decarboxylase (GluDC)		6.6B
[Chelidamic acid] (pyridininone)	Synthetic	GluDC [33]
Chelidonic acid (pyranone dicarboxylic acid)	<i>Chelidonium majus</i> (Papaveraceae); Amaryllidaceae, Liliaceae, Papaveraceae	GluDC [1]

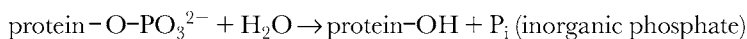
7 Cyclic nucleotide-, Ca²⁺- and nitric oxide-based signalling

7.1 Introduction

“Second messenger”-mediated signal transduction is a major signalling mechanism in eukaryotes. Essentially “primary messengers” (neurotransmitters (NTs), hormones, odorants and light) are registered by PM-located receptors with a consequent elevation of the intracellular concentration of “second messenger” substances such as cAMP, cGMP and Ca²⁺. These “second messengers” can activate “downstream” effectors, notably serine- and threonine-specific protein kinases that catalyse the transfer of the γ -phosphoryl (-PO₃) of ATP to a serine or threonine residue hydroxyl of the protein substrate:



The (reversible) phosphorylation of a protein substrate, X, typically results in a subtle change in the conformation of the phosphoprotein (denoted X-P) that is typically associated with a change in ligand binding and/or catalytic activity. Such phosphorylation is ultimately reversed through the operation of phosphoprotein phosphatases (PPs) that catalyse the hydrolytic dephosphorylation of phosphoproteins:



Calcium ion (Ca²⁺) is a major “second messenger” in eukaryote cells, the cytosolic levels of Ca²⁺ rising transiently in response to “primary messengers” that ultimately cause the opening of voltage-gated Ca²⁺ channels or ligand-gated Ca²⁺ channels (Chapter 4). Ca²⁺ concentration returns to a resting level of about 0.1 μM through the operation of Ca²⁺ pumps (Chapter 4). A variety of Ca²⁺-dependent enzymes are activated by the 1–10 μM free cytosolic Ca²⁺ concentration obtaining in “excited” cells. Such activation can occur through Ca²⁺ binding directly to the enzyme. Alternatively Ca²⁺ binding to the Ca²⁺-binding regulator protein calmodulin (CaM) forms a relatively hydrophobic Ca²⁺₄-CaM complex, which can bind to and activate a variety of enzymes. The most generally important Ca²⁺-dependent enzymes are Ca²⁺- or CaM-dependent protein kinases that catalyse the reversible phosphorylation and functional alteration of other proteins. Such phosphorylation is reversed through the operation of PPs including the Ca²⁺-dependent PP calcineurin (PP2B).

The cyclic nucleotides adenosine 3',5'-cyclic monophosphate (cyclic AMP (cAMP)) and guanosine 3',5'-cyclic monophosphate (cyclic GMP (cGMP)) are “second messengers” generated by adenylyl (adenylate) cyclase (AC) and guanylyl (guanylate) cyclase (GC), respectively, in response to receptor occupation by particular “primary messengers”, that is,

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hormones or NTs (see Chapter 5). Cyclic AMP and cGMP are ultimately hydrolysed to 5'-AMP and 5'-GMP, respectively, by cyclic nucleotide phosphodiesterases (PDEs). AC and GC are activated (switched on) by particular signalling molecules. The resultant elevated cytosolic cyclic nucleotide “second messengers” cAMP and cGMP, respectively, open cAMP- or cGMP-gated Na^+ channels (thereby depolarizing cell membranes) or activate cAMP-dependent protein kinase (PKA) or cGMP-dependent protein kinase (PKG). PKA and PKG are serine/threonine-specific protein kinases that catalyse the phosphorylation and functional alteration of particular proteins, which is ultimately reversed through the operation of PPs (Chapter 8).

Before outlining Ca^{2+} - and cyclic nucleotide-based signalling in greater detail, it should be noted that signalling pathways involving these different “second messengers” can interact in various ways (just as various law enforcement bodies interact in maintaining an orderly society). An example of this so-called “cross-talk” is provided by the Ca^{2+} -dependent PP calcineurin (PP2B) that catalyses the dephosphorylation of phosphoproteins phosphorylated by cAMP- or cGMP-dependent protein kinases. Similarly, Ca^{2+} -CaM (CaM for short hereafter) activates nitric oxide synthase (NOS), the nitric oxide (NO) generated thence activating a soluble GC which generates the “second messenger” cGMP.

7.2 Ca^{2+} - and calmodulin-dependent enzymes

A number of proteins are directly activated through the binding of Ca^{2+} . Troponin C is a CaM-like skeletal muscle protein that binds Ca^{2+} , the consequent troponin C conformational change triggering a conformational change in a tropomyosin–troponin C complex that exposes myosin-binding sites on actin filaments and thus enables skeletal muscle contraction. This process can be summarized as follows: nerve signal \rightarrow Ca^{2+} released from the sarcoplasmic reticulum \rightarrow Ca^{2+} binds to troponin C \rightarrow conformational change of troponin-C–tropomyosin complex \rightarrow myosin head-binding sites exposed on actin filaments (thin filaments) \rightarrow myosin-head-ADP- P_i complex binds to actin filaments (thereby linking myosin “thick filaments” with actin “thin filaments” with release of P_i) \rightarrow P_i release triggers a “power stroke” in which the myosin head moves the actin and myosin filaments relative to each other with the concomitant release of ADP \rightarrow ATP binds to the myosin head causing its dissociation from the actin filament \rightarrow ATP is hydrolysed to yield ADP and P_i bound to the myosin head \rightarrow the next round of interaction of myosin with the actin thin filament.

A large family of protein kinase C (PKC) isoenzymes (e.g. PKC isoforms α , β and γ) are variously activated (“switched on”) through binding Ca^{2+} and other ligands including phospholipid and diacylglycerol (DAG). Thus RTK- or GPCR-mediated signalling that activates phospholipase C (PLC) results in hydrolysis of $\text{PI}4,5\text{P}_2$ yielding DAG and IP_3 (Chapters 5 and 8). IP_3 binds to ER IP_3 -gated channels resulting in release of Ca^{2+} from ER stores into the cytosol with consequent activation of “autoinhibited” PKC by DAG, Ca^{2+} and PM-associated phospholipid depending upon the particular PKC isoenzyme involved.

A number of other protein kinases are activated by the Ca^{2+} -CaM complex generated as a result of elevation of cytosolic free Ca^{2+} concentration. CaM is a relatively small (17 kDa) acidic protein with four Ca^{2+} -binding sites (K_d values about 1 μM). Ca^{2+} binding to CaM generates a hydrophobic Ca^{2+} -CaM complex through a major conformational change in this small protein. The hydrophobic Ca^{2+} -CaM complex binds to and activates a variety of proteins including particular protein kinases. Various CaM-dependent protein kinases (CaMPKs I–IV) phosphorylate a variety of protein substrates. However, a particular CaM-dependent protein kinase called myosin light chain kinase (MLCK) phosphorylates myosin

light chains (MLCs) associated with myosin head groups. MLC phosphorylation by MLCK in smooth muscle triggers muscle contraction by permitting myosin heads to interact with actin filaments. Smooth muscle contraction is also regulated by “cross-talk” involving cAMP signalling: elevation of cAMP activates PKA which phosphorylates MLCK. PKA-phosphorylated MLCK is poorly activated by CaM, resulting in decreased MLC phosphorylation and muscle relaxation. Activated PKA also phosphorylates a muscle sarcoplasmic reticulum (ER) membrane protein called phospholamban, the phosphorylated form of which stimulates Ca^{2+} pumping into the ER lumen by the Ca^{2+} -ATPase (Chapter 4) with resultant lowering of cytosolic Ca^{2+} and smooth muscle relaxation.

CaM is an integral subunit of a further major protein kinase, namely phospholamban b kinase (PhosbK), which regulates glycogenolysis and is subject to dual control by Ca^{2+} and PKA. A CaM-domain-containing protein kinase (or Ca^{2+} -dependent protein kinase, CDPK) is present in plants and in the malaria-causing organism *Plasmodium falciparum* (which has an evolutionary origin involving a photosynthetic symbiont). These CDPKs have a C-terminal domain composed of four CaM-like Ca^{2+} -binding domains.

CaM (i.e. the Ca^{2+}_4 -CaM complex) activates a variety of other proteins including brain adenylyl cyclase, a Ca^{2+} -dependent Na^+ channel, ER Ca^{2+} release channels, calcineurin (PP2B), brain cAMP PDE, plant glutamate decarboxylase, the olfactory cAMP-gated Na^+ channel, retinal rod and cone cell cGMP-gated Na^+ channels, plant NAD^+ kinase, endothelial NO synthase (eNOS), phosphatidylinositol 3-kinase (PI3K), PM Ca^{2+} -ATPase and RNA helicase. It is clear from this list that many of these Ca^{2+} -dependent interactions involving CaM provide “cross-talk” between Ca^{2+} - and cyclic nucleotide-based signalling.

The Ca^{2+}_4 -CaM complex interacts with CaM-binding elements of the target effector proteins, which in many cases are amphipathic α -helices that can be envisaged as “cylindrical” structural elements in which one side of the cylinder is hydrophobic (i.e. water “fearing” or repelling) and the other side polar and hydrophilic (i.e. readily solvated by water molecules). Peptides of this kind can bind tightly to CaM. Thus, the bee venom peptide melittin has an amphipathic α -helical structure and binds tightly to Ca^{2+}_4 -CaM. Such CaM antagonists can be experimentally detected through inhibition of CaM-dependent enzymes (such as brain cAMP PDE or MLCK) or through fluorimetric detection of changes in the conformation of CaM. A number of plant defensive proteins interact with Ca^{2+}_4 -CaM as do some plant-derived secondary metabolites (Table 7.1).

7.3 Adenylyl cyclase

Adenylyl cyclase catalyses the reaction $\text{ATP} \rightarrow \text{cAMP} + \text{pyrophosphate (PP}_i\text{)}$. Membrane-bound ACs are activated by hormones and NTs that act via G protein-linked receptors to generate AC-activating $\text{G}\alpha\text{s-GTP}$ (Chapter 5). Particular AC isoforms are activated by Ca^{2+} -calmodulin, this representing an example of “cross-talk” between cAMP and Ca^{2+} signalling pathways. As outlined in Chapter 5, $\text{G}\alpha\text{i-GTP}$ inhibits AC and hence lowers cAMP concentration. A variety of hormones and NTs act via GPCRs to either activate or inhibit AC and in turn a variety of plant-derived compounds interfere with these processes (Chapter 5). The plant-derived diterpene forskolin and related compounds directly activate AC (Table 7.2).

7.4 Membrane-bound and soluble guanylyl cyclases

Guanylyl cyclase catalyses the reaction $\text{GTP} \rightarrow \text{cGMP} + \text{pyrophosphate (PP}_i\text{)}$. Heart stress (e.g. atrial stretch due to increased blood pressure and hence increased cardiac muscle work)

signals release of the peptide hormone atrial natriuretic factor/peptide (ANF/ANP). ANP binds to PM-located ANP receptors (ANPR-A and ANPR-B) that are transmembrane receptors having an external ANP-binding domain and a tyrosine kinase-like, cytosolic GC domain. ANP binding activates the GC with resultant elevation of intracellular cGMP and ultimately decreased blood pressure through vascular dilation. Another ANP receptor is coupled via a G protein to decrease cAMP and increase Ca^{2+} via PLC activation and IP_3 generation.

A further type of PM-located GC is gastrointestinal (GI) C-type GC that is activated by the paracrine peptide hormone guanylin. Guanylin is secreted by GI cells and resultant GC activation and cGMP elevation results in increased Cl^- transport via the cystic fibrosis transmembrane conductance regulator (CFTR) into the intestinal lumen with resultant increased water flow. The *Escherichia coli* heat-stable enterotoxin mimics guanylin in activating this intestinal C-type GC and consequently causes diarrhoea.

Soluble, haem-containing GCs are activated by NO generated by NOSs that are either constitutive (eNOS) or inducible (iNOS). Constitutive eNOS is regulated through phosphorylation by AMP-dependent protein kinase (AMPK) and is also activated by CaM (these regulatory phenomena providing further examples of signalling pathway “cross-talk”). Soluble GC is also activated *in vivo* by carbon monoxide (CO) generated from haem by haem oxygenase 2 (HEO2) that catalyses the reaction $\text{haem} \rightarrow \text{biliverdin} + \text{Fe}^{3+} + \text{CO}$. Activation of soluble GC by NO successively results in elevated cGMP, activation of cGMP-dependent protein kinase (PKG), specific protein phosphorylation and vascular dilation. The antiangiogenic drug nitroglycerin acts by generating NO with the successive consequences of cGMP generation, PKG activation, coronary artery dilation and increased blood flow to the heart (Table 7.3).

7.5 Nitric oxide synthesis

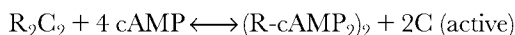
Nitric oxide is synthesized from the amino acid arginine in a reaction catalysed by NOS: $\text{L-arginine} + \text{O}_2 + \text{NADPH} \rightarrow \text{citrulline} + \text{NADP}^+ + \text{NO}$ (thiol, tetrahydrobiopterin, FMN and FAD being requisite cofactors in this process). NO subsequently acts by activating soluble GC, thereby successively causing elevation of cGMP and PKG activation. NO can also act by activating Ca^{2+} -dependent K^+ channels.

Nitric oxide and NOS can be constitutive or inducible. Constitutive nNOS and eNOS occur in neuronal and endothelial cells, respectively, and are activated by CaM. In endothelial cells acetylcholine, bradykinin or blood flow derived shear stress elevate cytosolic Ca^{2+} with the successive consequences of eNOS activation by CaM, NO production, GC activation by NO, elevation of cGMP, PKG activation, specific protein phosphorylation, vascular smooth muscle relaxation and vascular dilation.

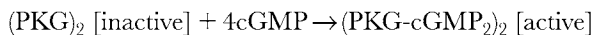
In immune responses iNOS is expressed in macrophages in response to bacterial lipopolysaccharide (LPS) and to cytokines such as interferon- γ (IFN- γ). The resultant elevated NO is cytotoxic through formation of reactive oxygen species (ROS), such as peroxynitrite (OONO^-), which react with and damage cellular constituents such as proteins. The induction of iNOS by IFN- γ and LPS successively involves ligand binding to PM receptors, downstream activation of inhibitor κB ($\text{I}\kappa\text{B}$) kinase ($\text{I}\kappa\text{BK}$), phosphorylation of $\text{I}\kappa\text{B}$, $\text{I}\kappa\text{B}$ proteolytic degradation, consequent activation (de-inhibition) of nuclear factor κB ($\text{NF}\kappa\text{B}$), translocation of $\text{NF}\kappa\text{B}$ to the nucleus and “switching on” of expression of iNOS as well as of enzymes such as COX-2 (inducible cyclooxygenase) (see Chapter 14).

7.6 Cyclic AMP- and cyclic GMP-dependent protein kinases

Cyclic AMP can act by opening cAMP-gated Na⁺ channels and hence depolarizing the PM (see Chapter 6) or by activating cAMP-dependent protein kinase (PKA) (Chapter 8). A further very specialized signalling function for cAMP is to act via specific 7 TM α -helix PM cAMP receptors as an extracellular aggregation-promoting agent in the slime mould *Dictyostelium discoideum*. PKA is heterotetrameric, the inactive holoenzyme subunit composition being R₂C₂ (where R = inhibitory cAMP-binding regulatory subunit and C = catalytic subunit). The catalytic subunit activity is inhibited by the regulatory subunits in the inactive holoenzyme but elevated cytosolic cAMP causes dissociation of the regulatory subunits and release of the now-active catalytic subunits:



Cyclic GMP (cGMP) can act to open cGMP-gated Na⁺ channels (and hence depolarize the PM) (see Chapter 5) and can also activate a dimeric cGMP-dependent protein kinase (PKG). PKG is homologous to PKA but differs from PKA in having cyclic nucleotide-binding regulatory domains and the catalytic domains on the same polypeptide chains, activation occurring through cGMP binding to the “autoinhibitory” regulatory domains:

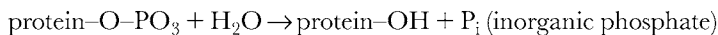


Activated PKA and PKG catalyse the transfer of the γ -phosphoryl (-PO₃) of ATP to a serine or threonine residue hydroxyl of their protein substrates with consequent changes in ligand binding and/or catalytic activity of the reversibly modified protein.

7.7 Protein kinase homologies and phosphoprotein phosphatases

The reversible phosphorylation of proteins with consequential change in protein function represents a major mechanism of signal transduction. While protein kinases are regulated by a variety of different mechanisms, the catalytic domains are homologous. Thus, a variety of plant substances that inhibit PKA by binding at or near the active site also inhibit other protein kinases (including tyrosine- as well as serine-/threonine-specific protein kinases). Accordingly, for economy and convenience, plant-derived inhibitors of Ca²⁺-, CaM- and cyclic nucleotide-dependent protein kinases, of other protein kinases and of PPs will be considered together in detail in Chapter 8.

Reversibility in signalling requires that phosphoproteins must ultimately be dephosphorylated. This is achieved by PPs that catalyse the following hydrolysis reaction:



There are many different kinds of PPs of which the best-known enzymes catalysing the dephosphorylation of serine- and threonine-phosphorylated proteins are PP1, PP2A, PP2B and PP2C. PP1 is inhibited by dinoflagellate-derived okadaic acid, by blue-green alga *Microcystis*-derived microcystins and by phosphorylated endogenous Inhibitor protein 1 (I1-P). PP2A is also inhibited by okadaic acid and microcystins but is less sensitive to these inhibitors than PP1. PP2B (calcineurin) is a CaM-activated, Ca²⁺-dependent PP having a catalytic A subunit and a CaM-like regulatory B subunit. PP2C is a Mg²⁺-dependent PP. A variety of other PPs catalyse the dephosphorylation of tyrosine-phosphorylated proteins (Chapter 8).

7.8 Cyclic nucleotide phosphodiesterases

Reversibility of signalling requires that second messenger concentrations are ultimately returned to the resting levels. The elevation of the cytosolic concentration of the second messengers cAMP and cGMP is rendered transient through the operation of cyclic nucleotide phosphodiesterases (PDEs) that catalyse the hydrolysis of the 3',5'-cyclic nucleoside monophosphates cAMP and cGMP to the corresponding non-cyclic 5'-nucleoside monophosphates adenosine 5'-monophosphate (5'-AMP) and guanosine 5'-monophosphate (5'-GMP), respectively.

A multiplicity of PDEs variously hydrolyse cAMP (cAMP PDEs), cGMP (cGMP PDEs) or both cyclic nucleotides. Particular brain cAMP PDEs are activated by CaM, this representing a further example of "cross-talk" between signalling pathways involving cAMP and Ca^{2+} as second messengers. In the process of vision, light reception by rhodopsin (a covalent complex of opsin protein with the chromophore 11-*cis*-retinal) successively results in retinal rod cell cGMP PDE activation by $\text{G}\alpha\text{t}$ -GTP (transducin) (Chapter 5), decreased cytosolic cGMP, closure of cGMP-gated Na^+ channels and cell membrane hyperpolarization that is communicated to the CNS.

Because of the importance of cyclic nucleotides as second messengers involved in regulation of smooth muscle and vascular dilation, PDEs are targets of particular drugs. Thus, a variety of plant-derived methylxanthines (notably tea- and coffee-derived caffeine and theophylline) inhibit cAMP PDEs (as well as interacting with some other targets). Inhibition of cAMP PDE successively results in elevation of cytosolic cAMP, PKA activation, phosphorylation of particular proteins, smooth muscle relaxation and consequent beneficial effects (such as bronchial dilation for asthmatics). Viagra (sildenafil), a synthetic analogue of the methylxanthine PDE inhibitors, selectively inhibits a specific PDE (cGMP PDE V) with the successive consequences of cGMP elevation, PKG activation, phosphorylation of particular proteins, vascular smooth muscle relaxation, vascular dilation, increased blood flow and penile erection (Table 7.4).

Table 7.1 Calmodulin

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Enzyme/process inhibited (other targets) in vivo effects </i>
Alkaloid		7.1a
Berberamine (= Berbenine) (bisbenzylisoquinoline)	<i>Berberis thunbergii</i> , <i>B. vulgaris</i> , <i>Mahonia aquifolium</i> (Berberidaceae), <i>Pycnarhena manillensis</i> , <i>Stephania sasakii</i> (Menispermaceae)	CaM-PDE [antitumour, antibacterial, curarizing, toxic, spasmolytic, vasodilatory]
Dauricine (bisbenzylisoquinoline)	<i>Menispermum dauricum</i> , <i>M. canadense</i> (Menispermaceae)	CaM-PDE [AL, anaesthetic, curarizing, hypotensive, toxic] [inhibits ADP-induced PA]
Daurisoline (bisbenzylisoquinoline)	<i>Menispermum dauricum</i> (Menispermaceae)	CaM-PDE (25), Dansyl-CaM-FC (1) (P-type Ca^{2+} channel) [inhibits ADP-induced PA]
[Daurisoline derivatives] (bisbenzylisoquinolines)	Semi-synthetic from Daurisoline	CaM-PDE (0.5–9), Dansyl-CaM-FC (0.5–9)
[O-(4-Ethoxybutyl) berbamine] (bisbenzylisoquinoline)	Semi-synthetic from Berbamine	CaM- Ca^{2+} -ATPase (0.4), CaM-PDE (2), Dansyl-CaM-FC (increased at 1)

(continued)

Table 7.1 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
(+)-Tetrandine (bisbenzylisoquinoline)	<i>Cissampelos pareira</i> , <i>Cyclea peltata</i> , <i>Stephania tetrandia</i> , <i>S. discolor</i> (Menispermaceae)	CaM-PDE (bovine), CaM-Ca ²⁺ - ATPase (40) [AI, analgesic, antipyretic]
Phenolic		7.1p
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	CaM-PDE (at 25), Dansyl-CaM-FC (at 25) (AR, F ₁ -ATPase, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, NEP, PS-EF-1 α , PK, RTK, TOPII) [AI, allergenic, antibacterial, antiviral]; major dietary flavonoid
Terpene		7.1t
Gossypol (dimeric phenolic sesquiterpenoid)	<i>Gossypium</i> spp. (cotton), <i>Montezuma speciosissima</i> , <i>Thespesia populnea</i> (Malvaceae) [seed]	CaM-Dansyl-CaM-FC (at 3) (Ca ²⁺ - ATPase, 11 β HSDH, PK) [antifungal, antitumour, inhibits spermatogenesis]
Other		7.10
<i>Brassica napin</i> large chains L1, L2 (10 kDa, 6 Cys)	<i>Brassica napus</i> (kohlrabi) (Brassicaceae) [seed]	CaM-MLCK (L1, 3; L2, 1)
<i>Brassica napin</i> small chains S1, S2, S3, S4 (5 kDa, 2 Cys)	<i>Brassica napus</i> (kohlrabi) (Brassicaceae) [seed]	CaM-MLCK (S1, 2; S2, 4; S3, 3; S4, 3)
<i>Brassica napin</i> (15 kDa, 8 Cys, S-L heterodimer)	<i>Brassica napus</i> (kohlrabi) (Brassicaceae) [seed]	CaM-MLCK (4), Dansyl-CaM-FC (at 10) [antifungal]
<i>Brassica napin</i> (15 kDa, 8 Cys, S-L heterodimer)	<i>Brassica napus</i> (rape) (Brassicaceae) [seed]	CaM-MLCK (4) [antifungal]
<i>Brassica napin</i> (15 kDa, 8 Cys, S-L heterodimer)	<i>Brassica rapa</i> (turnip) (Brassicaceae) [seed]	CaM-MLCK (2) [antifungal]
Oxalic acid (= Ethanedioic acid) (dicarboxylic acid)	<i>Chenopodium album</i> , <i>Spinacia oleracea</i> (Chenopodiaceae), <i>Oxalis</i> spp. (Oxalidaceae), <i>Cenchrus ciliaris</i> , <i>Digitaria decumbens</i> , <i>Pennisetum clandestinum</i> , <i>Setaria sphacelata</i> (Poaceae), <i>Fagopyrum esculentum</i> , <i>Rheum rhabonticum</i> (rhubarb) (Polygonaceae)	Ca ²⁺ chelator [toxic; prolonged feeding gives secondary hyperparathyroidism, bone mobilization & osteodystrophy in horses; hypocalcaemia in cattle & sheep (but greater rumen degradation)]
<i>Raphanus napin</i> small chains RCA1, RCA2, RCA3 (5 kDa, 2 Cys)	<i>Raphanus sativus</i> (radish) (Brassicaceae) [seed]	CaM-MLCK-RCA2 (7), RCA3 (2)
<i>Raphanus napin</i> (14 kDa, 8 Cys, S-L heterodimer)	<i>Raphanus sativus</i> (radish) (Brassicaceae) [seed]	CaM-PDE [CaM antagonist activity disappears during seed germination]
<i>Ricinus napin</i> small chains RS2A-D (5 kDa, 2 Cys)	<i>Ricinus communis</i> (castor bean) (Fabaceae) [seed]	CaM-MLCK (0.3); Dansyl-CaM-FC (at 10)

(continued)

Table 7.1 (Continued)

Compound (class)	Plant (family) / part/	Enzyme/process inhibited (other targets) / in vivo effects/
<i>Sinapis napin</i> small chains S1, S2, S3 (4 kDa, 2 Cys)	<i>Sinapis alba</i> (yellow mustard) (Brassicaceae) [seed]	CaM-MLCK (S1, 2; S2, 3; S3, 2)
<i>Sinapis napin</i> large chains L1, L2 (10 kDa, 6 Cys)	<i>Sinapis alba</i> (yellow mustard) (Brassicaceae) [seed]	CaM-MLCK (L1, 3; L2, 4)
<i>Sinapis napin</i> (15 kDa, S-L heterodimer)	<i>Sinapis alba</i> (yellow mustard) (Brassicaceae) [seed]	CaM-MLCK (2), Dansyl-CaM-FC
<i>Sinapis defensins</i> M1, M2A, M2B (6 kDa, 8 Cys, 4 S-S)	<i>Sinapis alba</i> (yellow mustard) (Brassicaceae) [seed]	CaM-MLCK (5 – M1), (6 – M2A); Dansyl-CaM-FC (M2A, M2B)
Non-plant reference		7.1n
[Calmidazolium] (chlorophenyl imidazole)	Synthetic CaM antagonist	CaM-Ca ²⁺ - ATPase (0.4)
[Chlorpromazine] (phenothiazine)	Synthetic	CaM (D-R) [antiemetic, antipsychotic, neuroleptic, tranquillizer]
[Melittin] (26 aa, 3 kDa, basic, amphipathic α -helical protein)	<i>Apis mellifica</i> (<i>mellifera</i>) (bee venom)	CaM antagonist [anti-rheumatic]
[Mitoxantrone] (anthraquinone)	Synthetic	Dansyl-CaM-FC (4) [anticancer drug, cytotoxic, immunomodulator]
[Ophiobolin A] (C25 terpene aldehyde)	<i>Cochliobolus setariae</i> , <i>Bipolaris</i> spp. (fungal pathogens on rice & maize)	CaM-PDE, CaM (reacts with lysine ϵ -NH ₂), PfcCDPK, Quercetin- stimulated intestinal Cl ⁻ secretion [phytotoxic]
[Purealin] (brominated polycyclic aryl imidazole)	<i>Psammaphysilla purea</i> (sea sponge)	CaM (cAMP PDE, MLCK)
[Trifluoperazine] (phenothiazine)	Synthetic CaM antagonist	CaM-PDE (8), PfcCDPK, Dansyl- CaM-FC (8), Quercetin-stimulated intestinal Cl ⁻ secretion [antipsychotic]
[N-(6-Aminoethyl)-5- chloro-1-naphthalene- sulfonamide (= W7)] (naphthalene- sulfonamide)	Synthetic	CaM antagonist, PfcCDPK

Table 7.2 Adenylyl cyclase and guanylyl cyclase

Compound (class)	Plant (family) / part/	Enzyme/process inhibited or activated (other targets) / in vivo effects/
Adenylyl cyclase (AC) activation	Earl Sutherland (USA, Nobel Prize, Medicine, 1971; cAMP as second messenger)	7.2A
Terpene 6-Acetyl-7- desacetylforskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae)	7.2At AC activator (rat brain) (40) [increases cAMP]

(continued)

Table 7.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) in vivo effects
9-Deoxyforskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae)	AC activator (rat brain) (100) [increases cAMP]
7-Desacetylforskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae)	AC activator (rat brain) (20) [increases cAMP]
1,9-Dideoxyforskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae)	Inactive as AC activator (nACh-R, Ca ²⁺ CH, MDR)
Forskolin (labdane diterpenoid)	<i>Coleus barbatus</i> , <i>C. forskohlii</i> (Lamiaceae)	AC activator (rat brain) (8) (nACh-R, Ca ²⁺ CH, MDR) [hypotensive, ↑ heart rate]
Other		7.2Ao
<i>Pyralaria</i> thionin (47 aa; 5 kDa; 8 Cys; 4 S-S; basic protein)	<i>Pyralaria pubera</i> (Santalaceae) [nut]	AC activator [per membrane PL interaction; cytotoxic, haemolytic, neurotoxic]
<i>Triticum</i> gliadin & gliadin peptides (peptides)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	Activates AC
Adenylyl (adenylate) cyclase (AC) inhibition		7.2B
Helénalin (sesquiterpene lactone)	<i>Arnica montana</i> , <i>Eupatorium perfoliatum</i> , <i>Helenium microcephalum</i> , <i>Inula helenium</i> (Asteraceae)	AC (at 100)
Hyménovin (sesquiterpene lactone)	<i>Hyménoxys richardsonii</i> (Asteraceae)	AC (at 100)
Lithospermic acid (phenylpropanoid, benzofuran)	<i>Cnicus benedictus</i> (Asteraceae), <i>Lycopus</i> spp., <i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AC (AO/FRS, ProH)
Lithospermic acid methyl ester (phenylpropanoid, benzofuran)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AC (AO/FRS, ProH)
Rosmarinic acid (phenylpropanoid)	<i>Anethum</i> , <i>Levisticum</i> , <i>Sanicula</i> , <i>Astrantia</i> (Apiaceae), <i>Symphytum</i> (Boraginaceae), <i>Lycopus</i> , <i>Melissa</i> , <i>Mentha</i> , <i>Ocimum</i> , <i>Oreganum</i> , <i>Prunella vulgaris</i> , <i>Rosmarinus</i> , <i>Teucrium</i> , <i>Salvia</i> , <i>Thymus</i> (Lamiaceae) spp.	AC (AR, COX-1, COX-2, HIV-1 INT) [AI; antiviral]
Rosmarinic acid methyl ester (phenylpropanoid)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AC (AR, COX-1, COX-2) [AI; antiviral]
Guanylyl (guanylate) cyclase (GC) activation	Robert Furchgott, Louis Ignarro & Ferid Murad (USA, Nobel Prize, Physiology/Medicine, 1998, NO, GC activation, vasodilation)	7.2C
Alkaloid		7.2Ca
Indole-3-acetic acid (= Auxin; IAA) (indole)	Universal in plants (plant hormone)	GC stimulation (at 1) [plant hormone; cell wall & cell expansion]

(continued)

Table 7.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects/
Terpene		7.2Ct
Gibberellic acid (gibbane diterpenoid)	Universal in plants (plant hormone); <i>Gibberella fujikuroi</i> (<i>Fusarium moniliforme</i>) plant pathogenic fungus (causes excessive growth in rice – Japan “ foolish rice seedling disease ”)	GC activation (10 pM to 1 mM) [plant hormone; breaks seed dormancy; barley seed aleurone α -amylase induction in brewing]
Ginsenosides (triterpene saponins)	<i>Panax ginseng</i> (Araliaceae)	Increase GC & cGMP via increased NO
Other		7.2Co
Carbon monoxide (= CO) (carbon oxide)	From combustion of carbon-containing compounds; brain neurotransmitter formed by haem oxygenase (HO) type HO ₂ ; used for execution of criminals by Romans & Greeks; biggest gaseous cause of human death; >6% motor vehicle exhaust	GC activation (ETC, Hb) [extremely toxic; blocks O ₂ -Hb formation; motor vehicle exhaust CO used in mass murder of Jews in WW2 by Nazi SS
Cigarette smoke (tars, NO)	<i>Ex. Nicotiana tabacum</i> (tobacco) (Solanaceae)	GC activation (mediated by NO?) [antihypertensive, vasodilatory]
3-Nitropropionic acid (aliphatic carboxylic acid)	<i>Astragalus membranaceus</i> , <i>A. spp.</i> (Fabaceae) – Huang-Qi, Chinese tonic	GC activation [antihypertensive, vasodilatory]
Nitric oxide (= NO) (nitrogen oxide)	Universal	Soluble GC activation
Plant protein binding anti-ANP antibodies (protein)	<i>Metasequoia glyptostroboides</i> (dawn red-wood) (Taxodiaceae) “ discovered ” in Szechuan, China (1945)	Animal ANP activates plant GC
Non-plant reference		7.2Cn
[Atrial natriuretic peptide (= ANP; Atrial natriuretic factor; ANF)] (protein)	Animals <i>ex</i> stressed heart	Activates PM GC (ANPR-A & ANPR-B) – via NPR-A & NPR-B (guanylyl cyclase-coupled receptors); induces plant stomatal opening inhibited by GC inhibitors LY83583 & Methylene blue
[N ⁶ -Benzyladenine] (purine)	Synthetic cytokinin	GC stimulation (at 1) [mitogenic in plants]
[<i>Escherichia coli</i> enterotoxin] (heat-stable protein)	Diarrhoea-producing <i>Escherichia coli</i> strains (anaerobic intestinal bacteria)	Activates C-type PM GC [CFTR activation, \uparrow Cl ⁻ & H ₂ O transport & diarrhoea]
[Guanylin] (2 kDa, 15 aa, 4 Cys protein)	Animals <i>ex</i> endocrine Paneth cells in small intestinal crypts of Lieberkühn	Activates C-type PM GC [ultimately CFTR activation & \uparrow Cl ⁻ & H ₂ O transport]

(continued)

Table 7.2 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects/
[Kinetin (= N^6 -Furfuryladenine)] (purine)	From DNA breakdown	Putatively activates GC (mimics ANP-induced stomatal opening inhibited by GC inhibitors LY83583 & Methylene blue
[Nitroglycerin (= Glycerol trinitrate)] (alkanol nitrate)	Synthetic; generates nitric oxide (NO); highly explosive (e.g. dynamite) – stabilized by Alfred Nobel (1866) (his brother & 4 workers died in experiments); guilt over war-use led to Nobel Prize bequest	Soluble GC activation by NO
Guanylyl (guanylate) cyclase (GC) inhibition		7.2D
[6-Anilino-5,8-quinoline-dione (=LY83583)] (aniline quinoline)	Synthetic	GC
[Methylene blue] (phenothiazine)	Synthetic	GC
[1H-(1,2,4)-Oxadiazole[4,3-a]quinoxaline-1-one (=ODQ)] (oxadiazole)	Synthetic	GC

Table 7.3 Nitric oxide synthesis

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects/
iNOS expression		7.3A
Alkaloid		7.3Aa
Higenamine (= (+/-)-Demethylcoclaurine racemic mixture) (bisbenzylisoquinoline)	<i>Annona squamosa</i> (Annonaceae), <i>Asiasarum heterotropoides</i> (Aristolochiaceae), <i>Aconitum japonicum</i> (Ranunculaceae) [aconite root], <i>Evodia rutaecarpa</i> (Rutaceae), <i>Nelumbo nucifera</i> (Nelumbonaceae)	↓ iNOS expression [inhibits NFκB activation & LPS- & IFN-γ-induced macrophage iNOS expression]
Oleandrin (cardenolide, cardiac glycoside)	<i>Nerium oleander</i> (oleander) (Apocynaceae) [leaf]	(Inhibits LPS- & TNF-induced AP-1 & NFκB activation) (Na^+ , K^+ -ATPase)

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects/
Thaliporphine (aporphine isoquinoline)	<i>Neolitsea konishii</i> (Lauraceae)	↓ iNOS expression [inhibits LPS-induced macrophage iNOS expression]
Tryptanthrine (= Couroupitine A) (quinazoline)	<i>Strobilanthes cusia</i> (Acanthaceae), <i>Isatis tinctoria</i> (woad) (Brassicaceae), <i>Couroupita guaianensis</i> (Lecithidaceae), <i>Polygonum tinctorum</i> (Polygonaceae); woad yielded blue dye and body paint of ancient Britons e.g. Boadicea	↓ iNOS expression (at 20) (AH-R, COX-2) [inhibits NO & PGE2 production]
Phenolic		7.3Ap
Anomalin (= acylated Khellactone) (coumarin)	<i>Angelica furcijuga</i> (Apiaceae) [root]	↓ iNOS expression [blocks LPS-induced macrophage iNOS expression; hepatoprotective]
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	<i>Apium graveolens</i> (Apiaceae), <i>Anisochilus</i> , <i>Mentha</i> , <i>Thymus</i> (Lamiaceae) spp., ferns [leaf surface]; <i>Digitaria exilis</i> (Poaceae) [seed]; as glycoside in <i>Apium graveolens</i> , <i>Petroselinum</i> (Apiaceae), <i>Cosmos bipennatus</i> , <i>Erigeron annuus</i> , <i>Dahlia variabilis</i> (Asteraceae), <i>Amorpha fruticosa</i> (Fabaceae)	↓ iNOS (& COX-2) expression (per IKK inhibition) (BZ-R-like R, EGF-RTK, EST-R, Na ⁺ /K ⁺ /Cl ⁻ TR, PK, RTK, TPO) [antibacterial, AI, diuretic, hypotensive]
Bilobetin (biflavone)	<i>Araucaria bidwillia</i> (monkey puzzle tree) (Araucaria), <i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [leaf]	↓ iNOS (& COX-2, TNF-α) (PLA ₂) [inhibits LPS-induced macrophage iNOS (& COX-2, TNF-α) expression]
Caffeic acid phenethyl ester (phenylpropanoid)	<i>Populus</i> sp. (Salicaceae), bee propolis	Blocks NFκB activation (AO/FRS, apoptotic, HIV-1 INT, 5-LOX) [AI, antioxidant]
Casuarinin (hydrolysable tannin)	<i>Melastoma dodecandrum</i> (Melastomaceae), <i>Punica granatum</i> (Punicaceae)	↓ iNOS expression (~5)
Casuarictin (hydrolysable tannin)	<i>Melastoma dodecandrum</i> (Melastomaceae)	↓ iNOS expression (~5)
Cnidicin (coumarin)	<i>Angelica koreana</i> (Apiaceae) [root]	↓ iNOS expression [inhibits induced macrophage iNOS expression]
Curcumin (= Diferuloylmethane; Turmeric yellow) (phenylpropanoid)	<i>Curcuma longa</i> (turmeric), <i>C. aromatica</i> , <i>C. xanthorrhiza</i> , <i>C. zedoaria</i> , <i>Zingiber officinale</i> (Zingiberaceae) [root]	↓ iNOS expression (CDPK, HIV-1-INT, IKK, PhosbK, PKA, PKC, p60 ^{src} TK, TYR) [AI, anti-oxidant, hypoglycaemic, cytotoxic]
Daidzein (isoflavone)	<i>Genista tinctoria</i> , <i>Glycine max</i> (soya), <i>Phaseolus</i> , <i>Psoralea</i> , <i>Pueraria</i> , <i>Sophora</i> , <i>Trifolium</i> , <i>Vigna</i> (Fabaceae) spp. [seed]	↓ iNOS expression (iNOS) [LPS-induced macrophage iNOS expression]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited or activated (other targets) / in vivo effects
(-)-Epigallocatechin 3-gallate (flavan-3-ol)	<i>Camellia sinensis</i> (tea leaf) (Theaceae), <i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark]	↓ iNOS expression (EST-R, PK, proteasome, 5 α R, RTK) [inhibits TNF α expression; oxidation products give tea taste]
Ferulaldehyde (= Coniferaldehyde; Coniferyl aldehyde) (phenylpropanoid)	<i>Acer saccharinum</i> (Aceraceae), <i>Cinnamomum verum</i> , <i>Sassafras albidum</i> (Lauraceae), <i>Senra incana</i> (Bombacaceae), <i>Linum usitatissimum</i> (Linaceae), <i>Quercus</i> sp. (Fagaceae), <i>Juglans cinerea</i> (Juglandaceae), <i>Fraxinus rhynchophylla</i> (Oleaceae), <i>Sequoia</i> sp. (Taxodiaceae)	↓ iNOS expression (COX) [inhibits LPS- & IFN- γ -induced macrophage iNOS expression; antifungal, phytoalexin (<i>Linum</i>)]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Genista</i> spp., <i>Glycine max</i> , <i>Phaseolus</i> , <i>Trifolium</i> (Fabaceae) spp., <i>Prunus</i> spp. (Rosaceae) [wood]; glucosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora japonica</i> (Fabaceae)	↓ iNOS expression (AD-R, GABAA-R, HISK, lipase, Na ⁺ /K ⁺ /Cl ⁻ TR, peroxidase, PK, RTK, TOPII, TPO) [inhibits LPS-induced macrophage iNOS expression; antifungal, oestrogenic]
Ginkgetin (biflavone)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [fruit, leaf]	↓ iNOS (& COX-2, TNF- α) (PLA ₂) [inhibits LPS-induced macrophage iNOS expression]
Glycitein (isoflavone)	<i>Glycine max</i> (soya) (Fabaceae) [seed]	↓ iNOS expression (iNOS) [inhibits LPS-induced macrophage iNOS expression]
Hinokiol (lignan)	<i>Tetraclinis articulata</i> (Cupressaceae), <i>Magnolia obovata</i> , <i>M. officinalis</i> (Magnoliaceae) [stem bark]	↓ iNOS expression (6) [inhibits LPS-induced macrophage iNOS expression]
Hirsutanonol (diarylheptanoid)	<i>Alnus hirsuta</i> (Betulaceae) [leaf]	↓ iNOS expression (14) [blocks LPS- & IFN- γ -induced macrophage iNOS expression]
Hypericin (bianthraquinone)	<i>Hypericum perforatum</i> (St John's wort), <i>H.</i> spp. (Hypericaceae); popular antidepressant herbal medicine	Blocks NF κ B activation ((HIV-1 INT, PI3K, PK, RTK) [photosensitising, red pigment]
Hyuganins A, B, C & D (= acylated Khellactones) (coumarins)	<i>Angelica furcijuga</i> (Apiaceae) [root]	↓ iNOS expression) [blocks LPS-induced macrophage iNOS expression; hepatoprotective]
Isoepoxypteryxin (= acylated Khellactone) (coumarin)	<i>Angelica furcijuga</i> (Apiaceae) [root]	↓ iNOS expression) [blocks LPS-induced macrophage iNOS expression; hepatoprotective]
Isopteryxin (= acylated Khellactone) (coumarin)	<i>Angelica furcijuga</i> (Apiaceae) [root]	↓ iNOS expression) [blocks LPS-induced macrophage iNOS expression; hepatoprotective]
β -Lapachone (naphthoquinone)	<i>Tabebuia</i> sp. (trumpet tree) (Bignoniaceae)	↓ iNOS expression (TOPII) [inhibits LPS-induced macrophage iNOS expression; cytotoxic, pro-apoptotic]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
Magnolol (lignan)	<i>Sassafras randaiense</i> (Lauraceae) [root], <i>Magnolia obovata</i> , <i>M. officinalis</i> (Magnoliaceae) [stem bark]	↓ iNOS expression (17) [inhibits LPS-induced macrophage iNOS expression]
Nobotannin B (hydrolysable tannin)	<i>Melastoma dodecandrum</i> (Melastomaceae)	↓ iNOS expression (~5)
Pedunculagin (hydrolysable tannin)	<i>Melastoma dodecandrum</i> (Melastomaceae)	↓ iNOS expression (~5)
Piceatannol (= 3,3',4,5'-Tetrahydroxystilbene) (stilbene)	<i>Laburnum anagyroides</i> (Fabaceae) [wood], <i>Morus alba</i> (Moraceae), <i>Picea</i> spp., <i>Pinus</i> spp., <i>Tsuga canadensis</i> (Pinaceae), <i>Rheum</i> spp. (rhubarb) (Polygonaceae)	↓ iNOS expression (CDPK, MLCK, PKA, PKC, p56 ^{lck} TK, p40 TK) [inhibits LPS-induced macrophage NO production; antifungal, inhibits NFκB activation]
Praeroside (coumarin glycoside)	<i>Angelica furcijuga</i> (Apiaceae) [root]	↓ iNOS expression [blocks LPS-induced macrophage iNOS expression; hepatoprotective]
Pteryxin (= acylated Khellactone) (coumarin)	<i>Angelica furcijuga</i> (Apiaceae) [root]	↓ iNOS expression [blocks LPS-induced macrophage iNOS expression; hepatoprotective]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Rhododendron cinnabarium</i> (Ericaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	↓ iNOS expression (LPS- & IFN-γ-stimulated macrophage) (AR, cAMP PDE, CFTR, F ₁ -ATPase, 11βHSDH, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, NEP, PK, PS-EF-1α, RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
cis- & trans-Resveratrol (stilbene)	<i>Cassia dentata</i> , <i>Intsia bijuga</i> , <i>Trifolium dubium</i> (Fabaceae), <i>Nothofagus</i> spp. (Fagaceae), <i>Veratrum grandiflorum</i> (Liliaceae), <i>Artocarpus</i> spp., <i>Morus</i> spp. (Moraceae), <i>Eucalyptus wandoo</i> (Myrtaceae), <i>Pinus</i> spp. (Pinaceae), <i>Polygonum</i> spp., <i>Rheum</i> spp. (Polygonaceae), <i>Vitis vinifera</i> (Vitaceae)	↓ iNOS expression (LPS- & IFN-γ-stimulated macrophage) [inhibits NFκB activation, inhibits LPS-induced macrophage NO production] (EST-R, p56 ^{lck} TK)
Rhaponticin-2''-O-gallate (stilbene glucoside gallate)	<i>Rheum</i> spp. (rhubarb) (Polygonaceae)	↓ iNOS expression [inhibits NFκB activation, inhibits LPS-induced macrophage NO production]
Rhaponticin-6''-O-gallate (stilbene glucoside gallate)	<i>Rheum</i> spp. (rhubarb) (Polygonaceae)	↓ iNOS expression [inhibits NFκB activation, inhibits LPS-induced macrophage NO production]
Rhapontigenin (stilbene)	<i>Rheum rhabarbarum</i> , <i>R.</i> spp. (rhubarb) (Polygonaceae) [root]	↓ iNOS expression [inhibits NFκB activation, inhibits LPS-induced macrophage NO production]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited or activated (other targets) / in vivo effects
Savinin (dibenzylbutyrolactone lignan)	<i>Pterocarpus santalinus</i> (sandalwood) (Santalaceae)	Inhibits TNF- α expression (LPS-activated macrophages & ConA-stimulated T cells)
Scopoletin (= 6-Methoxyumbelliferone) (coumarin)	Widespread; <i>Nerium odorum</i> (Apocynaceae) [flower], <i>Artemisia afra</i> , <i>A. feddei</i> (Asteraceae), <i>Convolvulus scammonia</i> , <i>Ipomoea orizabensis</i> (Convolvulaceae), <i>Diospyros maritima</i> (Ebenaceae), <i>Gelsemium sempervirens</i> (Loganaceae), <i>Avena sativa</i> (Poaceae), <i>Prunus serotina</i> (Rosaceae), <i>Atropa belladonna</i> (Solanaceae)	↓ iNOS expression [LPS- & IFN- γ -induced macrophage iNOS; antibacterial, antifungal, hypotensive, spasmolytic]
Suksdorfina (= acylated Khellactone) (coumarin)	<i>Angelica furcijuga</i> (Apiaceae) [root]	↓ iNOS expression [blocks LPS-induced macrophage iNOS expression; hepatoprotective]
Theaflavin (= mixture of Theaflavine-3-gallate, Theaflavin-3'-gallate & Thearubigin) (flavanol)	<i>Camellia chinensis</i> (tea leaf) (Theaceae)	↓ iNOS expression [blocks IKK, NF κ B activation, iNOS expression & hence inhibits activated macrophage NO production]
Theaflavin-3,3'-digallate (flavanol)	<i>Camellia chinensis</i> (tea leaf) (Theaceae)	↓ iNOS expression [blocks IKK, NF κ B activation, iNOS expression]
Torachryson 8-O- β -D-glucopyranoside (naphthalene glycoside)	<i>Rheum</i> spp. (rhubarb) (Polygonaceae)	↓ iNOS expression [inhibits NF κ B activation, inhibits LPS-induced macrophage NO production]
Wogonin (= Norwogonin 8-methyl ether) (flavone)	<i>Anodendron affine</i> (Apocynaceae) [stem], <i>Scutellaria baicalensis</i> , <i>S. discolor</i> , <i>S. galericulata</i> (Lamiaceae) [root]	↓ iNOS expression (COX-2, 12-LOX) [oestrogenic, anti-implantation]
Terpene		7.3At
15-Acetoxy-eremantholide B (germacranolide sesquiterpene lactone)	Asteraceae	NF κ B activation blocked (1) (& hence cytokine, TNF- α & iNOS expression)
Costunolide (germacranolide sesquiterpene lactone)	<i>Artemisia dracuncululus</i> , <i>Saussurea lappa</i> (costus root oil) (Asteraceae), <i>Laurus nobilis</i> (bay laurel) (Lauraceae)	↓ iNOS expression (3) (FPTase) [blocks IKK, NF κ B activation, iNOS expression; anti-schistosomal, antitumour, dermatitic]
Dehydrocostus lactone (sesquiterpene)	<i>Saussurea lappa</i> (castus, mu xiang) (Asteraceae); root extract Indian Ayurvedic aphrodisiac (oil irritates urethra & induces painful erection) ; <i>Laurus nobilis</i> (Lauraceae)	↓ iNOS (& TNF- α) macrophage expression induced by LPS (per inhibiting NF κ B activation) (3) [anti-endotoxaemia potential]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
EGb, EGb 761 (= <i>Ginkgo biloba</i> leaf extracts) (triterpene glycoside saponins)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [leaf]	↓ iNOS expression (endothelial cells)
2β,5-Epoxy-5,10-dihydroxy-6α-angeloyloxy-9β-isobutyloxy germacran-8α,12-olide (germacranolide sesquiterpene lactone)	<i>Carpesium divaricatum</i> (Asteraceae)	↓ iNOS expression [per inhibiting NFκB activation]
4β,15-Epoxy-miller-9E-enolide (germacranolide sesquiterpene lactone)	Asteraceae	NFκB activation blocked (& hence cytokine, TNF-α & iNOS expression)
Eremanthine (guaianolide sesquiterpene lactone)	<i>Eremanthus</i> , <i>Lychnophora</i> , <i>Vamillosmopsis</i> , <i>Vernonia</i> spp. (Asteraceae), <i>Laurus nobilis</i> (Lauraceae)	↓ iNOS expression (3) [blocks NFκB activation]
Ergolide (sesquiterpene lactone)	<i>Inula britannica</i> (Asteraceae)	↓ iNOS expression [per NFκB inactivation]
Excisanin A (kaurane diterpene)	<i>Isodon japonicus</i> (Lamiaceae)	↓ iNOS expression [blocks LPS-induced macrophage NFκB activation, iNOS & COX-2 expression & NO & PGE2 production]
Genipin (iridoid monoterpene lactone)	<i>Gardenia jasminoides</i> , <i>Genipa americana</i> (Rubiaceae)	↑ NOS [neuritogenic like nerve growth factor NGF (effects of both blocked by NOS & GC inhibitors); ↑ bile flow]
Geniposide (= Genipin glucoside) (iridoid monoterpene lactone glycoside)	<i>Cornus</i> sp. (Cornaceae), <i>Gardenia jasminoides</i> , <i>Genipa americana</i> (Rubiaceae), <i>Euphrasia officinalis</i> (Scrophulariaceae)	Yields Genipin [laxative]
15-(2-Hydroxy)-isobutyryloxy-micrantholide (germacranolide sesquiterpene lactone)	Asteraceae	NFκB activation blocked (38) (& hence cytokine, TNF-α & iNOS expression)
Hypoestoxide (diterpene)	<i>Hypoestes rosea</i> (Acanthaceae)	↓ iNOS expression (IKK) [blocks LPS-induced monocyte iNOS, TNF-α, IL-1β & IL-6 expression]
15-Isovaleroyl & 15-(2-methylbutyryl)-2α-acetoxymiguanin (germacranolide sesquiterpene lactone)	Asteraceae	NFκB activation blocked (1) (& hence cytokine, TNF-α & iNOS expression)
Kamebacetal A (kaurane diterpene)	<i>Isodon japonicus</i> (Lamiaceae)	↓ iNOS expression [blocks LPS-induced macrophage NFκB activation, iNOS & COX-2 expression & NO & PGE2 production]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited or activated (other targets) / in vivo effects
Kamebakaurin (kaurane diterpene)	<i>Isodon japonicus</i> (Lamiaceae)	↓ iNOS expression [blocks LPS-induced macrophage NFκB activation, iNOS & COX-2 expression & NO & PGE2 production]
Karnebanin (kaurane diterpene)	<i>Isodon japonicus</i> (Lamiaceae)	↓ iNOS expression [blocks LPS-induced macrophage NFκB activation, iNOS & COX-2 expression & NO & PGE2 production]
Labdane F2 (= ent-8α-Hydroxy-labda-13(16), 14-diene) (diterpene)	<i>Sideritis javalambrensis</i> (Lamiaceae)	↓ iNOS (& COX-2) expression [blocks LPS-induced macrophage iNOS & COX-2 expression]
Magnolialide (sesquiterpene lactone)	<i>Laurus nobilis</i> (Lauraceae)	↓ iNOS expression (3) [blocks NFκB activation]
Parthenolide (germacranolide sesquiterpene lactone)	<i>Ambrosia</i> sp., <i>Arctotis</i> sp., <i>Chrysanthemum parthenium</i> , <i>Tanacetum vulgare</i> (Asteraceae), <i>Michelia</i> spp. (Magnoliaceae)	Inactivates NFκB (alkylates p65 subunit at cysteine 38)
Pristimerin (friedelane triterpene)	<i>Catha edulis</i> , <i>Maytenus</i> sp., <i>Pristimera indica</i> , <i>Schaefferia cuneifolia</i> (Celastraceae)	↓ iNOS, COX-2 expression [antibacterial, antitumour, germination inhibitor, toxic]
Santamarine (= Balchanin) (eudesmanolide sesquiterpene lactone)	<i>Ambrosia confertiflora</i> , <i>Artemisia</i> spp., <i>Tanacetum vulgare</i> (Asteraceae), <i>Laurus nobilis</i> (Lauraceae), <i>Michelia compressa</i> (Magnoliaceae)	↓ iNOS expression (3) [blocks NFκB activation]
Spirafolide (sesquiterpene lactone)	<i>Laurus nobilis</i> (Lauraceae)	↓ iNOS expression (3) [blocks NFκB activation]
Tryptotoquinone A (diterpene)	<i>Tripterygium wilfordii</i> (Celastraceae)	↓ iNOS & IL-1β expression induced by LPS [~ Dexamethosone; AI]
Zaluzanin C (guaianolide sesquiterpene lactone)	<i>Podachaenium eminens</i> , <i>Vernonia</i> spp., <i>Zaluzania</i> spp., <i>Zinnia acerosa</i> (Asteraceae), <i>Laurus nobilis</i> (Lauraceae)	↓ iNOS expression (3) [blocks NFκB activation]
Other		7.3Ao
18-Acetoxy-octadeca-1,9-dien-4,6-diyne-3,8-diol (polyacetylene)	<i>Angelica gigas</i> (Apiaceae)	↓ iNOS expression [blocks induced macrophage iNOS expression]
Acidic polysaccharide (polysaccharide)	<i>Panax ginseng</i> (Araliaceae)	↑ iNOS [induces iNOS in macrophage ± IFN-γ]
Ajoene (aliphatic disulfide)	<i>Allium sativum</i> (garlic) (Liliaceae) [bulb]	↓ iNOS expression (at 5) [antithrombotic]
Alicin (aliphatic disulfide)	<i>Allium cepum</i> (onion), <i>A. sativum</i> (garlic) (Liliaceae) [bulb]	↓ iNOS expression (at 20) [antibacterial, antidiabetic, antihypertensive, antithrombotic, odorant]
Angelan (polysaccharide)	<i>Angelica gigas</i> (Apiaceae)	↑ iNOS [LPS mimetic; induces macrophage iNOS per NFκB activation]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
Falcarindiol (polyacetylene ketone)	<i>Angelica furcijuga</i> , <i>A. sinensis</i> , <i>Apium graveolens</i> , <i>Daucus carota</i> , <i>Saposhnikovia divaricata</i> (Apiaceae), <i>Lycopersicon esculentum</i> (Solanaceae) [leaf] (phytoalexin)	↓ iNOS expression (2) [blocks LPS- & IFN- γ -induced macrophage iNOS expression, dermatitic, phytoalexin]
Falcarinol (polyacetylene alcohol)	<i>Angelica furcijuga</i> , <i>A. sinensis</i> , <i>Daucus carota</i> , <i>Falcaria vulgaris</i> , <i>Oenanthe crocata</i> (Apiaceae) [root], <i>Hedera helix</i> , <i>Schefflera arboricola</i> (Araliaceae), <i>Lycopersicon esculentum</i> (Solanaceae)	↓ iNOS expression (5-LOX) [blocks LPS-induced macrophage iNOS expression, dermatitic]
Falcarinone (polyacetylene ketone)	<i>Angelica sinensis</i> , <i>Apium graveolens</i> , <i>Carum carvi</i> , <i>Comium maculatum</i> , <i>Falcaria vulgaris</i> [root], <i>Oplopanax chironium</i> , <i>Petroselinum crispum</i> , <i>Saposhnikovia divaricata</i> (Apiaceae), <i>Hedera helix</i> (Araliaceae)	↓ iNOS expression (>20) [blocks LPS- & IFN- γ -induced macrophage iNOS expression, dermatitic, phytoalexin]
Octadeca-1,9-dien-4,6-diyn-3,8,18-triol (polyacetylene)	<i>Angelica gigas</i> (Apiaceae)	↓ iNOS expression [blocks induced macrophage iNOS expression]
Oregonin (diarylheptanoid)	<i>Alnus hirsuta</i> (Betulaceae) [leaf]	↓ iNOS expression (4) [blocks LPS- & IFN- γ -induced macrophage iNOS expression]
Panaxydol (polyacetylene ketone)	<i>Panax ginseng</i> , <i>P. quinquefolium</i> (Araliaceae)	↓ iNOS expression (7) [blocks LPS- & IFN- γ -induced macrophage iNOS expression]
Panaxynol (polyacetylene ketone)	<i>Panax ginseng</i> , <i>P. quinquefolium</i> (Araliaceae)	↓ iNOS expression (2) (HPGDH, 5-LOX) [blocks LPS- & IFN- γ -induced macrophage iNOS expression]
Panaxytriol (polyacetylene ketone)	<i>Panax quinquefolium</i> (Araliaceae)	↓ iNOS expression (10) [blocks LPS- & IFN- γ -induced macrophage iNOS expression]
Perseone A (long-chain aliphatic ester)	<i>Persea americana</i> , <i>P. spp.</i> (avocado) (Lauraceae)	Blocks LPS- & IFN- γ -induced iNOS (& COX-2) expression (at 20) [AI]
Saffron proteoglycan (proteoglycan)	<i>Crocus sativus</i> (saffron) (Iridaceae) [corm]	↑ iNOS [induces macrophage NF κ B activation, iNOS expression & NO production]
Taxol (= Paclitaxel; Taxol A) (polycyclic peptide)	<i>Cephalotaxus mannii</i> (Cephalotaxaceae), <i>Taxus baccata</i> , <i>T. brevifolia</i> , <i>T. cuspidata</i> , <i>T. spp.</i> (yew) (Taxaceae); Briton king Catuvolcus committed suicide by drinking yew sap	Mimics LPS (in mouse but not man) ↑ iNOS (induces macrophage NF κ B activation, iNOS expression) (TUB) [antitumour]
[3,8,18-Triacetoxyoctadeca-1,9-dien-4,6-diyn] (polyacetylene)	Semi-synthetic from acetylation of Octadeca-1,9-dien-4,6-diyn-3,8,18-triol from <i>Angelica gigas</i> (Apiaceae)	↓ iNOS expression [blocks induced macrophage iNOS expression]
Induced in vivo NO production (probably per iNOS expression)		7.3B

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited or activated (other targets) / in vivo effects
Alkaloid		7.3Ba
4,8-Dimethoxy-1-vinyl- β -carboline (β -carboline)	<i>Melia azedarach</i> (Meliaceae)	↓ NO [blocks macrophage LPS- & IFN- γ -induced NO]
4-Methoxy-1-vinyl- β -carboline (β -carboline)	<i>Melia azedarach</i> (Meliaceae)	↓ NO [blocks macrophage LPS- & IFN- γ -induced NO]
Sinomenine (morphinan isoquinoline)	<i>Sinomenium acutum</i> (Menispermaceae)	↓ NO [blocks macrophage LPS- & IFN- γ -induced NO; AI, analgesic, anti-rheumatic]
Phenolic		7.3Bp
Batatasin III (phenolic)	<i>Scaphyglottis livida</i> (Orchidaceae)	↑ NO [↑ NO (inhibited by L-NAME) & hence ↑ cGMP (inhibited by ODQ); spasmolytic]
Bergamottin (coumarin)	<i>Citrus aurantiifolia</i> (lime), <i>C. hystrix</i> , <i>C. limon</i> (lemon), <i>C. paradisi</i> (grapefruit) (Rutaceae) [fruit]	↓ NO (14) [blocks macrophage LPS- & IFN- γ -induced NO]
Casuarictin (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Osbeckia</i> (Melastomaceae), <i>Eucalyptus</i> , <i>Psidium</i> , <i>Syzygium</i> (Myrtaceae), <i>Rubus</i> (Rosaceae), <i>Stachyurus</i> (Stachyuraceae) spp.	↓ NO [blocks macrophage LPS-induced NO]
Casuarinin (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Quercus</i> (Fagaceae), <i>Liquidambar</i> (Hamamelidaceae), <i>Osbeckia</i> (Melastomaceae), <i>Eucalyptus</i> , <i>Feijoa</i> (Myrtaceae), <i>Punica granatum</i> (Punicaceae), <i>Stachyurus</i> (Stachyuraceae) spp.	↓ NO (CA) [blocks macrophage LPS-induced NO]
Ciliatoside A (lignan glycoside)	<i>Justicia ciliata</i> (Acanthaceae) [whole plant]	↓ NO [blocks macrophage LPS-induced NO (27)]
Ciliatoside B (lignan glycoside)	<i>Justicia ciliata</i> (Acanthaceae) [whole plant]	↓ NO [blocks macrophage LPS-induced NO (29)]
Coelonin (phenolic)	<i>Scaphyglottis livida</i> (Orchidaceae)	↑ NO [↑ NO (inhibited by L-NAME) & hence ↑ cGMP (inhibited by ODQ); spasmolytic]
[<i>trans</i> -Dehydroosthol] (prenyl coumarin)	Semi-synthetic from Osthol	↓ NO (<50) [blocks macrophage LPS- & IFN- γ - induced NO]
7-Demethylsuberosin (prenyl coumarin)	<i>Angelica dahurica</i> (Apiaceae) [root]	↓ NO (<50) [blocks macrophage LPS- & IFN- γ -induced NO]
Dentatin (coumarin)	<i>Clausenia harmandiana</i> (Rutaceae)	↓ NO (<10) [blocks macrophage LPS- & IFN- γ -induced NO; anti-plasmodial]
3,4'-Dihydroxy-5,5'-dimethoxybibenzyl (phenolic)	<i>Scaphyglottis livida</i> (Orchidaceae)	↑ NO [↑ NO (inhibited by L-NAME) & hence ↑ cGMP (inhibited by ODQ); spasmolytic]
3,7-Dihydroxy-2,4-dimethoxyphenanthrene (phenolic)	<i>Scaphyglottis livida</i> (Orchidaceae)	↑ NO [↑ NO (inhibited by L-NAME) & hence ↑ cGMP (inhibited by ODQ); spasmolytic]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
5,4'-Dihydroxy-6,7,8,3',5'-pentamethoxyflavone (flavone)	<i>Cleome droserifolia</i> (Capparidaceae)	↓ NO [inhibits LPS-induced macrophage NO production]
5,4'-Dihydroxy-6,7,8,3'-tetramethoxyflavone (flavone)	<i>Cleome droserifolia</i> (Capparidaceae)	↓ NO [inhibits LPS-induced macrophage NO production]
Diocleins (flavone)	<i>Dioclea grandiflora</i> (Fabaceae)	↑ NO [↑ NO & hence ↑ cGMP]
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea leaf) (Theaceae)	↓ NO (EGF-RTK, EST-R, FGF-RTK, PDGF-RTK, pp60 ^{v-src} , PKA, PKC, proteasome, 5αR) [blocks macrophage LPS- & IFN-γ-induced NO; oxidation products give tea taste]
Eupatilin (flavone)	<i>Artemisia rubripes</i> , <i>Chrysanthemum indicum</i> [flower], <i>Eupatorium semiserratum</i> , <i>Tanacetum vulgare</i> (Asteraceae) [aerial], <i>Sideritis tomentosa</i> , <i>S. spp.</i> (Lamiaceae) [aerial], <i>Citrus reticulata</i> (Rutaceae) [fruit peel]	↓ NO (42) [inhibits LPS-induced macrophage NO production] (5-LOX)
5-Geranyloxy-7-methoxycoumarin (coumarin)	<i>Citrus limon</i> (Rutaceae) [lemon peel]	↓ NO [blocks macrophage LPS- & IFN-γ-induced NO production]
5-Geranyloxy-psoralen (= Bergamottin) (coumarin)	<i>Citrus limon</i> (Rutaceae) [lemon peel]	↓ NO [blocks macrophage LPS- & IFN-γ-induced NO production]
8-Geranyloxy-psoralen (coumarin)	<i>Citrus limon</i> (Rutaceae) [lemon peel]	↓ NO [blocks macrophage LPS- & IFN-γ-induced NO production]
Grapenol (= Grape seed proanthocyanidins) (proanthocyanidin mixture)	<i>Vitis vinifera</i> (grape) (Vitaceae) [seed]	↓ NO [blocks astrocyte LPS/IFN-γ-induced NO release; AI]
Green tea polyphenols (polyphenols)	<i>Camellia sinensis</i> (tea leaf) (Theaceae)	↓ NO [blocks hepatocyte TPA-induced NO production]
4-Hydroxyderricin (chalcone)	<i>Angelica keiskei</i> (Apiaceae)	↑ NO [↑ endothelium-derived relaxation factor (EDRF) & NO; inhibits phenylephrine-induced vasoconstriction]
Imperatorin (= Marmelosin) (prenyl furanocoumarin)	<i>Ammi</i> , <i>Angelica</i> , <i>Chnidium</i> , <i>Foeniculum</i> , <i>Heracleum</i> , <i>Levisticum</i> , <i>Pastinaca</i> , <i>Petroselinum</i> , <i>Pimpinella</i> (Apiaceae), <i>Chenopodium</i> (Chenopodiaceae), <i>Fragaria</i> (Rosaceae), <i>Citrus</i> , <i>Aegle</i> (Rutaceae) spp.	↓ NO (>50) [blocks macrophage LPS- & IFN-γ-induced NO]
Kaempferide 3-O-neohesperidoside (flavonol glucoside)	<i>Costus spicatus</i> (Costaceae) [leaf]	↓ NO (at 100) [LPS-induced macrophage NO production]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited or activated (other targets) / in vivo effects
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Ammi</i> , <i>Cuminum</i> , <i>Daucus</i> (Apiaceae), <i>Lavandula</i> , <i>Mentha</i> , <i>Ocimum</i> , <i>Origanum</i> , <i>Rosmarinus</i> , <i>Thymus</i> (Lamiaceae); widespread as glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Chrysanthemum indicum</i> (Asteraceae) [flower], <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	↓ NO (20) (ACE, AR, AROM, CDPK, iNOS, ITDI, MLCK, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PKA, PKC, succinate DH, TOPII, TPO) [LPS-induced macrophage NO production; antibacterial, AI, nodulation signal]
5-Methoxyseselin (coumarin)	<i>Citrus grandis</i> (Rubiaceae)	↓ NO (<50) [blocks macrophage LPS- & IFN-γ-induced NO]
Nobotannin B (hydrolysable tannin)	<i>Melastoma dodecandrum</i> (Melastomataceae)	↓ NO (4) [LPS-induced macrophage NO production]
Osthol (prenyl coumarin)	<i>Angelica</i> , <i>Peucedanum</i> , <i>Prangos</i> (Apiaceae), <i>Citrus</i> , <i>Clausenia</i> , <i>Creoridium</i> , <i>Flindersia</i> , <i>Haplophyllum</i> (Rutaceae) spp.	↓ NO (<50) [blocks macrophage LPS- & IFN-γ-induced NO]
Pedunculagin (ellagitannin)	<i>Casuarina</i> (Casuarinaceae); <i>Quercus</i> (Fagaceae), <i>Juglans</i> (Juglandaceae), <i>Rubus</i> , <i>Potentilla</i> (Rosaceae), <i>Stachyurus</i> (Stachyuraceae), <i>Camellia</i> (Theaceae) spp.	↓ NO (4) [LPS-induced macrophage NO production] (NADH DH)
Polyphenol (polyphenol)	<i>Vitis vinifera</i> (Vitaceae) [red wine]	↑ NO – inferred from ↑ cGMP sensitive to NOS inhibitor L-NAME
Pycnogenol (= Pine bark proanthocyanidins) (proanthocyanidin mixture)	<i>Pinus maritima</i> (Pinaceae) [bark]	↓ NO [blocks macrophage LPS-& IFN-γ-induced NO]
Quercetin 3-O-neohesperidoside (flavonol glucoside)	<i>Costus spicatus</i> (Costaceae) [leaf]	↓ NO (at 100) [LPS-induced macrophage NO production]
Rhaponticin 2'-O-gallate (stilbene glucoside gallate)	<i>Rheum</i> spp. (rhubarb) (Polygonaceae)	↓ NO [inhibits NFκB activation, inhibits LPS-induced macrophage NO production]
Rhaponticin 6'-O-gallate (stilbene glucoside gallate)	<i>Rheum</i> spp. (rhubarb) (Polygonaceae)	↓ NO [inhibits NFκB activation, inhibits LPS-induced macrophage NO production]
<i>epi</i> -Rhododendrin (= (+)-Rhododendrol glucoside) (phenolic glycoside)	<i>Acer nikoense</i> (Aceraceae), <i>Betula</i> spp. (Betulaceae), <i>Rhododendron chrysanthum</i> , <i>R. fauriae</i> , <i>R. ferrugineum</i> , <i>R. ponticum</i> (Ericaceae)	↓ NO [AI]
(+)-Rhododendrol (phenolic)	<i>Acer nikoense</i> (Aceraceae); aglycone from <i>epi</i> -Rhododendrin	↓ NO [AI]
Seselin (coumarin)	<i>Foeniculum vulgare</i> , <i>Pimpinella anisum</i> (Apiaceae), <i>Citrus aurantium</i> (bitter orange), <i>C. limon</i> (lemon), <i>C. paradisi</i> (grapefruit), <i>C. sinensis</i> (orange) (Rutaceae) [fruit]	↓ NO (>50) [blocks macrophage LPS- & IFN-γ-induced NO]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
Silymarin (= Silychristin; Silymarin II) (flavanolignan)	<i>Silybum marianum</i> (Asteraceae)	↓ NO [blocks astrocyte LPS/IFN- γ -induced NO release; AI, hepatoprotective]
Suberosin (prenyl coumarin)	<i>C. limon</i> (lemon), <i>C. paradisi</i> (grapefruit), <i>C. sinensis</i> (orange) (Rutaceae) [root]	↓ NO (<50) [blocks macrophage LPS- & IFN- γ -induced NO]
Tamarixetin 3-O-neohesperidoside (flavonol glucoside)	<i>Costus spicatus</i> (Costaceae) [leaf]	↓ NO (at 100) [LPS-induced macrophage NO production]
Tannic acid (gallotannin)	Widespread; e.g. <i>Quercus</i> spp. (oak) (Fagaceae) [bark]	↓ NO [blocks hepatocyte TPA-induced NO production]
Torachryson 8-O- β -D-glucoside (naphthalene glucoside)	<i>Rheum</i> spp. (rhubarb) (Polygonaceae)	↓ NO [inhibits NF κ B activation, inhibits LPS-induced macrophage NO production]
Wooenosides I, II, III, IV & V (dihydrobenzofuran neolignan)	<i>Coptis japonica</i> (Ranunculaceae)	↓ NO [inhibits mitogen-induced macrophage iNOS & TNF- α production]
Xanthoangelol (chalcone)	<i>Angelica keiskei</i> (Apiaceae)	↑ NO [↑ endothelium-derived relaxation factor (EDRF) & NO; inhibits phenylephrine-induced vasoconstriction]
Xanthoangelol E (chalcone)	<i>Angelica keiskei</i> (Apiaceae)	↑ NO [↑ endothelium-derived relaxation factor (EDRF) & NO; inhibits phenylephrine-induced vasoconstriction]
Xanthoangelol F (chalcone)	<i>Angelica keiskei</i> (Apiaceae)	↑ NO [↑ endothelium-derived relaxation factor (EDRF) & NO; inhibits phenylephrine-induced vasoconstriction]
Xanthoxyletin (coumarin)	<i>Angelica archangelica</i> (Apiaceae), <i>Citrus grandis</i> , <i>C. limon</i> , <i>C. paradisi</i> , <i>C. sinensis</i> [root], <i>Zanthoxylum elephantiasis</i> (Rutaceae) [bark]	↓ NO (>50) [blocks macrophage LPS- & IFN- γ -induced NO]
Xanthyletin (coumarin)	<i>Citrus aurantiifolia</i> , <i>C. grandis</i> , <i>C. limon</i> , <i>C. medica</i> , <i>C. paradisi</i> , <i>C. sinensis</i> [root], <i>Ruta graveolens</i> (rue), <i>Zanthoxylum americanum</i> , <i>Z. elephantiasis</i> (Rutaceae) [bark] (Rutaceae)	↓ NO (>50) [blocks macrophage LPS- & IFN- γ -induced NO]
Terpene		7.3Bt
1 α ,5 α -bis-Acetoxy-8-angeloyloxy-3 β ,4 β -epoxy-bisabola-7(14),10-dien-2-one (bisabolene epoxide sesquiterpene)	<i>Tussilago farfara</i> (Asteraceae) [flower bud]	↓ NO [blocks macrophage LPS-induced NO]
Aerugidiol (sesquiterpene)	<i>Curcuma zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine/TNF α -induced hepatotoxicity; hepatoprotective]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited or activated (other targets) / in vivo effects
Carnosol (abietane diterpene)	<i>Salvia officinalis</i> (sage), <i>Rosmarinus officinalis</i> (rosemary) (Lamiaceae)	↓ NO [inhibits LPS- & IFN- γ -induced macrophage NO production]
Caryolane 1,9- β -diol (sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (at 100) [LPS-induced macrophage NO production]
Clovanediol (sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (at 100) [LPS-induced macrophage NO production]
Costunolide (sesquiterpene)	<i>Artemisia dracuncululus</i> , <i>Saussurea lappa</i> (Asteraceae), <i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae) [leaf]	↓ NO (~3) [LPS-induced macrophage NO production]
Curcumenol (sesquiterpene)	<i>Curcuma longa</i> , <i>C. zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine / TNF α -induced hepatotoxicity; hepatoprotective]
Curcumenone (sesquiterpene)	<i>Curcuma zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine / TNF α -induced hepatotoxicity; hepatoprotective]
Curcumin (sesquiterpene)	<i>Curcuma longa</i> , <i>C. xanthorrhiza</i> , <i>C. zedoaria</i> (Zedoariae Rhizoma), <i>Zingiber officinale</i> (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS- & IFN- γ -induced NO; blocks D-Galactosamine / TNF α -induced hepatotoxicity; hepatoprotective]
Curdione (sesquiterpene)	<i>Curcuma longa</i> , <i>C. zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine / TNF α -induced hepatotoxicity; hepatoprotective]
Dehydrocostus lactone (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae) [leaf]	↓ NO (~3) [LPS-induced macrophage NO production]
Deltoin (furanocoumarin)	<i>Ammi majus</i> , <i>Angelica archangelica</i> , <i>Saposhnikovia divaricata</i> (Apiaceae) [root]	↓ NO [blocks macrophage LPS-induced NO]
Eremanthine (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae) [leaf]	↓ NO (~3) [LPS-induced macrophage NO production]
Furanodiene (sesquiterpene)	<i>Commiphora myrrha</i> (myrrh) [essential oil] (Bursaceae), <i>Curcuma zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]; frankincense & myrrh – gifts of the magi to the infant Jesus	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine / TNF α -induced hepatotoxicity; hepatoprotective]
Ginsenosides Rb1, Rg1 (triterpene glycoside saponins)	<i>Panax ginseng</i> , <i>P. spp.</i> (Araliaceae) [root]; increased endothelial NO release linked to vasorelaxant aphrodisiac effect of <i>Panax ginseng</i>	↑ NO [successive ↑ NO & cGMP; antinephritic]
Ginsenoside Rb1 (triterpene glycoside saponin)	<i>Panax ginseng</i> , <i>P. spp.</i> (Araliaceae) [root]	↓ NO [neuroprotective – ↓ NO-mediated glutamate-induced neurotoxicity]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
Ginsenoside Rg3 (triterpene glycoside saponin)	<i>Panax ginseng</i> , <i>P. spp.</i> (Araliaceae) [root]	↓ NO [neuroprotective – ↓ NO-mediated glutamate-induced neurotoxicity]
Ginsenoside-Rh1 (triterpene glycoside saponin)	<i>Panax ginseng</i> , <i>P. spp.</i> (Araliaceae) [root]	↓ NO [blocks macrophage LPS- & IFN-γ-induced NO]
Ginsenoside-Rh2 (triterpene glycoside saponin)	<i>Panax ginseng</i> , <i>P. spp.</i> (Araliaceae) [root]	↓ NO [blocks macrophage LPS- & IFN-γ-induced NO]
Germacrone (sesquiterpene)	<i>Rhododendron dauricum</i> (Ericaceae), <i>Curcuma zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine/TNFα-induced hepatotoxicity; hepatoprotective]
Imperatorin (furanocoumarin)	<i>Ammi</i> , <i>Angelica</i> , <i>Cnidium</i> , <i>Foeniculum</i> , <i>Heracleum</i> , <i>Levisticum</i> , <i>Pastinaca</i> , <i>Petroselinum</i> , <i>Pimpinella spp.</i> , <i>Saposhnikovia divaricata</i> (Apiaceae), <i>Chenopodium</i> (Chenopodiaceae), <i>Fragaria</i> (Rosaceae), <i>Citrus</i> , <i>Aegle spp.</i> (Rutaceae)	↓ NO [blocks macrophage LPS-induced NO; anti-mutagenic, toxic]
Isocurcumenol (sesquiterpene)	<i>Curcuma zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine/TNFα-induced hepatotoxicity; hepatoprotective]
Kikkanol B (germacrane sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (100) [LPS-induced macrophage NO production]
Kikkanol D monoacetate (germacrane sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (at 100) [LPS-induced macrophage NO production]
Kikkanol E (germacrane sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (at 100) [LPS-induced macrophage NO production]
Kikkanol F monoacetate (germacrane sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (91) [LPS-induced macrophage NO production]
Magnolialide (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae) [leaf]	↓ NO (~3) [LPS-induced macrophage NO production]
Neocurdinone (sesquiterpene)	<i>Curcuma zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine/TNFα-induced hepatotoxicity; hepatoprotective]
Oplopalone (sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (at 100) [LPS-induced macrophage NO production]
[Pruioside A acetylated derivative] (acetylated terpene glycoside)	Semi-synthetic from Prunioside A ex <i>Spiraea prunifolia</i> (Rosaceae)	↓ NO [induced macrophage NO production]
Santamarine (sesquiterpene)	<i>Tanacetum vulgare</i> (tansy) (Asteraceae), <i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae) [leaf]	↓ NO (~3) [LPS-induced macrophage NO production]
Spirafolide (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae) [leaf]	↓ NO (~3) [LPS-induced macrophage NO production]
Zaluzanin C (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae) [leaf]	↓ NO (~3) [LPS-induced macrophage NO production]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
Zeaxanthin dipalmitate (= Physalinen; Physalin) (carotene)	<i>Physalis alkekengi</i> (Chinese lantern) (Solanaceae) [fruit, petal]	↓ NO [yellow]
Zedoarondiol (sesquiterpene)	<i>Curcuma zedoaria</i> (Zedoariae Rhizoma) (Zingiberaceae) [rhizome]	↓ NO [blocks macrophage LPS-induced NO; blocks D-Galactosamine/TNF α -induced hepatotoxicity; hepatoprotective]
Yomogin (sesquiterpene lactone)	<i>Artemisia princeps</i> (Asteraceae)	↓ iNOS expression [AI, anti-endotoxaemia, antiseptic shock; blocks macrophage LPS-induced NO]
Other		7.3Bo
Acemannan (carbohydrate)	<i>Aloe vera</i> (aloe vera) (Liliaceae) [leaf, gel]; most popular cosmetic & toiletry ingredient in USA ; for burns, bruises, wounds & hypoglycaemic	↑ NO (& IL-6, TNF- α) in macrophage
Bidensynoeside A ₁ (= 3(R),8(E)-8-Decene-4,6-diyne-1,3-diol 1-O- β -D-glucoside) (polyacetylene glycoside)	<i>Bidens parviflora</i> (Fabaceae) [whole plant]	↓ NO (0.1; 0.2) [inhibits LPS- & LPS/IFN- γ -induced macrophage NO production; inhibits mast cell histamine release (0.1)]
Bidensynoeside A ₂ (= Deca-3(R),8(E)-8-Decene-4,6-diyne-1,3-diol 1-O- β -D-glucoside) (polyacetylene glycoside)	<i>Bidens parviflora</i> (Fabaceae) [whole plant]	↓ NO (>1) [inhibits LPS- & LPS/IFN- γ -induced macrophage NO production; inhibits mast cell histamine release (0.1)]
Bidensynoeside B (= 3(R)-Deca-4,6,8-triyne-1,3-diol 1-O- β -D-glucoside) (polyacetylene glycoside)	<i>Bidens parviflora</i> (Fabaceae) [whole plant]	↓ NO (0.1) [inhibits LPS- & LPS/IFN- γ -induced macrophage NO production; inhibits mast cell histamine release (0.2)]
Bidensynoeside C (= 3(R),8(E)-8-Decene-4,6-diyne-1,3,10-triol 1-O- β -D-glucoside) (polyacetylene glycoside)	<i>Bidens parviflora</i> (Fabaceae) [whole plant]	↓ NO (0.1; 0.2) [inhibits LPS- & LPS/IFN- γ -induced macrophage NO production; inhibits mast cell histamine release (0.1)]
3-Deoxybidensynoeside B (= 8(E)-8-Decene-4,6-diyne-1,10-diol 1-O- β -D-glucoside) (polyacetylene glycoside)	<i>Bidens parviflora</i> (Fabaceae) [whole plant]	↓ NO (0.1) [inhibits LPS- & LPS/IFN- γ -induced macrophage NO production; inhibits mast cell histamine release (0.1)]
Diallyl trisulfide (aliphatic sulfide)	<i>Allium sativum</i> (garlic) (Liliaceae) [bulb]	↓ NO [blocks macrophage LPS-induced NO; antibacterial, antifungal, PA, ↑ TX formation]
Falcarindiol (polyacetylene)	<i>Angelica sinensis</i> , <i>Apium graveolens</i> , <i>Daucus carota</i> , <i>Saposhnikovia divaricata</i> (Apiaceae), <i>Panax quinquefolium</i> (Araliaceae), <i>Lyopersicon esculentum</i> (Solanaceae)	↓ LPS/IFN- γ -induced NO production (2)

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
Falcarinone (polyacetylene)	<i>Angelica sinensis</i> , <i>Apium graveolens</i> , <i>Saposhnikovia divaricata</i> (Apiaceae), <i>Panax quinquefolium</i> (Araliaceae)	↓ LPS/IFN- γ -induced NO production (>20)
(2 <i>R</i>)-(12 <i>Z</i> ,15 <i>Z</i>)-2-Hydroxy-4-oxoheneicosa-12,15-dien-1-yl acetate (long-chain aliphatic ester)	<i>Persea americana</i> (avocado) (Lauraceae) [fruit]	↓ NO (4) [blocks macrophage LPS- & IFN- γ -induced NO]
Karasurin-A (type I ribosome-inactivating protein)	<i>Trichosanthes kirilowii</i> (Cucurbitaceae) [root, tuber]	↓ NO [↓ LPS-induced macrophage NO production; blocks LPS-, ConA- & PHA-induced lymphocyte proliferation; immunosuppressive]
Panaxydol (polyacetylene)	<i>Saposhnikovia divaricata</i> (Apiaceae), <i>Panax ginseng</i> , <i>P. quinquefolium</i> (Araliaceae)	↓ LPS/IFN- γ -induced NO production (7)
Panaxynol (polyacetylene)	<i>Saposhnikovia divaricata</i> (Apiaceae), <i>Panax ginseng</i> , <i>P. quinquefolium</i> (Araliaceae)	↓ LPS/IFN- γ -induced NO production (2)
Panaxatriol (polyacetylene)	<i>Saposhnikovia divaricata</i> (Apiaceae), <i>Panax quinquefolium</i> (Araliaceae)	↓ LPS/IFN- γ -induced NO production (10)
Persenone A (long-chain aliphatic ester)	<i>Persea americana</i> (avocado) (Lauraceae) [fruit]	↓ NO (1) [blocks macrophage LPS- & IFN- γ -induced NO]
Persenone B (long-chain aliphatic ester)	<i>Persea americana</i> (avocado) (Lauraceae) [fruit]	↓ NO (4) [blocks macrophage LPS- & IFN- γ -induced NO]
<i>cis</i> -Spiroketalenoether polyynes (aliphatic polyynes)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (38) [LPS-induced macrophage NO production]
<i>trans</i> -Spiroketalenoether polyynes (aliphatic polyynes)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	↓ NO (60) [LPS-induced macrophage NO production]
Non-plant reference [Docosahexaenoic acid] (long-chain aliphatic ester)	Fish oil	7.3Bn ↓ NO (4) [blocks macrophage LPS- & IFN- γ -induced NO]
NOS		7.3C
Phenolic		7.3Cp
β -Lapachone (α -naphthoquinone)	<i>Haplophragma adenophyllum</i> , <i>Phyllarthron comorense</i> [wood], <i>Tabebuia avellanedae</i> [wood] (Bignoniaceae), <i>Tectona grandis</i> (Verbenaceae) [root]	iNOS (TOP, RT) [AI, antimicrobial, antitumour]
Daidzein (isoflavone)	<i>Genista tinctoria</i> , <i>Glycine max</i> (soya), <i>Phaseolus</i> , <i>Psoralea</i> , <i>Pueraria</i> , <i>Sophora</i> , <i>Trifolium</i> , <i>Vigna</i> (Fabaceae) spp. [seed]	iNOS (90) [inhibits LPS-induced macrophage iNOS expression]
Genistein (isoflavone)	<i>Genista</i> spp., <i>Glycine max</i> , <i>Phaseolus</i> , <i>Trifolium</i> (Fabaceae) spp., <i>Prunus</i> spp. (Rosaceae) [wood]; glucosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora japonica</i> (Fabaceae)	iNOS (50) [inhibits LPS-induced macrophage iNOS expression]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme / process inhibited or activated (other targets) / in vivo effects
Glycitein (isoflavone)	<i>Glycine max</i> (soya) (Fabaceae) [seed]	iNOS (90) [inhibits LPS-induced macrophage iNOS expression]
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Ammi</i> , <i>Cuminum</i> , <i>Daucus</i> (Apiaceae), <i>Lavandula</i> , <i>Mentha</i> , <i>Ocimum</i> , <i>Origanum</i> , <i>Rosmarinus</i> , <i>Thymus</i> (Lamiaceae); widespread as glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Chrysanthemum indicum</i> (Asteraceae), <i>Digitaria exilis</i> (Poaceae)	iNOS (250) (ACE, AR, AROM, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TOPII, TPO) [↓ LPS-induced NO; antibacterial, AI, modulation signal]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Haplopappus canescens</i> (Asteraceae), <i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplopappus canescens</i> (Asteraceae); glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Myrica rubra</i> (Myricaceae), <i>Primula sinensis</i> (Primulaceae), <i>Camellia sinensis</i> (Theaceae)	iNOS (250) (F ₁ -ATPase, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, 5αR, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic]
Other		7.3Co
Canavanine (alkylguanidine)	<i>Canavalia ensiformis</i> , <i>Glycine max</i> , <i>Robinia pseudoacacia</i> (Fabaceae) [seed]	cNOS, iNOS (Alk Pase, Arginase) [cytotoxic]
Indospicine (= 1,2-Amino-6-amidinohexanoic acid) (amino acid)	<i>Indigofera spicata</i> , <i>I. spp.</i> (Fabaceae)	cNOS, iNOS (Arginase) [abortefacient, hepatotoxic, teratogenic]
Non-plant reference		7.3Cn
[Aminoguanidine] (guanidine)	Synthetic	NOS (notably iNOS)
[N ^G -Methyl-L-arginine (= L-NMMA)] (methylated amino acid)	Synthetic	cNOS, iNOS (28), nNOS
[N ^ω -Nitro-L-arginine methyl ester (= L-NAME)] (amino acid ester)	Synthetic	nNOS, iNOS
NOS activation		7.3D
Other		7.3Do
Arginine (amino acid)	Universal; <i>Helianthus annuus</i> (Asteraceae), <i>Cucurbita foetidissima</i> (Cucurbitaceae), <i>Ceratonia siliqua</i> (Fabaceae), <i>Allium sativum</i> (garlic) (Liliaceae) [bulb], <i>Rehmannia glutinosa</i> (Scrophulariaceae) [root]	NOS substrate
Calmodulin (CaM) (18 kDa protein)	Universal in eukaryotes	eNOS activation by active Ca _v ²⁺ -CaM complex
<i>Glycine</i> CaM SCaM-1 (18 kDa protein)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	NOS activation (180 nM)
<i>Glycine</i> CaM SCaM-4 (18 kDa protein)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Inhibits NOS activation by SCaM-1 [120 nM]

(continued)

Table 7.3 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited or activated (other targets) / in vivo effects
Nitric oxide (= NO) (nitrogen oxide)	Universal	NOS product [activates soluble GC; induces plant stomatal closure; pro-inflammatory]
[Nitroglycerin (= Glyceryl trinitrate)] (glycerol nitric acid triester)	Synthetic; explosive – $4\text{C}_3\text{H}_5(\text{ONO}_2)_3 \rightarrow 12\text{CO}_2 + 10\text{H}_2\text{O} + 6\text{N}_2 + \text{O}_2$	Yields NO (activates soluble GC) [antianginal coronary vasodilator]

Table 7.4 Cyclic nucleotide phosphodiesterases

Compound	Plant (family) part	Target inhibited (other targets) / in vivo effect
Alkaloid α -Allocryptopine (= β -Homochelidonine; α -Fagarine) (protopine)	<i>Bocconia</i> sp., <i>Chelidonium</i> sp., <i>Corydalis</i> sp., <i>Dicentra</i> sp., <i>Eschscholtzia</i> sp., <i>Glaucium arabica</i> , <i>Sanguinaria</i> sp. (Papaveraceae), <i>Zanthoxylum</i> sp. (Rutaceae)	7.4a [cAMP PDE inhibition, ileal smooth muscle relaxation]
[Apomorphine] (dibenzoquinoline, aporphine)	[Synthetic, from morphine]	cAMP PDE (15) [emetic, expectorant]
Atherosperminine (Isoquinoline)	<i>Annona montana</i> , <i>A. muricata</i> , <i>Fissistigma glaucescens</i> , <i>Guatteria discolor</i> (Annonaceae)	cAMP PDE [elevates cAMP; smooth muscle relaxant]
Bulbocapnine (= <i>N</i> -Methyl-launobine) (aporphine isoquinoline)	<i>Corydalis bulbosa</i> , <i>C. cava</i> , <i>C. decumbrens</i> , <i>C. solida</i> , <i>Fumaria officinalis</i> , <i>Glaucium flavum</i> , <i>G. pulchrum</i> (Papaveraceae)	cAMP PDE (46) [cataleptic, sedative]
Caffeine (= 1,3,7-Trimethylxanthine; Coffeine; Guaranine; Thein; Theine) (purine, methylxanthine); most consumed plant bioactive alkaloid? Over 4 million tons of coffee produced each year	<i>Ilex paraguayensis</i> (maté) (Aquifoliaceae), <i>Coffea arabica</i> , <i>Coffea</i> spp. (coffee) (Rubiaceae) [coffee bean], <i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Cola acuminata</i> (cola) (Sterculiaceae) [seed], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]; African slave labour especially for Brazil coffee plantations plus cotton, & sugar plantations in the Americas – about 15 million kidnapped & transported to the Americas	cAMP PDE (150), cGMP PDE (PDE5) (>100) (A_1 AD-R, A_2 AD-R, RY-R, ATP-, Ca^{2+} - & V-K^+ CH) [bitter, cardiac, CNS & respiratory stimulant, diuretic, smooth muscle relaxant, vasodilator]; 8000 tons of coffee part of unsuccessful WW2 offer for 1 million Hungarian Jews (Joel Brand, 1944)

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part	Target inhibited (other targets) / in vivo effect
3',5'-Cyclic AMP (= cAMP) (cyclic nucleotide); Earl Sutherland (USA, Nobel Prize, Medicine, 1971, cAMP as second messenger); Edwin Krebs & Edmond Fischer (USA, Nobel Prize, Medicine, 1992, PKA)	Universal; quantitated in various plants e.g. <i>Agave</i> (Agavaceae), <i>Kalanchoe</i> (Crassulaceae), <i>Lolium</i> (Poaceae) spp.; regulatory role in plants unclear	Substrate for cAMP PDE (activates PKA, opens cAMP-gated Na ⁺ channels & binds to <i>Dictyostelium</i> cAMP receptor)
3',5'-Cyclic GMP (= cGMP) (cyclic nucleotide); Robert Furchgott, Louis Ignarro & Ferid Murad (USA, Nobel Prize, Physiology/Medicine, 1998, NO, cGMP)	Eukaryotes; quantitated in various plants e.g. <i>Phaseolus vulgaris</i> , <i>Pisum sativum</i> (Fabaceae) & <i>Zea mays</i> (Poaceae) seedling tissues; involvement in plant defence & stomatal opening	Substrate for cGMP PDE (activates PKG, opens cGMP-gated Na ⁺ channels)
Glaucine (= Boldine dimethyl ether) (aporphine isoquinoline)	<i>Annona squamosa</i> (Annonaceae), <i>Dicentra eximia</i> , <i>Corydalis ambigua</i> (Fumariaceae), <i>Beilschmiedia podagrica</i> (Lauraceae), <i>Eschscholzia californica</i> , <i>Glaucium flavum</i> (Papaveraceae)	cAMP PDE [38] [antitussive, hypotensive]
Papaverine (benzylisoquinoline); Sir Robert Robinson (UK, Nobel Prize, 1947, Chemistry, alkaloids)	<i>Rauwolfia serpentina</i> (Apocynaceae), <i>Papaver bracteatum</i> , <i>P. somniferum</i> (opium poppy) (Papaveraceae) [opium flower exudate]	cAMP PDE (22; 30;180), cGMP PDE [30] (A-R, L-Ca ²⁺ CH, Na ⁺ K ⁺ ATPase) [spasmolytic (6), smooth muscle relaxant, vasodilator, coronary vasodilator, antitussive]
Theobromine (= 3,7-Dimethylxanthine) (methylxanthine)	<i>Ilex paraguayensis</i> (Aquifoliaceae), <i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Cola acuminata</i> (cola), <i>Theobroma cacao</i> (cocoa) (Sterculiaceae) [seed], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]; 200 tons of cocoa part of unsuccessful offer for 1 million Hungarian Jews (Joel Brand, 1944)	cAMP PDE (150) (AD-R) [cardiac stimulant, diuretic, smooth muscle relaxant, vasodilator]
Theophylline (= 1,3-Dimethylxanthine) (methylxanthine)	<i>Ilex paraguayensis</i> (Aquifoliaceae), <i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Theobroma cacao</i> (cocoa) (Sterculiaceae) [seed], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]; 800 tons of tea part of unsuccessful offer for 1 million Hungarian Jews (Joel Brand, 1944)	cAMP PDE (150; 720) (AD-R, Ca ²⁺ -K ⁺ CH) [cardiac stimulant, coronary vasodilator, diuretic, smooth muscle relaxant, anti-asthmatic]
Phenolic Acacetin-7-O-6"- α -L-Rha-(6-1)- β -D-Glc (flavone glycoside)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower], <i>Buddleja officinalis</i> (Loganiaceae) [flower]	7.4p cAMP PDE (>100) (AR, ITD) [allergenic]

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part	Target inhibited (other targets) / in vivo effect
(+)-1-Acetoxy-pinoreosinol (lignan)	<i>Olea europaea</i> (Oleaceae) [bark]	cAMP PDE (32)
(+)-1-Acetoxy-pinoreosinol 4'- <i>O</i> -glucoside (lignan)	<i>Olea europaea</i> (Oleaceae) [bark]	cAMP PDE (44)
[(+)-1-Acetoxy-pinoreosinol 4',4''-di- <i>O</i> -Glc] (lignan diglucoside)	[Semi-synthetic from (+)-1-Hydroxy-pinoreosinol 4',4''-di- <i>O</i> -glucoside from <i>Eucommia ulmoides</i> (Eucommiaceae) [bark]	cAMP PDE (11)
Agathisflavone (= 6',8''-Biapigenin)	<i>Agathis dammara</i> , <i>Araucaria bidwillii</i> (Araucariaceae)	cAMP PDE (HIV-1 RT)
Amentoflavone (= 3',8''-Biapigenin) (biflavone)	<i>Viburnum prunifolium</i> (Caprifoliaceae), <i>Cycas revoluta</i> (cycad) (Cycadaceae), <i>Ginkgo biloba</i> (Ginkgoaceae), <i>Podocarpus montanus</i> (Podocarpaceae), <i>Rhus succedanea</i> (Anacardiaceae)	cAMP PDE (0.7), cGMP PDE (0.5) (BZ-R, HIV-1 RT) [antifungal]
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	<i>Apium</i> , <i>Daucus</i> (Apiaceae), <i>Achillea</i> , <i>Artemisia</i> (Asteraceae), <i>Mentha</i> , <i>Thymus</i> (Lamiaceae), ferns [leaf surface], <i>Buddleja officinalis</i> (Loganiaceae) [flower]	cAMP PDE (9; 53), cGMP PDE (35) (AD-R, AR, PK, RTK) [antibacterial, AI, diuretic, hypotensive]
Apiin (= Apigenin 7-Api-Glc; Apioside; 4',5,7-Trihydroxyflavone-7-Api-Glc) (flavone <i>O</i> -glycoside)	<i>Apium graveolens</i> (celery), <i>Petroselinum crispum</i> (parsley) (Apiaceae) [leaf, seed], <i>Capsicum</i> spp. (Solanaceae)	cAMP PDE (100) (AR)
Bilobetin (biflavone)	<i>Araucaria bidwillii</i> (Araucariaceae), <i>Ginkgo biloba</i> (Ginkgoaceae)	cAMP PDE
(+)-Catechin (= Catechinic acid; Catechol; Catechuic acid; (+)-Cyanidanol; (+)-Cyanidan-3-ol) (flavan-3-ol)	Widespread; <i>Gossypium</i> spp. (Malvaceae), <i>Agrimonia eupatoria</i> (Rosaceae), <i>Salix caprea</i> (willow) (Salicaceae) [flower]	cAMP PDE (500; 640; 1200), cGMP PDE (170)
Chrysin (= 5,7-Dihydroxyflavone) (flavone)	<i>Daucus carota</i> (Apiaceae), <i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (poplar) (Salicaceae) [leaf bud], <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	cAMP PDE (10–100; >100) (AR, iodothyronine deiodinase, PGP TR) [AI, antibacterial, inhibits histamine release]
4-Cinnamoylmussatioside (phenylpropanoid)	<i>Mussatia</i> sp. (Bignoniaceae)	cAMP PDE [inhibits ADP-induced PA]
Columbianadin (dihydrofuranocoumarin)	<i>Angelica laxiflora</i> , <i>Peucedanum oreoselinum</i> (Apiaceae) [root]	cAMP PDE (260) [spasmolytic (55), coronary vasodilatory]
Cyanidin chloride (= 3,5,7,3',4'-Pentahydroxyflavilium chloride) (anthocyanidin)	Widespread especially as cyanidin glycosides; <i>Hibiscus rosasinensis</i> (Malvaceae), <i>Musa</i> sp. (banana) (Musaceae)	cAMP PDE [10] [red pigment]
Diacetyl <i>cis</i> -khellactone (dihydropyranocoumarin)	<i>Seseli libanotis</i> (Apiaceae) [root]	cAMP PDE (320) [spasmolytic (200), coronary vasodilatory]
Diacetyl vaginiol (dihydrofuranocoumarin)	<i>Ligusticum pyrenaicum</i> (Apiaceae)	cAMP PDE (290) [spasmolytic (160), coronary vasodilatory]

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part/	Target inhibited (other targets) / in vivo effect/
3', 3''-Dimethoxy-4', 4''-hydroxy-2,3-di-benzyl-butyrolactone (lignan)	<i>Trachospermum asiaticum</i> (Apocynaceae) [stem]	cAMP PDE (98)
3', 3''-Dimethoxy-4', 4''-hydroxy-2,3-di-benzyl-butyrolactone 4'-O-Glc (lignan glucoside)	<i>Trachospermum asiaticum</i> (Apocynaceae) [stem]	cAMP PDE (>5000)
3', 3''-Dimethoxy-4', 4''-hydroxy-2,3-di-benzyl-butyrolactone 4', 4''-di-O-Glc (lignan diglucoside)	<i>Trachospermum asiaticum</i> (Apocynaceae) [stem]	cAMP PDE (111)
Dihydrofisetin (= Fustin) (dihydroflavonol)	<i>Rhus</i> sp., <i>Schinopsis</i> sp. (Anacardiaceae), <i>Gleditsia triacanthos</i> , <i>Robinia pseudoacacia</i> (Fabaceae), <i>Platanus</i> sp. (Platanaceae), <i>Tilia</i> spp. (Tiliaceae)	cAMP PDE (320)
(+)-Dihydroquercetin (= Taxifolin; Distylin; 3,5,7,3',4'-Pentahydroxyflavanone) (dihydroflavonol)	<i>Engelhardtia chrysolepis</i> (Juglandaceae), <i>Acacia catechu</i> (Fabaceae), <i>Pinus sylvestris</i> (Pinaceae), <i>Polygonum nodosum</i> (Polygonaceae), <i>Salix capraea</i> (Salicaceae),	cAMP PDE (94; 320), cGMP PDE (170), (AR, NADH DH, succinate DH, 5-LOX)
4-Dimethylcaffeoyl-cinnamoylmussatioside (phenylpropanoid)	<i>Mussaia</i> sp. (Bignoniaceae)	cAMP PDE [inhibits ADP-induced PA]
Diseneciyl <i>cis</i> -khellactone (dihydropyranocoumarin)	<i>Seseli incanum</i> , <i>S. libanotis</i> (Apiaceae) [root]	cAMP PDE (21) [coronary vasodilatory, spasmolytic (14)]
(-)-Epicatechin (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), <i>Pterocarpus</i> spp. (Fabaceae), <i>Podocarpus nagi</i> (Podocarpaceae), <i>Crataegus monogyna</i> (hawthorn) (Rosaceae), <i>Camellia sinensis</i> (Theaceae)	cAMP PDE (500) [antibacterial, AI]
Fisetin (flavonol)	<i>Acacia catechu</i> , <i>Glycine max</i> , <i>Robinia pseudoacacia</i> , <i>Trigonella</i> spp. (Fabaceae), <i>Rhus glabra</i> , <i>Rhus toxicodendron</i> (Anacardiaceae)	cAMP PDE (36; 10–100), (ITD, PKC, succinate DH, NADH DH, 5-LOX) [blocks basophil histamine release, antibacterial, inhibits SM contraction]
Flavone (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	cAMP PDE (>100) [23] (COX, 5-LOX) [proapoptotic, AI, antifungal, inhibits basophil histamine release]
Forsythiaside (= Forsythoside A) (phenylpropanoid glycoside)	<i>Forsythia suspensa</i> , <i>F. koreana</i> (Oleraceae) [fruit]	cAMP PDE (5-LOX, AO/FRS)
Galangin (= 3,5,7-Trihydroxyflavone) (flavonol)	Betulaceae, Salicaceae [bud excretion], ferns [frond], Lamiaceae [leaf], <i>Datisca cannabina</i> (Datiscaceae), <i>Escallonia</i> spp. (Saxifragaceae), <i>Alpinia officinarum</i> (Zingiberaceae)	cAMP PDE (9) (A1-, A2A- & A3-AD-R, COX, PGP TR) [antibacterial]

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part/	Target inhibited (other targets) / in vivo effect/
Ginkgetin (= Amentoflavone 7,4'-dimethyl ether) (biflavone)	<i>Dacrydium</i> spp. (Podocarpaceae), <i>Zamia augustifolia</i> (Cycadaceae), <i>Ginkgo biloba</i> (Ginkgoaceae), <i>Taxus</i> spp. (Taxaceae)	cAMP PDE
Glabridin (isoflavan)	<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (82) [antibacterial, anti-mycobacterial]
Glycycomarin (prenylated coumarin)	<i>Glycyrrhiza uralensis</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (7)
Glycycomarin 7-O-methyl ether (= Glycyrin) (prenylated coumarin)	<i>Glycyrrhiza uralensis</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (>5000)
Glycyrol (coumestan)	<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (44)
Hellicoside (phenylpropanoid glycoside)	<i>Plantago asiatica</i> (Plantaginaceae)	cAMP PDE (5-LOX) [AI, anti-asthmatic]
Hesperetin (= Eriodictyol 4'-methyl ether; 3',5,7-Trihydroxy-4'-methoxyflavanone) (flavanone)	<i>Citrus paradisi</i> (grapefruit), <i>Citrus</i> spp. (Rutaceae), <i>Mentha aquatica</i> , <i>Mentha piperita</i> (Lamiaceae)	cAMP PDE (26) (AR) [antibacterial, antiviral, insect feeding deterrent]
Hinokiflavone (biflavone)	<i>Rhus succedanea</i> (Anacardiaceae), <i>Araucaria bidwillii</i> (Araucariaceae), <i>Cycas revoluta</i> (Cycadaceae), <i>Cupressus funebris</i> , <i>Juniperus macrospora</i> (Cupressaceae), <i>Podocarpus macrophyllus</i> (Podocarpaceae), <i>Selaginella tamariscina</i> (water fern) (Selaginellaceae)	cAMP PDE (HIV-1 RT)
cis-Hinokiresinol (= Nyasol) (lignan, phenylpropanoid)	<i>Araucaria angustifolia</i> (Araucariaceae), <i>Chamaecyparis obtusa</i> (Cupressaceae), <i>Anemarrhena asphodeloides</i> (Liliaceae)	cAMP PDE (EST-R)
(+)-1-Hydroxypinoresinol (lignan)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark]	cAMP PDE (213)
(+)-1-Hydroxypinoresinol 4'-O-Glc (lignan glucoside)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark]	cAMP PDE (286)
(+)-1-Hydroxypinoresinol 4"-O-Glc (lignan glucoside)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark]	cAMP PDE (332)
(+)-1-Hydroxypinoresinol 4',4"-di-O-Glc (lignan diglucoside)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark]	cAMP PDE (100)
Isoamidin (dihydropyrano-coumarin)	<i>Seseli libanotis</i> (Apiaceae) [root]	cAMP PDE (33) [spasmolytic (16), coronary vasodilatory]
Isoglycyrol (coumestan)	<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (>5000)

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part/	Target inhibited (other targets) / in vivo effect/
Isoginkgetin (biflavone)	<i>Ginkgo biloba</i> (Ginkgoaceae)	cAMP PDE
Isoliquiritigenin (= 2',4',4-Trihydroxychalcone) (chalcone)	<i>Astragalus membranaceus</i> , <i>Glycine max</i> , <i>Glycyrrhiza glabra</i> , <i>Glycyrrhiza uralensis</i> (Fabaceae) [root, rhizome]	cAMP PDE (180), [cAMP PDE III] (ARI, COX, 5-LOX, AR, mitochondrial MAO, uncouples plant mitochondria) [yellow pigment]
Isoliquiritigenin-4'-O-Api-Glc (= 2',4',4-Trihydroxychalcone-4'-O-Api-Glc) (chalcone)	<i>Glycyrrhiza uralensis</i> (licorice) (Fabaceae) [root, rhizome]	cAMP PDE (1710)
Isomangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	cAMP PDE (47)
Isonarthogenin 3-O- α -1-Rha-(1 \rightarrow 2)-O-[α -Rha-(1 \rightarrow 4)]- β -D-Glc (tetrasaccharide steroidal saponin)	<i>Smlax china</i> (Liliaceae) [rhizome, root]	cAMP PDE
Isopeucenidin (dihydrofuranocoumarin)	<i>Peucedanum oreoselinum</i> (Apiaceae)	cAMP PDE (90) [spasmolytic (65), coronary vasodilatory]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread; Hippocastanaceae [aerial], <i>Brassica oleracea</i> (Brassicaceae), <i>Pisum sativum</i> (Fabaceae), <i>Thespesia populnea</i> (Malvaceae), <i>Azadirachta indica</i> (neem tree) (Meliaceae)	cAMP PDE (3; 45) (CAMPK, Iodothyronine deiodinase, 5-LOX, MLCK, myosin ATPase, Pases, PGP TR, PKC) [blocks COX-2 & iNOS induction; AI, antibacterial, mutagenic, radical scavenger]
cis-Khellactone (dihydropyranocoumarin)	<i>Amni visnaga</i> , <i>Seseli libanotis</i> (Apiaceae) [root]	cAMP PDE (>400) [spasmolytic (>200)]
Lomatina acetate (dihydropyranocoumarin)	<i>Seseli libanotis</i> (Apiaceae) [root]	cAMP PDE (350) [spasmolytic (140), vasodilatory]
Licoaryl coumarin (coumarin)	<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (10)
Licoricidin (prenylated isoflavan)	<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (49)
Licoricone (prenylated isoflavone)	<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (23)
Liquiritigenin (= 7,4'-Dihydroxyflavone) (flavanone)	<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i> (liquorice) [root, rhizome], <i>Cicer arietinum</i> , <i>Medicago sativa</i> [phytoalexin], <i>M. lupulina</i> [phytoalexin] (Fabaceae)	cAMP PDE (1080)
Liquiritin (= 7,4'-Dihydroxyflavone 4'-O-Glc) (flavanone)	<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i> , <i>G. spp.</i> (liquorice) [root, rhizome] (Fabaceae)	cAMP PDE (>5000)

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part	Target inhibited (other targets) / in vivo effect
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread; <i>Ammi</i> , <i>Cuminum</i> , <i>Daucus</i> (Apiaceae), <i>Lavandula</i> , <i>Mentha</i> , <i>Ocimum</i> , <i>Origanum</i> , <i>Rosmarinus</i> , <i>Thymus</i> (Lamiaceae); widespread as glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Chrysanthemum indicum</i> (Asteraceae) [flower], <i>Digitaria exilis</i> (Poaceae)	cAMP PDE (9) (A ₁ AD-R, ITD, PKC, NADH DH, succinate DH, ARI, PEP)
α-Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	cAMP PDE (24) (Ca ²⁺ ATPase, EST-R, HIV-1 PR, H-R, PK) [antibacterial, AI, antiulcer]
γ-Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	cAMP PDE (50) (cAMP PDE, HIV-1 PR, PK)
Medioresinol (lignan)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark]	cAMP PDE (121)
Medioresinol 4'-O-Glc (lignan glucoside)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark]	cAMP PDE (297)
Medioresinol 4',4''-di-O-Glc (lignan diglucoside)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark]	cAMP PDE (63)
4- <i>p</i> -Methoxycinnamoyl-mussatioside (phenylpropanoid)	<i>Mussatia</i> sp. (Bignoniaceae)	cAMP PDE [inhibits ADP-induced PA]
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Morus alba</i> , <i>M.</i> spp. (mulberry), <i>Chlorophora tinctoria</i> , <i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> (Moraceae)	cAMP PDE [48] (Iodothyronine deiodinase, ARI, 5-LOX) [antiviral, antibacterial, allergenic, silkworm feeding attractant]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Haplopappus canescens</i> (Asteraceae), <i>Acacia leucophloea</i> (Fabaceae), <i>Aesculus hippocastanum</i> (Hippocastanaceae), <i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae)	cAMP PDE (10–100) (NADH DH, succinate DH, anti-gonadotropin, cAMP, PDE, 5-LOX) [antibacterial, AI]
Naringenin (= 5,7,4'-Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia</i> spp., (Asteraceae), <i>Citrus sinensis</i> (orange) (Rutaceae)	cAMP PDE (45; 48), (Histidine decarboxylase, serotonin secretion, AR) (IC ₅₀ 1–10 μM) [antibacterial, antifungal]
Pelargonidin chloride (3,5,7,4'-Tetrahydroxyflavilium chloride) (anthocyanidin)	3-glucoside in <i>Fagus sylvatica</i> (Fagaceae) [leaf]; 3-galactoside in <i>Fragaria vesca</i> (strawberry) (Rosaceae) [fruit]	cAMP PDE (8; 70), cGMP PDE (23)
[Pentaacetylquercetin] (flavonol)	Semi-synthetic; polyacetylated quercetin	cAMP PDE (>100)
Peucedanin (dihydrofuranocoumarin)	<i>Libanotis pyrenaicum</i> , <i>Peucedanum bourgaei</i> , <i>P. oreoselinum</i> (Apiaceae)	cAMP PDE (110) [spasmolytic (29), coronary vasodilatory]
(+)-Pinoresinol (lignan)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark], <i>Pinus strobus</i> (Pinaceae)	cAMP PDE (75)
(+)-Pinoresinol 4'-O-Glc (lignan glucoside)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark], <i>Pinus strobus</i> (Pinaceae)	cAMP PDE (142)

(continued)

Table 7.4 (Continued)

Compound	Plant (family) part	Target inhibited (other targets) / in vivo effect
(+)-Pinoresinol 4',4''-di- <i>O</i> -Glc (lignan diglucoside)	<i>Eucommia ulmoides</i> (Eucommiaceae) [bark], <i>Pinus strobus</i> (Pinaceae)	cAMP PDE (89)
Pteryxin (dihydropyranocoumarin)	<i>Seseli libanotis</i> (Apiaceae) [root]	cAMP PDE (110) [spasmolytic (13), coronary vasodilatory]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	cAMP PDE (4; 13; 23), cGMP PDE (15), (AD-R, AR, cAMP PDE, PK) [SM contraction, radical scavenger allergenic, antiviral LOX [AI, feeding stimulant]]
Quercetrin (= Quercetin-3- <i>O</i> -1-Rha; 3,5,7,3',4'-Pentahydroxyflavone 3- <i>O</i> -Rha) (flavonol <i>O</i> -glycoside)	Widespread; <i>Chamaemelum nobile</i> (Asteraceae), <i>Quercus tinctoria</i> (Fagaceae) [bark], <i>Eucalyptus globulus</i> , <i>Myrcia multiflora</i> (Myrtaceae) [leaf], <i>Polygonum</i> spp. (Polygonaceae), <i>Cistus</i> spp. (Cistaceae), <i>Artemisia dracuncululus</i> (Asteraceae), <i>Ammi visnaga</i> (Lamiaceae); glycosides in <i>Thalictrum foetidum</i> (Ranunculaceae), <i>Rhamnus cathartica</i> (Rhamnaceae), <i>Tamarix aphylla</i> (Tamaricaceae)	cAMP PDE (10–100) (AHR, AR, PKA) [antibacterial, anti-mutagenic, antiviral, feeding attractant]
Rhamnetin (= 3,5,7,3',4'-Pentahydroxy-flavone 7-methyl ether; Quercetin 7-methyl ether) (flavonol)	<i>Cistus</i> spp. (Cistaceae), <i>Artemisia dracuncululus</i> (Asteraceae), <i>Ammi visnaga</i> (Lamiaceae); glycosides in <i>Thalictrum foetidum</i> (Ranunculaceae), <i>Rhamnus cathartica</i> (Rhamnaceae), <i>Tamarix aphylla</i> (Tamaricaceae)	cAMP PDE (8; 10–100) (AD-R, AR) [allergenic, antibacterial]
Robinetin (= 3,7,3',4',5'-Pentahydroxyflavone) (flavonol)	<i>Acacia decurrens</i> , <i>A. mearnsii</i> , <i>Gleditsia monosperma</i> , <i>Gliricidia sepium</i> , <i>Milletia stuhlmannii</i> , <i>Robinia pseudacacia</i> (Fabaceae)	cAMP PDE (HIV-1 INT) (10–100) [antibacterial]
Robustaflavone (= 3',6'-Biapigenin) (biflavone)	<i>Araucaria</i> spp. (Araucariaceae), <i>Juniperus</i> spp. (Cupressaceae), <i>Rhus succedanea</i> (Anacardiaceae)	cAMP PDE (RT)
Samidin (dihydropyranocoumarin)	<i>Ammi visnaga</i> , <i>Seseli libanotis</i> (Apiaceae) [root]	cAMP PDE (80) [spasmolytic (6), coronary vasodilatory]
Senecioid dihydrorooselol (dihydrofuranocoumarin)	<i>Peucedanum oreoselinum</i> (Apiaceae)	cAMP PDE (250) [spasmolytic (29), coronary vasodilatory]
Sequoiainflavone (biflavone)	<i>Ginkgo biloba</i> (Ginkgoaceae), <i>Taxus baccata</i> (Taxaceae)	cAMP PDE
Suspensaside (phenylpropanoid glycoside)	<i>Forsythia suspensa</i> (Oleaceae) [fruit]	cAMP PDE (AO/FRS, 5-LOX) [AI, anti-asthmatic]
Vaginidin (dihydrofuranocoumarin)	<i>Peucedanum oreoselinum</i> (Apiaceae)	cAMP PDE (300) [spasmolytic (100), coronary vasodilatory]
Terpene		
Agapanthussaponin A (= (25 <i>R</i>)-5 α -Spirostane-2 α ,3 β ,5 α -triol 3- <i>O</i> -Rha-[Gal]-Glc) (triterpene glycoside)	<i>Agapanthus inapertus</i> (Liliaceae) [bulb, root]	7.4t cAMP PDE (7)
Agapanthussaponin B (= (25 <i>R</i>)-5 α -Spirost-7-ene-2 α ,3 β ,5 α -triol 3- <i>O</i> -Rha-[Gal]-Glc) (triterpene glycoside)	<i>Agapanthus inapertus</i> (Liliaceae) [bulb, root]	cAMP PDE (12)

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part	Target inhibited (other targets) / in vivo effect
Agapanthussaponin C (= (25 <i>R</i>)-5 α -Spirosta-7,9-diene-2 α ,3 β ,5 α -triol 3- <i>O</i> -Rha-[Gal]-Glc) (triterpene glycoside)	<i>Agapanthus inapertus</i> (Liliaceae) [bulb, root]	cAMP PDE (11)
Agapanthussaponin D (= (25 <i>R</i>)-5 α -Spirostan-2 α ,3 β ,5 α ,9 α -tetrol 3- <i>O</i> -Rha-[Gal]-Glc) (triterpene glycoside)	<i>Agapanthus inapertus</i> (Liliaceae) [bulb, root]	cAMP PDE (20)
Ardisicrenoside C (= 3 β ,16 α ,28-Trihydroxy-olean-12-en-30-oic acid 3- <i>O</i> -Rha-Glc-[Glc]-Ara-30- <i>O</i> -Glc) (triterpene glycoside)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (46)
Ardisicrenoside D (= 3 β ,16 α ,28-Trihydroxy-olean-12-en-30-oic acid 3- <i>O</i> -Xyl-Glc-[Glc]-Ara-30- <i>O</i> -Glc) (triterpene glycoside)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (950)
Brisbagenin 1- <i>O</i> -Rha-acetylAra (= (25 <i>R</i>)-5 α -Spirostan-1 β ,3 β -diol 1- <i>O</i> -Rha-acetylAra) (disaccharide steroidal saponin)	<i>Dichelostemma multiflorum</i> (Liliaceae) [tuber]	cAMP PDE (206)
Brisbagenin-1- <i>O</i> -Rha-Ara (= (25 <i>R</i>)-5 α -Spirostan-1 β ,3 β -diol 1- <i>O</i> -Rha-Ara) (trisaccharide steroidal saponin)	<i>Dichelostemma multiflorum</i> (Liliaceae) [tuber]	cAMP PDE (762)
Brisbagenin-1- <i>O</i> -Rha-[Rha]-acetylAra (= (25 <i>R</i>)-5 α -Spirostan-1 β ,3 β -diol 1- <i>O</i> -Rha-[Rha]-acetylAra) (trisaccharide steroidal saponin)	<i>Dichelostemma multiflorum</i> (Liliaceae) [tuber]	cAMP PDE (118)
Brisbagenin-1- <i>O</i> -Rha-[Rha]-Ara (= (25 <i>R</i>)-5 α -Spirostan-1 β ,3 β -diol 1- <i>O</i> -Rha-[Rha]-Ara) (trisaccharide steroidal saponin)	<i>Dichelostemma multiflorum</i> (Liliaceae) [tuber]	cAMP PDE (100)
Brownioside (= (25 <i>R</i>)-27- <i>O</i> -[3-Hydroxy-3-methylglutaroyl]-spirost-5-ene-3 β ,27-diol 3- <i>O</i> -Rha-Glc) (disaccharide steroidal saponin)	<i>Lilium brownii</i> , <i>L. henryi</i> , <i>L. regale</i> (Liliaceae) [bulb]	cAMP PDE (29)
Brudioside A (= Ruscogenin tetrasaccharide) (sterol tetrasaccharide)	<i>Brodiaea californica</i> (Liliaceae) [tuber]	cAMP PDE (89)
Brudioside B (= Spirostanol tetrasaccharide) (sterol tetrasaccharide)	<i>Brodiaea californica</i> (Liliaceae) [tuber]	cAMP PDE (100)
15-Deoxoecosterol 3- <i>O</i> -Rha-[Glc-Glc]-Glc-Ara-Glc (phytosterol hexasaccharide saponin)	<i>Chionodoxa gigantea</i> (Liliaceae) [bulb]	cAMP PDE (132)

(continued)

Table 7.4 (Continued)

Compound	Plant (family) part	Target inhibited (other targets) / in vivo effect
23- <i>epi</i> -15-Deoxoeucosterol 3- <i>O</i> -Rha-[Glc-Glc]-Glc-Ara-Glc (phytosterol hexasaccharide saponin)	<i>Chionodoxa gigantea</i> (Liliaceae) [bulb]	cAMP PDE (163)
Desglucolanatigonin II (tetrasaccharide steroidal saponin)	<i>Dichelostemma multiflorum</i> (Liliaceae) [tuber]	cAMP PDE (123)
Dioscin (= 25 <i>R</i>)-Spirost-5-en- 3β-ol 3- <i>O</i> -Rha-[Rha]-Glc) (trisaccharide steroidal saponin)	<i>Smilax china</i> (Liliaceae) [rhizome, root]	cAMP PDE (333)
Diosgenin 3- <i>O</i> -Rha-Gal-Glc (steroidal trisaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (162)
Diosgenin 3- <i>O</i> -Rha-Glc (steroidal disaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (131)
Diosgenin 3- <i>O</i> -Glc-[Xyl]-Glc- Gal (= (25 <i>R</i>)-Spirost-5-en-3-β- ol 3- <i>O</i> -Glc-[Xyl]-Glc-Gal) (tetrasaccharide steroidal saponin)	<i>Reineckia carnea</i> (Liliaceae) [bulb, root]	cAMP PDE (117)
Diosgenin 3- <i>O</i> -Rha-Glc-Glc (steroidal trisaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (61)
Diosgenin 3- <i>O</i> -Rha-Rha-Glc (steroidal trisaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (113)
Ecdysterone (= Ecdysone; α-Ecdysone) (sterol); insect & crustacean moulting hormone	<i>Lychnis fulgens</i> (Caryophyllaceae), <i>Ipheion uniflorum</i> (Liliaceae), <i>Blechnum minus</i> , <i>Polypodium vulgare</i> , <i>Pteridium aquilinum</i> (Pteridophyta)	cAMP PDE (183) [insect moulting hormone]
(25 <i>R</i>)-5α-Furostane-2α,3β,6β, 22ξ, 26-pentol 22- <i>O</i> -methyl-26- <i>O</i> -Glc-3- <i>O</i> -Glc-[Xyl]-Glc-Gal (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (44)
Furastanol hexasaccharides (2, 3 & 4) (sterol saponins)	<i>Ipheion uniflorum</i> (Liliaceae) [bulb]	cAMP PDE (145; 412; 983)
(24 <i>S</i> ,25 <i>S</i>)-5α-Furostane- 2α,3β,5α,6β, 22ξ,26-hexol 3- <i>O</i> -acetyl-22- <i>O</i> -methyl-26- <i>O</i> - Glc-2- <i>O</i> -Glc (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (5)
(25 <i>R</i>)-5α-Furostane- 2α,3β,5α,6β, 22ξ,26-hexol 3- <i>O</i> -benzoyl-22- <i>O</i> -methyl-26- <i>O</i> - Glc-2- <i>O</i> -Glc (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (2)
Gitogenin 3- <i>O</i> -Glc-Glc-Xyl- Glc-Gal (steroidal pentasaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (84)
Gitogenin 3- <i>O</i> -Rha-Glc-Xyl- Glc-Gal (steroidal pentasaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (142)

(continued)

Table 7.4 (Continued)

<i>Compound</i>	<i>Plant (family) part </i>	<i>Target inhibited (other targets) / in vivo effect </i>
Gitonin (tetrasaccharide steroidal saponin)	<i>Dichelostemma multiflorum</i> (Liliaceae) [tuber]	cAMP PDE (114)
26- <i>O</i> -Glc-furostan-3 β , 22 ξ diol 3- <i>O</i> -Rha-[Glc]-Glc (trisaccharide steroidal saponin)	<i>Lilium hansonii</i> (Liliaceae) [bulb]	cAMP PDE (1030)
26- <i>O</i> -Glc-furost-5-en-3 β , 22 ξ diol 3- <i>O</i> -Rha-[Glc]-Glc (trisaccharide steroidal saponin)	<i>Lilium hansonii</i> (Liliaceae) [bulb]	cAMP PDE (485)
Gracillin (= (25 <i>R</i>)-Spirost-5-en-3 β -ol 3- <i>O</i> -Rha-[Glc]-Glc (disaccharide steroidal saponin)	<i>Lilium regale</i> (Liliaceae) [bulb]	cAMP PDE (61)
(25 <i>R</i>)-27- <i>O</i> -[3-Hydroxy-3-methylglutaroyl]-spirost-5-ene-3 β ,27-diol 3- <i>O</i> -Rha-[Glc(1 \rightarrow 3)]-Glc (disaccharide steroidal saponin)	<i>Lilium regale</i> (Liliaceae) [bulb], <i>Costus speciosus</i> (Zingiberaceae)	cAMP PDE (22)
(25 <i>R</i>)-27- <i>O</i> -[3-Hydroxy-3-methylglutaroyl]-spirost-5-ene-3 β ,27-diol 3- <i>O</i> -Rha-[Glc(1 \rightarrow 4)]-Glc (disaccharide steroidal saponin)	<i>Lilium brownii</i> , <i>L. henryi</i> , <i>L. mackliniae</i> , <i>L. regale</i> (Liliaceae) [bulb]	cAMP PDE (31)
Isonarthogenin 3- <i>O</i> -Rha-[Rha]-Glc (= (25 <i>S</i>)-Spirost-5-ene-3 β ,27-diol 3- <i>O</i> -Rha-[Rha]-Glc) (trisaccharide steroidal saponin)	<i>Smilax china</i> (Liliaceae) [rhizome, root]	cAMP PDE (93)
Kitigenin (= (25 <i>R</i>)-5 β -Spirostane-1 β ,3 β ,4 β ,5 β -tetrol (steroidal saponin)	<i>Reineckia carnea</i> (Liliaceae) [bulb, root]	cAMP PDE (179)
Laxogenin 3- <i>O</i> -Glc-[Ara]-Glc (= (25 <i>R</i>)-5 α -Spirostan-3 β -ol-6-one 3- <i>O</i> -Glc-[Ara]-Glc) (trisaccharide steroidal saponin)	<i>Smilax sieboldii</i> (Liliaceae) [rhizome]	cAMP PDE (83)
Laxogenin 3- <i>O</i> -Ara-Glc (= (25 <i>R</i>)-5 α -Spirostan-3 β -ol-6-one 3- <i>O</i> -acetylAra-Glc) (disaccharide steroidal saponin)	<i>Smilax sieboldii</i> (Liliaceae) [rhizome]	cAMP PDE (34)
Laxogenin-3- <i>O</i> -acetylAra-Glc (= (25 <i>R</i>)-5 α -Spirostan-3 β -ol-6-one 3- <i>O</i> -acetylAra-Glc) (disaccharide steroidal saponin)	<i>Allium chinense</i> , <i>Smilax sieboldii</i> (Liliaceae) [bulb]	cAMP PDE (33)
Laxogenin-3- <i>O</i> -Ara-Glc (= (25 <i>R</i>)-5 α -Spirostan-3 β -ol-6-one 3- <i>O</i> -Ara-Glc) (disaccharide steroidal saponin)	<i>Allium chinense</i> , <i>Smilax sieboldii</i> (Liliaceae) [bulb]	cAMP PDE (34; 112)
Laxogenin-3- <i>O</i> -Xyl-[Ara]-Glc (= (25 <i>R</i>)-5 α -spirostan-3 β -ol-6-one 3- <i>O</i> -Xyl-[Ara]-Glc) (trisaccharide steroidal saponin)	<i>Allium chinense</i> (Liliaceae) [bulb]	cAMP PDE (123)
Methylprotodioscin (= 26- <i>O</i> -Glucosyl-22- <i>O</i> -methyl-(25 <i>R</i>)-furosa-5-ene-3 β ,22,26-triol 3- <i>O</i> -Rha-[Rha]-Glc) (tetrasaccharide steroidal saponin)	<i>Smilax china</i> (Liliaceae) [rhizome, root]	cAMP PDE (294)

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part	Target inhibited (other targets) / in vivo effect
Neotigogenin-3- <i>O</i> -Glc-[Rha]-Glc (= (25 <i>S</i>)-5 α -Spirostan-3- β -ol 3- <i>O</i> -Glc-[Rha]-Glc) (disaccharide steroidal saponin)	<i>Smilax riparia</i> (Liliaceae) [rhizome, root]	cAMP PDE (55)
Neotigogenin-3- <i>O</i> -Rha-Glc (= (25 <i>S</i>)-5 α -Spirostan-3- β -ol 3- <i>O</i> -Rha-Glc) (disaccharide steroidal saponin)	<i>Smilax riparia</i> (Liliaceae) [rhizome, root]	cAMP PDE (102)
Neoruscogenin 1- <i>O</i> -Rha-Ara (= Spirosta-5,25(27)-diene-1 β ,3 β -diol 1- <i>O</i> -Rha-Ara) (disaccharide steroidal saponin)	<i>Nolina recurvata</i> (Agavaceae) [stem]	cAMP PDE (84)
Neoruscogenin 1- <i>O</i> -Rha-[Xyl]-Ara (= Spirosta-5,25(27)-diene-1 β ,3 β -diol 1- <i>O</i> -Rha-[Xyl]-Ara) (trisaccharide steroidal saponin)	<i>Nolina recurvata</i> (Agavaceae) [stem]	cAMP PDE (92)
Neoruscogenin 1- <i>O</i> -Rha-[Xyl]-Fuc (= Spirosta-5,25(27)-diene-1 β ,3 β -diol 1- <i>O</i> -Rha-[Xyl]-Fuc) (trisaccharide steroidal saponin)	<i>Nolina recurvata</i> (Agavaceae) [stem]	cAMP PDE (161)
Neotigogenin-3- <i>O</i> -Glc-[Rha]-Glc (= (25 <i>S</i>)-5 α -Spirostan-3- β -ol-3- <i>O</i> -Glc-[Rha]-Glc) (trisaccharide steroidal saponin)	<i>Smilax riparia</i> (Liliaceae) [rhizome, root]	cAMP PDE (55)
Nuatigenin 3- <i>O</i> -Rha-Rha-Glc (steroidal trisaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (104)
Pennogenin 3- <i>O</i> -Rha-Gal-Glc (steroidal trisaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (389)
Pennogenin 3- <i>O</i> -Rha-Glc (steroidal disaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (127)
Pennogenin 3- <i>O</i> -Rha-Glc-Glc (steroidal trisaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (172)
Pennogenin 3- <i>O</i> -Rha-Rha-Glc (steroidal trisaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (180)
Pseudoprotodioscin (= 26- <i>O</i> - β -D-Glc-(25 <i>R</i>)-furosa-5,20-diene-3 β ,26-diol 3- <i>O</i> -Rha-[Rha]-Glc) (tetrasaccharide steroidal saponin)	<i>Smilax china</i> (Liliaceae) [rhizome, root]	cAMP PDE (47)
(25 <i>S</i>)-Ruscogenin 1- <i>O</i> -Rha-[Xyl]-Ara (= (25 <i>S</i>)-Spirost-5-ene-1 β ,3 β -diol 1- <i>O</i> -Rha-[Xyl]-Ara) (trisaccharide steroidal saponin)	<i>Nolina recurvata</i> (Agavaceae) [stem]	cAMP PDE (87)
Scillasaponin C (= Lanosterol-3- <i>O</i> -Rha-[Glc-Glc]-Glc-Ara-Glc) (phytosterol hexasaccharide saponin)	<i>Chionodoxa gigantea</i> (Liliaceae) [bulb]	cAMP PDE (112)
Scillasaponin D (= Lanosterol-3- <i>O</i> -Rha-Glc-Ara-Glc) (phytosterol tetrasaccharide saponin)	<i>Chionodoxa gigantea</i> (Liliaceae) [bulb]	cAMP PDE (215)

(continued)

Table 7.4 (Continued)

<i>Compound</i>	<i>Plant (family) part </i>	<i>Target inhibited (other targets) / in vivo effect </i>
(25 <i>R</i>)-5β-Spirostane-1β,2β,3β,4β,5β-pentol 1- <i>O</i> -Xyl (steroidal glycoside saponin)	<i>Reineckia carnea</i> (Liliaceae) [bulb, root]	cAMP PDE (27)
(25 <i>R</i>)-5β-Spirostane-1β,2β,3β,4β,5β,6β-hexol (steroidal saponin)	<i>Reineckia carnea</i> (Liliaceae) [bulb, root]	cAMP PDE (104)
(22 <i>R</i> ,25 <i>S</i>)-5α-Spirostan-3β-ol-3- <i>O</i> -Gal-[Xyl]-Glc-Gal (tetrasaccharide steroidal saponin)	<i>Dichelostemma multiflorum</i> (Liliaceae) [tuber]	cAMP PDE (154)
(25 <i>R</i> , <i>S</i>)-5α-Spirostan-3β-ol 3- <i>O</i> -Glc-[Glc]-Glc-Gal (tetrasaccharide steroidal saponin)	<i>Allium chinense</i> (Liliaceae) [bulb]	cAMP PDE (70) (Na ⁺ K ⁺ ATPase)
(25 <i>R</i> , <i>S</i>)-5α-Spirostan-2α,3β-diol 3- <i>O</i> -Glc-Glc-Galactoside (trisaccharide steroidal saponin)	<i>Allium chinense</i> (Liliaceae) [bulb]	cAMP PDE (421)
(25 <i>R</i> , <i>S</i>)-5α-Spirostan-2α,3β-diol 3- <i>O</i> -Glc-[Glc]-Glc-Gal (tetrasaccharide steroidal saponin)	<i>Allium chinense</i> (Liliaceae) [bulb]	cAMP PDE (369)
(25 <i>R</i>)-5α-Spirostan-3β,12α-diol 3- <i>O</i> -Rha-[Glc]-Glc (trisaccharide steroidal saponin)	<i>Lilium hansonii</i> (Liliaceae) [bulb]	cAMP PDE (1770)
(25 <i>S</i>)-5α-Spirostan-3β,27-diol-6-one 3- <i>O</i> -Glc[Ara]-Glc (trisaccharide steroidal saponin)	<i>Smilax sieboldii</i> (Liliaceae) [rhizome]	cAMP PDE (>500)
(25 <i>R</i>)-5α-Spirostane-2α,3β,6β-triol 3- <i>O</i> -Glc-[3-hydroxy-3-methylglutaroyl-Xyl]-Glc-Gal (= Agigenin-3- <i>O</i> -Glc-[3-hydroxy-3-methylglutaroyl-Xyl]-Glc-Gal) (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (24)
(25 <i>R</i>)-5α-Spirostane-2α,3β,6β-triol 3- <i>O</i> -Glucosyl-[Xyl]-Glc-Gal (= Aginoside) (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (75)
(25 <i>R</i>)-5α-Spirostane-2α,3β,5α,6β-tetrol 3- <i>O</i> -acetyl 2- <i>O</i> -Glc (= Alliogenin) (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (74)
(24 <i>S</i> ,25 <i>S</i>)-5α-Spirostane-2α,3β,5α,6β,24-pentol 3- <i>O</i> -acetyl 2- <i>O</i> -Glc (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (41)
(24 <i>S</i> ,25 <i>S</i>)-5α-Spirostane-2α,3β,5α,6β,24-pentol 2- <i>O</i> -Glc (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (69)
(24 <i>S</i> ,25 <i>S</i>)-5α-Spirostane-2α,3β,5α,6β,24-pentol (steroidal saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (264)

(continued)

Table 7.4 (Continued)

Compound	Plant (family) / part	Target inhibited (other targets) / in vivo effect
(24 <i>S</i> ,25 <i>S</i>)-5 α -Spirostane-2 α ,3 β ,5 α ,6 β -tetrol 2- <i>O</i> -Glc (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (67)
Spirost-25(27)-en-2 α ,3 β -diol 3- <i>O</i> -Glc-Glc-Xyl-Glc-Gal (steroidal pentasaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (91)
(24 <i>S</i> ,25 <i>S</i>)-5 α -Spirostane-2 α ,3 β ,5 α ,6 β -tetrol 3- <i>O</i> -benzoyl 2- <i>O</i> -Glc (steroidal glycoside saponin)	<i>Allium giganteum</i> (Liliaceae)	cAMP PDE (97)
(25 <i>R</i>)-5 α -Spirost-5-en-3 β ,12 α -diol 3- <i>O</i> -Rha-[Glc]-Glc (trisaccharide steroidal saponin)	<i>Lilium hansonii</i> (Liliaceae) [bulb]	cAMP PDE (345)
Spirostanol pentasaccharides (2a & 3a) (pentasaccharide steroidal saponins)	<i>Ipheion uniflorum</i> (Liliaceae) [bulb]	cAMP PDE (299 & 200)
Tigogenin 3- <i>O</i> -Glc-[Ara]-Glc (= (25 <i>R</i>)-5 α -Spirostan-3 β -ol 3- <i>O</i> -Glc-[Ara]-Glc) (trisaccharide steroidal saponin)	<i>Smilax sieboldii</i> (Liliaceae) [rhizome]	cAMP PDE (32)
Tigogenin 3- <i>O</i> -Glc-Glc (= (25 <i>R</i>)-5 α -Spirostan-3 β -ol 3- <i>O</i> -Glc-Glc) (disaccharide steroidal saponin)	<i>Lilium hansonii</i> (Liliaceae) [bulb]	cAMP PDE (>500)
Tigogenin 3- <i>O</i> -Rha-[Glc]-Glc (= (25 <i>R</i>)-5 α -Spirostan-3 β -ol 3- <i>O</i> -Rha-[Glc]-Glc) (trisaccharide steroidal saponin)	<i>Lilium hansonii</i> (Liliaceae) [bulb]	cAMP PDE (7)
Tigogenin 3- <i>O</i> -Rha-Glc-Xyl-Glc-Gal (steroidal pentasaccharide saponin)	<i>Triteleia lactea</i> (Liliaceae) [bulb]	cAMP PDE (109)
3 β ,16 α ,28-Trihydroxy-olean-12-en-30-oic acid 3- <i>O</i> -Rha-Glc-[Glc]-Ara-30- <i>O</i> -methyl ester (triterpenoid tetrasaccharide saponin)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (49)
3 β ,16 α ,28-Trihydroxy-olean-12-en-30-oic acid 3- <i>O</i> -Xyl-Glc-[Glc]-Ara-30- <i>O</i> -methyl ester (triterpenoid tetrasaccharide saponin)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (>5000)
3 β ,16 α ,28-Trihydroxy-olean-12-en-13,17-epoxy-30-al 3- <i>O</i> -Rha-Glc-[Glc]-Ara (triterpenoid tetrasaccharide saponin)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (126)
3 β ,16 α ,28-Trihydroxy-olean-12-en-13,17-epoxy-30-al 3- <i>O</i> -Xyl-Glc-[Glc]-Arabinoside (triterpenoid tetrasaccharide saponin)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (52)

(continued)

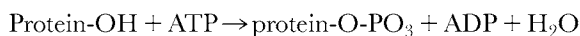
Table 7.4 (Continued)

Compound	Plant (family) part	Target inhibited (other targets) / in vivo effect
3 β ,16 α ,28-Trihydroxy-olean-12-en-30-oic acid -30-O-methyl ester (triterpenoid saponin)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (46)
[3 β ,16 α ,28,30-Tetrahydroxy-olean-12-ene (triterpenoid artefactual saponin)]	[<i>Ardisia crenata</i> (Myrsinaceae) saponin hydrolysis product]	cAMP PDE (30)
3 β ,16 α ,28,30-Tetrahydroxy-olean-12-en-13,17-epoxy 3-O-Rha-Glc-[Glc]-Ara (triterpenoid tetrasaccharide saponin)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (54)
3 β ,16 α ,28,30-Tetrahydroxy-olean-12-en-13,17-epoxy 3-O-Xyl-Glc-[Glc]-Ara (triterpenoid tetrasaccharide saponin)	<i>Ardisia crenata</i> (Myrsinaceae) [root]	cAMP PDE (72)
Visnadin (dihydropyranocoumarin)	<i>Seseli libanotis</i> (Apiaceae) [root]	cAMP PDE (170) [spasmolytic (17), coronary vasodilatory]
Non-plant reference		7.4n
[Flavanone (= 2,3-Dihydroflavone) (flavanone)]	Synthetic	cAMP PDE [100] [antifungal]
[3-Hydroxyflavone (= Flavonol) (flavonol)]	Synthetic	cAMP PDE (10–100) (PGP TR)
[3-Isobutyl-1-methylxanthine] (methylxanthine)	Synthetic	cAMP PDE [10; 55], cGMP PDE (PDE5) (8)
[Purealin] (brominated polycyclic aryl imidazole)	<i>Psammaphysilla purea</i> (sea sponge)	cAMP PDE (7) (CaM, MLCK) [modulates smooth muscle myosin]
[Rolipram] (aryl pyrrolidinone)	Synthetic	cAMP PDE 4 [antidepressant]
[Sildenafil (= Viagra)] (methyl xanthine analogue)	Synthetic; “Viagra makes plants stand up straight” – increases shelf-life of cut flowers by inhibiting degradation of cGMP (generated per NO elevation)	cGMP PDE (PDE5) (0.004) [increases cGMP, vasodilator, promotes penile erection]

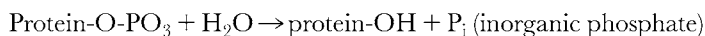
8 Signal-regulated protein kinases

8.1 Introduction

A major signalling mechanism in eukaryotes involves “primary messengers” (such as hormones, neurotransmitters and other extracellular signals) interacting with specific plasma membrane (PM) receptors with a resultant transient increase in the cytosolic concentration of so-called “second messenger” substances such as 3',5'-cyclic AMP (cAMP), guanosine 3',5'-cyclic monophosphate (cGMP), inositol-1,4,5- triphosphate (IP₃), diacylglycerol (DAG) and Ca²⁺ (Chapters 5 and 7). The “second messengers” ultimately act by activating protein kinases (PKs) that catalyse the phosphorylation of specific target proteins:



Protein phosphorylation alters protein ligand binding and/or catalytic functions and hence specific cellular processes, this representing the cellular “response” to the “stimulus” of the original “primary messenger”. The signalling system must be reversible and the protein phosphorylation step of the “stimulus–response” pathway is reversed through the action of phosphoprotein phosphatases (PPs), which are phosphohydrolases that catalyse the hydrolytic dephosphorylation of proteins:



Of the approximately 35,000 genes in the human genome, it has been estimated that about 1000 encode PKs and that several hundred encode PPs. These enzymes have a regulatory function (a useful analogy would be that of law officers in society) and often have overlapping functions or are otherwise backed up. (Thus, the absence of particular law officers might make society more disorderly but does not cause total anarchy.) For example, a “gene knockout” mouse lacking a regulatory subunit for the cAMP-activated PK (PKA) survives to breed but does not become obese on a diet of plenty. Lack of obesity arises because PKA is activated in the absence of the inhibitory regulatory subunit, the enzyme triglyceride lipase (TGL) is consequently mostly in the phosphorylated and activated form and triglycerides are rapidly broken down and catabolized. A mouse lacking phosphorylase b kinase (PhosbK) (a key PK involved in regulating glycogen breakdown and catabolism) survives to breed but as a “wee timorous beastie” that shivers uncontrollably.

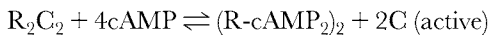
The “second messenger”-regulated PKs catalyse the phosphorylation of specific serine (R = –CH₂OH) and threonine (R = –CH(OH)–CH₃) R groups in proteins and are referred to as Ser/Thr-specific PKs. PM-located receptor Ser/Thr-specific PKs are also involved in signalling. However, another major group of PKs involved in signalling are the PM-located receptor tyrosine kinases (RTKs) such as the insulin-binding RTK. RTKs are activated by

the binding of specific hormones and catalyse the phosphorylation of tyrosine ($R = -CH_2-Phe-OH$) residues on substrate proteins. Soluble tyrosine kinases (TKs) also exist. It should be noted that phosphorylation of other amino acid residues in proteins can also occur (e.g. aspartate, glutamate and histidine phosphorylation) but will not be dealt with in this chapter.

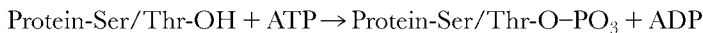
The three-dimensional structures of a number of Ser/Thr-PKs and RTKs have been determined. As a generality, these PKs have homologous catalytic domains but differ in the protein architecture concerned with regulation. This is reflected in the interaction of many plant compounds with both Ser/Thr-PKs and RTKs and with a number of PKs within each group. Accordingly, for the sake of efficiency, Ser/Thr-PK, RTK and TK targets are considered together in Table 8.1. Before summarizing PK-plant compound interactions (Table 8.1), it is useful to outline the structure and function of some of the major PKs.

8.2 Cyclic AMP-dependent protein kinase

Cyclic AMP (cAMP) can act by opening cAMP-gated Na^+ channels (and hence depolarizing the PM) (see Chapter 6) or by activating cAMP-dependent protein kinase (PKA). (A further specialized signalling function for cAMP is to act via PM G protein-coupled receptors (GPCRs) as an extracellular aggregation-promoting agent for the slime mould *Dictyostelium discoideum*.) PKA is heterotetrameric (inactive holoenzyme subunit composition R_2C_2 , where R is the inhibitory cAMP-binding regulatory subunit and C is the catalytic subunit). The catalytic subunit activity is inhibited by the regulatory subunits in the inactive holoenzyme but elevated cytosolic cAMP causes dissociation of the regulatory subunits and release of the now-active catalytic subunits:



Several kinds of regulatory subunits (Rs) can interact with C, namely RI and RII, and RII can indeed be phosphorylated by C to yield a phosphoprotein (P-II). The three-dimensional structure of the catalytic subunit involves two major domains, namely a smaller antiparallel β -sheet-rich domain and a larger α -helix-rich domain. Near the conjunction of these two domains there is a hydrophobic pocket (that binds the adenine of ATP) and a glycine-rich phosphate-binding loop (that binds the phosphoryl groups of ATP). Within the larger α -helix-rich domain are located substrate protein-binding determinants, residues interacting with the regulatory subunit and a catalytic loop that is involved in the transfer of the γ -phosphoryl ($-PO_3$) of ATP to a serine or threonine residue hydroxyl of the protein substrate:



The phosphorylation of a protein substrate X results in a subtle change in the conformation of the phosphoprotein (denoted P-X) that is typically associated with a change in ligand binding and/or catalytic activity. The specificity of PKA for phosphorylatable proteins is determined by residues immediately adjacent to the phosphorylated Ser or Thr as well as by longer range interactions of the substrate protein with the catalytic subunit. The consensus substrate phosphorylation site amino acid sequence for PKA is basic-basic-X-Ser-hydrophobic as typified by the synthetic PKA peptide substrate LRRASLG (Kemptide) that is widely used experimentally by biochemists in this area. A Walsh-Krebs PKA inhibitor protein ensures that free active C subunits are “mopped up” in the resting state of the cell, allowing for an “all-or-nothing” cellular response to signals causing a transient elevation of cAMP. A further regulatory complexity is introduced through the “targeting” of PKA to particular locations within cells.

As outlined in Chapter 7, cAMP is a “hunger” signal in prokaryotes and non-plant eukaryotes. In man, fasting and the consequent decrease in blood glucose causes secretion of glucagon which acts via GPCRs to increase cytosolic cAMP. Stress ultimately causes secretion of epinephrine from the adrenal medulla with a consequent increase in cAMP concentration in target cells (Chapters 5 and 7). PKA phosphorylates various proteins with generally catabolic consequences as outlined below.

Cyclic AMP activated protein kinase phosphorylates PP inhibitor protein-1 (I-1), the phosphorylated protein (P-I-1) being an inhibitor of protein phosphatase 1 (PP1). Similarly, phosphorylation of the glycogen targeting subunit of PP1 on site 2 results in PP1 release and inhibition. Such PP inhibition increases the levels of phosphoenzymes phosphorylated by PKA and avoids a futile cycle involving simultaneous protein phosphorylation and dephosphorylation. Increased phospho-acetylCoA carboxylase (P-ACC) through this mechanism results in decreased fatty acid synthesis (P-ACC being less active than ACC) and increases fatty acid oxidation (because carnitine acyltransferase is no longer inhibited by malonylCoA, the product of ACC action, and accordingly fatty acids can enter mitochondria as fatty acylcarnitine).

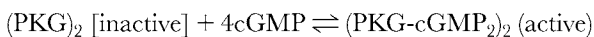
Phosphorylation of PhosbK by PKA yields a more active phospho-form of the enzyme (P-PhosbK) (with consequent generation of the more active phosphoenzyme phosphorylase a and increased breakdown of glycogen). Glycogen synthase (GS) phosphorylation yields the inactive P-GS form and hence inhibition of glycogen synthesis. Phosphorylation of adipocyte TGL yields the active P-TGL form with consequent increased breakdown in triglycerides to yield glycerol and fatty acids for export and catabolism.

Fructose-2,6-bisphosphate (F26BP) is a “plenty” signal, the levels of F26BP rising during “plenty” and decreasing during fasting. F26BP is produced in the liver from fructose-6-phosphate (F6P) in a reaction catalysed by a dual kinase-phosphatase enzyme (PFK2-FBPase2) that catalyses both the synthesis and hydrolysis of F26BP. Liver phospho-PFK2-FBPase2 (generated via PKA) has decreased kinase activity and increased phosphatase activity (with consequent decreased liver F26BP). Decreased F26BP decreases glycolysis and increases gluconeogenesis from lactate and amino acids (see Chapter 2). Similarly, phosphorylation of liver pyruvate kinase (PYK) by PKA yields the less active P-PYK and hence inhibits carbon flow in the glycolytic direction.

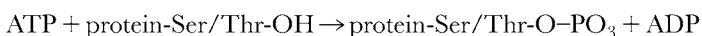
Elevated cAMP switches on the expression of particular enzymes controlled by the Cyclic AMP Response Element (CRE) promoter, notably the key gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK). PKA phosphorylates and activates a transcription factor (TF) (CRE binding protein, CREB protein) that binds to CRE and switches on specific gene transcription. Thus, the hunger signal cAMP acts via PKA to elevate glucose by gluconeogenesis through gluconeogenic enzyme synthesis and through phosphorylation of key enzymes.

8.3 Cyclic GMP-dependent protein kinase

Cyclic GMP (cGMP) can act to open cGMP-gated Na^+ channels (and hence depolarize the PM) (see Chapter 3) and can also activate a dimeric cGMP-dependent protein kinase (PKG). PKG is homologous to PKA but differs from PKA in having cyclic nucleotide-binding autoinhibitory domains and the catalytic domains on the same polypeptide chains, activation occurring through cGMP binding to the autoinhibitory domains:



Activated PKG phosphorylates specific protein substrates on Ser or Thr residues:



Phosphorylation of specific protein substrates results in a conformational change of the phosphoproteins associated with a change in ligand binding and/or catalytic properties. Thus PKG has an important role in regulation of vascular smooth muscle, PKG-catalysed phosphorylation of specific proteins resulting in smooth muscle relaxation, vascular dilation and increased blood flow (see Chapter 7).

8.4 Protein kinase C

A family of homologous protein kinase C isoenzymes (e.g. PKC- α , β , γ , δ , ζ and η) are variously activated by Ca^{2+} , phospholipids (notably phosphatidylserine) and diacylglycerol (DAG). The inactive PKC is autoinhibited by an inhibitory domain and binding of the activating ligands changes the conformation of the autoinhibitory domain in a subtle way that overcomes the inhibition.

Protein kinase C isozymes when activated shift in location to the PM and are cleared from the cytosol. A major target of PKC is the RTK signalling pathway component Raf. Raf (a mitogen activated kinase kinase kinase or MAPKKK) is switched on by Ras-GTP and phosphorylation by PKC with the successive consequences of MAP kinase kinase (MAPKK) phosphorylation and activation, MAP kinase (MAPK) activation through Tyr- and Thr-phosphorylation, TF phosphorylation by activated MAPK and specific gene expression (for further amplification, see Section 8.7 on RTK). Thus, PKC is involved in mitogen-activated signalling pathways ending in specific gene expression and cell division. Further major targets for PKC are proteins of the myristoylated alanine-rich C kinase substrate (MARCKS) family. The effector domains of MARCKS proteins are phosphorylated by PKC, bind calmodulin (CaM) and are involved in membrane binding and a variety of membrane processes such as endocytosis, exocytosis, phagocytosis, cellular migration and neurosecretion.

Protein kinase C isozymes are activated by Euphorbiaceae plant-derived phorbol esters such as tetradecanoylphorbolacetate (TPA) that bind to the DAG-activation site. PKC can phosphorylate specific TFs that bind to DNA regulatory “promoters” called TPA response elements (TREs). This interaction enables transcription of specific genes. This process can be summarized as follows: signalling giving elevated Ca^{2+} \rightarrow PKC activation \rightarrow TF phosphorylation \rightarrow P-TF binding to TRE \rightarrow specific gene transcription switched on \rightarrow specific gene expression.

8.5 Ca^{2+} -calmodulin-dependent protein kinases

Cytosolic free Ca^{2+} concentration is elevated by a variety of signals and can either directly activate particular proteins or activate proteins via the Ca^{2+} -binding regulator protein calmodulin (CaM). Ca^{2+} -CaM activates a number of Ca^{2+} -CaM-dependent protein kinases (CaMPKs), namely CaMPKs I–IV. These PKs phosphorylate a variety of protein substrates. CaMKII is autoinhibited and Ca^{2+} -CaM binding to a specific site on the enzyme causes a subtle conformational change resulting in displacement of the autoinhibitory domain. The activated CaMKII can also autophosphorylate yielding an activated P-CaMKII that is not activated by CaM. This property and the formation of oligomers by CaMKII have suggested a further type of molecular “signalling memory” device (in addition to receptor desensitizing by phosphorylation and receptor internalization and destruction). CaMKII catalyses the phosphorylation of specific TFs with resultant switching on of specific gene expression.

A Ca^{2+} -CaM-dependent PK with a very specific protein substrate is myosin light chain kinase (MLCK) that phosphorylates myosin light chains (MLCs) associated with the “head”

of the muscle contractile protein myosin. Myosin has an elongated tail and a globular “head” that interacts with the filamentous protein actin in the process of muscle contraction. MLCK is autoinhibited and Ca^{2+} -CaM binding results in activation through a change in positioning of the autoinhibitory domain. Signals increasing cytosolic Ca^{2+} -CaM in smooth muscle successively result in increased Ca^{2+} -CaM, MLCK activation, MLC phosphorylation and tropomyosin repositioning (this allowing actin-myosin head interactions and smooth muscle contraction).

Increased cAMP in smooth muscle cells causes muscle relaxation through activation of cAMP-dependent PK (PKA). PKA phosphorylates MLCK and phospho-MLCK (P-MLCK) is poorly activated by Ca^{2+} -CaM. PKA also phosphorylates an ER protein called phospholamban, the P-phospholamban entity increasing the activity of the ER membrane Ca^{2+} -ATPase which lowers cytosolic Ca^{2+} concentration and thus prevents smooth muscle contraction.

8.6 AMP-dependent protein kinase

Nutrient stress, exercise and (pathologically) ischaemia (blockage of blood supply) cause a decrease in ATP and an increase in 5'-AMP (AMP). AMP activates AMPK kinase (AMPKK) which phosphorylates and activates AMP-dependent protein kinase (AMPK). Phospho-AMPK (P-AMPK) is activated further by AMP and AMP also inhibits PP-catalysed dephosphorylation of P-AMPK. AMPK is a heterotrimer (subunit composition $\alpha\beta\gamma$). The catalytic α subunit domain structure involves a successive [catalytic domain (phosphorylated)]-[autoregulatory (autoinhibitory) domain]-[subunit targeting domain] arrangement. Maximum α activity requires phosphorylation of a key Thr residue and β and γ subunit interactions. The AMP binding site is between the β and γ subunits and N-terminal myristoylation of the β subunit enables membrane binding. The AMPK system is related to a primitive catabolism-regulating system. Thus, the yeast α homologue snfPK is activated at low glucose concentration.

AMP-dependent protein kinase recognizes a decrease in so-called “adenylate charge” (i.e. decreased ATP and increased AMP) that typically arises from exercise (or pathologically from ischaemia). AMPK phosphorylates various proteins with consequent increased fatty acid catabolism by cardiac and skeletal muscle, increased vascular dilation (better O_2 and nutrient supply to tissue) and better glucose transport through increased mobilization of the glucose transporter. The properties of AMPK provide a molecular explanation for the beneficial effects of exercise for people with type 2 diabetes mellitus, AMPK activation causing better glucose utilization and hence lowering blood glucose.

A key target of AMPK is acetylCoA carboxylase (ACC). Phospho-ACC (P-ACC) is less active through being less activated by citrate and more sensitive to inhibition by palmitoylCoA. The lowered activity of P-ACC results successively in decreased malonylCoA, decreased fatty acid synthesis, increased fatty acyl carnitine transferase (which is inhibited by malonylCoA), increased fatty acyl translocation into mitochondria (as fatty acylcarnitine) and increased fatty acid oxidation and ketone body production by liver mitochondria. Note that this regulatory process of switching off cytosolic fatty acid synthesis and stimulating mitochondrial fatty acid oxidation avoids a “futile cycle” involving simultaneous anabolic synthesis and catabolic degradation of fatty acids.

Further processes involving AMPK include: phosphorylation of creatine kinase (CK) (P-CK being less active and thus maximizing ATP levels for immediate use); phosphorylation of hydroxymethylglutarylCoA reductase (HMGCoAR) (P-HMGCoAR being inhibited

and hence anabolic cholesterol synthesis being reduced); and phosphorylation of endothelial nitric oxide synthase (eNOS) (P-eNOS being activated with the successive consequences of elevated NO, soluble guanyl cyclase activation by NO, increased cGMP, PKG activation by cGMP, phosphorylation of particular muscle proteins, smooth muscle relaxation, vascular dilation and increased O₂ and nutrient supply to tissues). Activation of AMPK also results in decreased apoptosis, decreased glucose-dependent fatty acid synthase expression and increased mobilization of the glucose transporter to the PM.

8.7 Receptor tyrosine kinases

A variety of growth-regulating hormones such as insulin, insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) act via PM receptors that are RTKs. The RTKs span the PM and have an extracellular hormone-binding domain, a transmembrane domain and a cytosolic domain with tyrosine kinase activity that phosphorylates protein substrates on the phenolic OH of tyrosine residues (R = -CH₂-Phe-OH). The initial hormone binding to the extracellular domain results in aggregation of the RTKs, activation of the TK of the RTK and autophosphorylation (on Tyr residues) of the cytosolic RTK domain. The activated TK activity can now also phosphorylate other proteins and the phospho-tyrosine (P-Tyr) groups can interact with other proteins as outlined below.

A number of cytosolic proteins have SH domains (“Src homology” domains being also found on the soluble TK Src). SH2 domains bind P-Tyr and SH3 domains bind to proline-rich regions on proteins. Proteins having SH2 and SH3 domains can variously bind to activated RTKs and to each other in a type of very specific molecular “Lego”. Many of the proteins involved in RTK-mediated signalling are encoded by normal “proto-oncogenes” that can be mutated by various mechanisms to give “oncogenes” or genes contributing to transformation of normal cells to cancerous cells in which the growth hormone signalling pathways are altered. Thus, the soluble TK Src is normally switched off by RTK-catalysed tyrosine phosphorylation but mutant Src forms encoded by oncogenic *src* genes are altered so that this control is prevented.

“Downstream” proteins involved in RTK-mediated signalling include the following: RTK substrates (e.g. the insulin receptor substrates, IRS1 and IRS2, are phosphorylated by the insulin RTK); Syp (a phosphotyrosine phosphatase with SH2 domains that binds to RTK, is Tyr phosphorylated and binds other effectors); Grb2 (an adaptor protein that binds to RTK via SH2 domains and binds other effectors via its SH3 domains); PLC γ (a phospholipase C enzyme with SH2 and SH3 domains, that is activated by RTK by phosphorylation on Tyr and catalyses the hydrolysis of PI45P₂ to DAG and IP₃ with resultant release of Ca²⁺ from the ER via IP₃-gated Ca²⁺ pores and PKC activation by phospholipid, DAG and Ca²⁺); GTPase activating protein (GAP) (a protein with SH2 and SH3 domains that activates the GTPase activity of the small GTP-binding protein Ras); Sos (a guanyl nucleotide exchange factor (GEF) that promotes inactive Ras-GDP conversion to the active Ras-GTP form); phosphatidylinositol-3-kinase (PI3K) (that is activated by interaction with P-IRS-1 and catalyses conversion of PM-located PI4,5P₂ to the second messenger PI3,4,5P₃, a 5'-hydrolase thence yielding the further second messenger PI3,4P₂); Src (a soluble protein tyrosine kinase with SH2 and SH3 domains that can be myristoylated to allow PM association) and Raf (a MAPKKK).

The various ways in which these downstream “Lego” components interact can be conveniently illustrated through the action of insulin, a hormone secreted in response to elevated

blood glucose. Insulin is mitogenic (i.e. it promotes cell division). However, insulin also switches on anabolic processes of glycogen synthesis, protein synthesis and fat synthesis. These two types of insulin signalling pathways are outlined below.

Insulin binds to its specific RTK → RTK aggregation, RTK activation and Tyr phosphorylation → IRS-1 Tyr phosphorylation → Grb2 binds to P-IRS-1 via a SH2 domain → Sos, GEF binds to a proline-rich region of Grb2 via a SH3 domain → active Ras-GTP is formed from inactive Ras-GDP (this being reversed by the GTPase activating protein GAP which has SH2 and SH3 domains). Ras-GTP and PKC (activated by DAG and Ca^{2+} through PLC γ activation as described above) combine to activate a Ser/Thr-specific PK Raf (an MAPKKK) that initiates a PK cascade. Thus, Raf (MAPKKK) (activated by Ras-GTP and phosphorylation by PKC) phosphorylates and activates MAPKK which then activates MAPK (otherwise known as ERK or “external signal-regulated protein kinase”) by phosphorylating Thr and Tyr within a critical Thr–Glu–Tyr sequence. Activated MAPK phosphorylates specific TFs which interact with specific promoters in the nucleus and “switch on” transcription of specific genes and hence specific gene expression. This pathway is reversed through the operation of P-Tyr phosphatases (PTPases) and P-Ser/P-Thr phosphatases (PPs).

Insulin also acts to ultimately activate a Ser/Thr-specific PK Akt (PKB) through a pathway successively involving: insulin-RTK binding and RTK activation; IRS-1 Tyr phosphorylation; PI3K binds to P-IRS-1 via a SH2 domain; activated PI3K catalyses the phosphorylation of the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PI4,5P_2) to yield the second messenger PI3,4,5P_3 which is thence converted to PI3,4P_2 (via PI3,4,5P_3 5'-phosphohydrolase). The second messengers PI3,4,5P_3 and PI3,4P_2 activate the phosphatidylinositol lipid-dependent PKs (PDPKs) PDK1 and PDK2, the second messengers PI3,4,5P_3 and PI3,4P_2 binding to “pleckstrin homology” (PH) domains on the PKs. PI3,4,5P_3 and PI3,4P_2 also bind to a PH domain on a further Ser/Thr PK called protein kinase B (PKB) (Akt) which is then phosphorylated by PDPKs on a Ser and a Thr residue to yield fully activated PKB. PKB is involved in anabolic control by phosphorylating various proteins as outlined in Section 8.8.

8.8 Protein kinase B

Activated PKB (Akt) phosphorylates the following proteins with the indicated anabolic consequences: Bad phosphorylation yields P-Bad which then dissociates from a Bcl-2-Bcl- x_L complex in the mitochondrial outer membrane and is sequestered by 14.3.3 proteins. Mitochondrial pore blockage by the Bad-free Bcl-2-Bcl- x_L complex successively prevents cytochrome c release from mitochondria, blocks procaspase activation by cytochrome c and thus inhibits apoptosis and increases cell survival. Phosphorylation of p70S6 kinase by PKB results in activation of this PK, phosphorylation of ribosomal small subunit protein S6 and enhancement of translation (protein synthesis). Phosphorylation of glycogen synthase (GS) kinase 3 (GSK3) by PKB results in an inactive P-GSK3, a consequent increase in the amount of the active non-phosphorylated form of GS and increased glycogen synthesis.

Protein kinase B also contributes to mobilization of the glucose transporter GLUT4 to the PM of glucose importing cells (e.g. muscle cells) with consequent increase in glucose transport and glucose utilization. The signal for insulin production is elevated blood glucose and hence PKB-dependent GLUT4 mobilization enables a homeostatic reduction of blood glucose. PKB is involved in the activation by phosphorylation of the glycogen targeting protein subunit of glycogen-bound protein phosphatase 1 (PP1) at site 1. This results in an increased

activity of PP1 with important metabolic consequences. Thus, increased PP1 activity dephosphorylates phospho-glycogen synthase (P-GS) yielding the active dephospho-GS (GS) and hence an increased rate of glycogen synthesis. Similarly, PP1 dephosphorylates P-ACC resulting in a more active dephospho-ACC, increased fatty acid synthesis and decreased fatty acid oxidation (through malonylCoA inhibition of carnitine acyl transferase and hence of fatty acid translocation into mitochondria). PP1 activation also results in decreased glycogen breakdown (glycogenolysis) and decreased gluconeogenesis from lactate and amino acids.

The above outline summarizes the molecular mechanisms involved in the insulin response. Insulin is released in response to elevated blood glucose (or “plenty”) and increases anabolic processes (glycogen, protein and fat synthesis), increases glucose uptake and glucose utilization (glycolysis) and decreases glycogen, protein and fat breakdown and gluconeogenesis. Overall, insulin restores “balance” by increasing anabolic reactions and decreasing blood glucose in a period of “plenty”.

8.9 Cytokine activation of the JAK/STAT pathway

Cytokines are immunomodulatory and growth regulatory proteins produced by leucocytes, this cytokine production being associated with infection and wounding. Cytokines including interleukins (ILs) and interferons (IFNs) activate the Janus or 2-faced kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) pathway with resultant induction of specific gene transcription. Cytokines and related bioactive proteins acting via the JAK/STAT pathway can be grouped into several classes based on the nature of the PM receptors.

The cytokine subfamily 1 includes erythropoietin (EPO) (that increases red blood cell production and has accordingly been involved in sports drug abuse), granulocyte colony stimulating factor (G-CSF) (that stimulates leucocyte differentiation), GH (used clinically for growth impairment due to GH deficiency), prolactin (PRL) (that promotes milk production), IL-4 and IL-7. The members of this family act via homodimeric receptors. The leucocyte-derived cytokines of this group variously modulate haematopoiesis and immune responses.

Cytokine subfamily 2 includes proteins with heterodimeric α - β or α -gp130 receptors. Thus, granulocyte macrophage colony stimulating factor (GM-CSF), IL-3 and IL-5 act via α - β receptors and share β receptors. Cardiotrophin-1 (CT-1), ciliary neurotrophic factor (CNTF), IL-6, IL-1, leukaemia inhibitory factor (LIF) and oncostatin M (OSM) act via heterodimeric α -gp130 receptors with a shared gp130 receptor subunit. Leucocyte-derived cytokines of this family have immunomodulatory and haematopoietic effects.

Cytokines of subfamily 3 include the leucocyte-derived interleukins IL-2, IL-4, IL-7, IL-9 and IL-15 that act via heterotrimeric α - β - γ receptors and variously modulate haematopoiesis and immune responses.

Interferons α , β and γ (IFN α , IFN β and IFN γ) act via heterodimeric IFN receptors. The interferons are leucocyte-derived antiviral factors that ultimately inhibit viral replication through RNase cleavage of ssRNA and inhibition of transcription and translation. The interferons induce expression of dsRNA-dependent PK (dsRNAPK) (that inhibits translation through phosphorylation of the translation initiation factor eIF2 α), 2,5-A synthetase (which generates 2',5'-oligoadenylates (2,5-As), these compounds activating a 2,5-A-dependent RNase resulting in RNA cleavage) and Mx GTPase (which inhibits transcription).

Leptin reports adipose fat status to the CNS. Leptin is anorectic and regulates anorectic and orexigenic hormone expression by acting via dimeric Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd and Ob-Re JAK/STAT-associated receptors.

The JAK/STAT pathway can be conveniently illustrated by the action of a cytokine acting via a dimeric receptor. The hormone binds to its specific receptor that is an $\alpha\beta$ heterodimer in which the extracellular α subunit binds the hormone and the intracellular β subunit transduces the signal. Hormone-binding causes the formation of a dimerized receptor ($\beta\alpha$ -H- $\alpha\beta$). The TKs JAK1 and JAK2 associate with the activated receptor dimer resulting in reciprocal transphosphorylation on Tyr residues by the JAKs. The activated JAKs phosphorylate Tyr residues on the receptor that are recognized by SH2 domains of STAT β and STAT α . The bound STATs are then phosphorylated by JAKs and form a STAT β -STAT α homodimer which is translocated to the nucleus. The phosphorylated STAT dimer binds to a specific DNA regulatory element (GAF) resulting in specific gene transcription and thence the ultimate response to the initial cytokine signal of specific protein expression.

8.10 Cell cycle control

Cell division (mitosis) is a process requiring rigorous control and indeed the neoplastic, cancerous state involves uncontrolled cell division. Cells can exist in a quiescent state called G_0 . After entry into G_1 , an irreversible committed “start” step occurs resulting in successive entry into an S stage (in which DNA synthesis occurs), G_2 , M (in which mitosis occurs) and thence back to G_1 and further progression through the so-called “cell cycle”. Progression through the various stages of the “cell cycle” requires activation of cell division PKs (CDKs) and the synthesis of cyclins (substrate-specifying proteins that are newly synthesized and then destroyed via ubiquitination and proteasome-mediated proteolysis).

Each cell cycle stage is associated with specific CDKs. Thus, the CDK specific for G_2 is p34cdc2. Activation requires dephosphorylation of Thr-14 and Tyr-15, phosphorylation of Thr-167 and the presence of a G_2 stage-specific cyclin for activity. CDK substrates include lamins and histone H1 that are phosphorylated on Ser residues within a Ser-Pro-X-X sequence. The control of the CDKs involves regulation of cyclin synthesis and degradation and regulation of a complex set of Ser/Thr-specific PKs, signal-regulated tyrosine kinases (RTKs and other TKs), P-Ser-, P-Thr- and P-Tyr-hydrolysing protein phosphatases and inhibitor proteins. The anti-mitotic, synthetic, 5,7-dihydroxyflavone (chrysin)-derivative flavopiridol inhibits the CDKs CDK1, CDK2, CDK4 and CDK7 (Table 8.1).

8.11 Receptor serine/threonine kinases

Transforming growth factor β (TGF β) (that suppresses cell proliferation), the related developmentally important activins (involved in mesoderm induction) and bone morphogenetic proteins (involved in bone formation) act via PM-located transmembrane receptors that are Ser/Thr-specific PKs. Thus, TGF β binds to the extracellular domain of a specific TGF β receptor with the successive consequences of activation of the receptor Ser/Thr-specific PK activity, phosphorylation of a protein Mad to yield P-Mad and downstream consequences resulting in developmentally important specific gene expression. Thus, dorso-ventral differentiation in *Xenopus* embryos involves Mad-like proteins and a *Mad*-like gene is a tumour suppressor gene.

8.12 Other protein kinases

As indicated above, there may be as many as a thousand PKs encoded by the human genome. In addition to the Ser/Thr PKs described above, there are other PKs that have been

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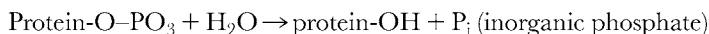
extensively studied, notably casein kinases I and II and the interferon-induced dsRNA-dependent PK (dsRNAPK) (that inhibits translation through phosphorylation of the translation initiation factor eIF2 α).

Translation can be inhibited through the phosphorylation of eukaryote initiation factor 2 (eIF2) by dsRNA-dependent PK (activated by viral dsRNA as a consequence of viral infection), by hemin-inhibited PK (activated in the absence of hemin in reticulocytes) and by GCN2 kinase (general control non-derepressible kinase) (activated by amino acid starvation and excess free tRNA). Phosphorylation of RNA polymerase II is a key process in the regulation of transcription (Chapter 9).

A major signalling pathway involving a key PK is that involving the cytokines tumour necrosis factor (TNF α) and IL-1. The mammalian innate defence system Toll-like receptors (TLRs 1–6) (related to the *Drosophila* Toll transmembrane protein) recognize bacterial cell wall components such as peptidoglycans (via TLR2) and lipopolysaccharide (LPS) (via TLR4). These various ligands bind to the corresponding specific PM receptors with consequent activation of a PK that catalyses the phosphorylation of I κ B (the protein inhibitor of the TF NF κ B). P-I κ B dissociates from NF κ B and is destroyed by proteolysis. The now-activated NF κ B moves to the nucleus, interacts with specific promoter sequences and switches on the synthesis of a variety of pro-inflammatory proteins including inducible cyclooxygenase (COX-2) (Chapter 14), inducible nitric oxide synthase (iNOS) (Chapters 7 and 14) and a variety of cytokines. A similarly initiated pathway results in c-Jun N-terminal kinase (JNK) activation and transcriptional activation. (It should be noted that TNF α also acts via PM receptors to activate the caspase proteolytic cascade leading to apoptosis.) The anti-inflammatory phenolic curcumin from *Curcuma* species (turmeric) (Zingiberaceae) inhibits the I κ B kinase (IKK) and thus inhibits NF κ B activation and the pathway leading to expression of pro-inflammatory proteins such as iNOS.

8.13 Phosphoprotein phosphatases

Reversibility in signalling requires that ultimately phosphoproteins must be dephosphorylated. This is achieved by PPs that catalyse the following hydrolysis reaction:



There are many different kinds of PPs of which the best known are PP1, PP2A, PP2B and PP2C that catalyse the dephosphorylation of P-Ser and P-Thr residues on substrate proteins. PP1 is inhibited by dinoflagellate-derived okadaic acid, by blue-green alga *Microcystis*-derived microcystins and by phosphorylated endogenous Inhibitor protein 1 (I1-P). PP2A is also inhibited by dinoflagellate-derived okadaic acid and by blue-green alga *Microcystis*-derived microcystins but is less sensitive to these inhibitors than PP1. PP2B is a Ca²⁺-dependent PP having a catalytic A subunit and a calmodulin (CaM)-like regulatory subunit B. PP2C is a Mg²⁺-dependent PP. A variety of PPs catalyse the dephosphorylation of phosphotyrosine-phosphorylated proteins.

In addition to the P-Ser- and P-Thr-specific PPs described above, there are a number of P-Tyr-specific PPases that reverse the consequences of protein Tyr phosphorylation deriving from RTK and TK activation. Substrates include RTKs themselves and downstream Tyr-phosphorylated signalling proteins such as PKC γ , MAPK (ERK), JAK/STAT receptors, kinases, STATs and the CDKs described above.

Table 8.1 lists a variety of plant-derived compounds that inhibit PKs. As previously discussed, the homologies between the catalytic domains of Ser/Thr-specific PKs and Tyr-specific PKs

mean that many such compounds inhibit both classes of PKs. Of particular note are the pro-inflammatory, co-carcinogenic Euphorbiaceae plant-derived phorbol esters and related compounds that activate particular PKC isoenzymes (Table 8.2). Some other plant compounds that interfere with RTKs, P13K and PP are described in Tables 8.3, 8.4 and 8.5, respectively.

Table 8.1 Eukaryote protein kinases

<i>Compound (class)</i>	<i>Plant source (family) plant part </i>	<i>Target inhibited (other targets) / in vivo effects/</i>
cAMP-dependent PK (PKA), Ca²⁺-dependent PK (CDPK), cell division/cyclin-dependent PK (CDK), Ca²⁺ & PL-dependent PK (PKC), cGMP-dependent PK (PKG), myosin-light chain kinase (MLCK), receptor tyrosine kinase (RTK)	Earl Sutherland (USA, Nobel Prize, Medicine, 1971; cAMP as second messenger); Paul Nurse (UK, Nobel Prize, Physiology/Susan Medicine 2001 (CDK)) with Tim Hunt (UK, cyclins) & Leland Hartwell (USA, CDC genes); Edwin Krebs & Edmond Fischer (USA, Nobel Prize, Medicine, 1992; PKA); Bruce Kemp (Australia, PKs, MLCK),	8.1 Yuichiro Nishizuka (Japan, PKC), Phillip Cohen (UK, PKA, PKB, PKs), Taylor (USA, PKA)
Alkaloid		8.1a
[Apomorphine] (aporphine isoquinoline)	Semi-synthetic from Morphine (morphinan isoquinoline alkaloid from <i>Papaver somniferum</i> , opium poppy) (Papaveraceae) [aerial]	CDPK (270), MLCK (11), PKA (1), PKC (8)
(+)-Boldine (aporphine isoquinoline)	<i>Desmos</i> (Annonaceae), <i>Laurelia</i> (Atherospermataceae), <i>Litsea</i> , <i>Sassafras</i> (Lauraceae), <i>Liriodendron</i> (Magnoliaceae), <i>Boldea</i> , <i>Peumus</i> , <i>Monimia</i> (Monimiaceae), <i>Retanilla</i> (Rhamnaceae) spp.	MLCK (12), PKA (82)
Bulbocapnine (= <i>N</i> -Methyl-launobine) (aporphine isoquinoline)	<i>Fumaria officinalis</i> (Fumariaceae), <i>Corydalis bulbosa</i> , <i>C. cava</i> , <i>C. decumbrens</i> , <i>C. solida</i> , <i>Glaucium flavum</i> , <i>G. pulchrum</i> (Papaveraceae)	MLCK (30) [sedative]
α -Chaconine (steroidal alkaloid glycoside)	<i>Notholirion hyacinthium</i> , <i>Veratrum stenophyllum</i> (Liliaceae), <i>Solanum chacoense</i> , <i>S. nigrum</i> , <i>S. tuberosum</i> (potato) (Solanaceae) [tuber]	CDPK (290), PKA (130), PKC (217)
Chelerythrine (benzophenanthridine)	<i>Argemone mexicana</i> , <i>Bocconia arborea</i> , <i>B. frutescens</i> , <i>Chelidonium majus</i> , <i>Eschscholzia californica</i> , <i>Glaucium flavum</i> , <i>Sanguinaria canadensis</i> (Papaveraceae), <i>Zanthoxylum americanum</i> (Rutaceae)	PKA (170), PKC (0.7) [0.8], TK (100), CaM-PK (>100) (DNAL, GABAA-R, V-R)
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Chelidonium</i> , <i>Dicentra</i> , <i>Eschscholtzia</i> , <i>Papaver</i> , <i>Sanguinaria</i> (Papaveraceae), <i>Fumaria</i> (Fumariaceae), <i>Zanthoxylum</i> (Rutaceae), <i>Pteridophyllum</i> (Sapindaceae) spp.	CDPK (41), MLCK (158), PKA (6), PKC (217) (ATPase, Ca ²⁺ -ATPase, Diamine oxidase, V-R) [antibacterial, AI]

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part/	Target inhibited (other targets) / in vivo effects/
Phenolics		
Acacetin (= Apigenin 4'-methyl ether; 5,7,4'-Trihydroxyflavone 4'-methyl ether) (flavone)	Fern [leaf exudate], <i>Ammi visnaga</i> (Apiaceae), Asteraceae [leaf], Betulaceae [leaf bud exudate], <i>Ginkgo biloba</i> (Ginkgoaceae) <i>Agastache foeniculum</i> , <i>Mentha aquatica</i> (Lamiaceae); glycosides in <i>Cirsium</i> (Asteraceae), <i>Linaria</i> (Scrophulariaceae) spp., Tiliaceae	8.1p EGF-RTK (141) (AR, ITD) [allergenic, inhibits histamine release]
Acteoside (= Kusagin; Verbascoside) (phenylethanoid glycoside)	<i>Stachys sieboldii</i> (Lamiaceae), <i>Buddleja</i> , <i>Forsythia</i> (Oleaceae), <i>Penstemon</i> , <i>Verbascum</i> (Scrophulariaceae) spp., Acanthaceae, Bignoniaceae, Gesneriaceae, Plantaginaceae, Orobanchaceae, Verbenaceae	PKC α (9) [5-LOX] [AI, hypertensive, antihepatotoxic]
Alizarin (= 1,2-Dihydroxy-9,10-anthraquinone) (anthraquinone)	<i>Rheum palmatum</i> (Polygonaceae) [root], <i>Rubia cordifolia</i> , <i>R. tinctorum</i> (madder), <i>Galium</i> spp., <i>Asperula odorata</i> [root], <i>Morinda citrifolia</i> (Rubiaceae) [wood] <i>Paeollia</i> sp. (Paeonaceae) [root]	CDPK (100), MLCK (14), PKA (19), PKC (13) (HIV-1 INT) [antineoplastic, red pigment & dye] CKII (2)
Anthocyanidin trimer (condensed tannin)		
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Lamiaceae [leaf surface]; [seed]; <i>Apium</i> , <i>Daucus</i> (Apiaceae), <i>Achillea</i> , <i>Artemisia</i> (Asteraceae), <i>Mentha</i> , <i>Thymus</i> (Lamiaceae), ferns [leaf surface], <i>Buddleja officinalis</i> (Loganiaceae) [flower], <i>Digitaria exilis</i> (Poaceae); as glycoside in <i>Apium</i> (celery), <i>Petroselinum</i> (parsley) (Apiaceae), <i>Cosmos</i> , <i>Erigeron</i> , <i>Dahlia</i> (Asteraceae), <i>Amorpha</i> (Fabaceae) spp.	CDK2, EGF-RTK (93), IKK, MLCK, PKA, PKC (> 50), RTK (FGF-RTK, insulin-RTK, IGF-1-RTK, TPO) (BZ-R-like R, EST-R, F ₁ -ATPase, Na ⁺ /K ⁺ /Cl ⁻ TR) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
[Apigenin 7-O-methyl ether (= 5,7,4'-Trihydroxyflavone 7-O-methyl ether)] (flavone)	Semi-synthetic cf. trihydroxyflavones	CDPK (>160), PKA (17)
Arecatannin A-1 (tannin)	<i>Paeollia</i> sp. (Paeonaceae) [root]	PKA (0.2)
Baicalein (= 5,6,7-Trihydroxyflavone) (flavone)	<i>Scutellaria</i> spp. (Lamiaceae) [root, leaf], <i>Oroxylum indicum</i> (Bignoniaceae) [leaf], <i>Plantago major</i> (Plantaginaceae)	PKC signalling (AROM, HIV-1 INT, HIV-1RT, TOPII) [apoptotic]
Biochanin A (= 5,7-Dihydroxy-4'-methoxyisoflavone; Pratensol) (isoflavone)	<i>Cicer arietum</i> , <i>Medicago sativa</i> , <i>Trifolium pratense</i> , <i>Baptisia</i> spp., <i>Dalbergia</i> spp. (Fabaceae), <i>Viola cadudifolia</i> (Myristicaceae) [wood], <i>Cotoneaster pannosa</i> (Rosaceae) [fruit]	EGF-RTK (92), MLCK (303), PKA (100) (EST-R, F ₁ -ATPase, TPO) [oestrogenic, hypolipidaemic]
Butein (= 2',4',3,4-Tetrahydroxy-chalcone) (chalcone)	<i>Vicia faba</i> , <i>Dalbergia odorifera</i> , <i>Robinia pseudoacacia</i> (Fabaceae) [wood]; glycosides in <i>Coreopsis</i> , <i>Bidens</i> (Asteraceae), <i>Butea</i> (Fabaceae) spp.	EGF-RTK (65), p60 ^{c-src} TK (65) (F ₁ -ATPase, GST, 5 α R) [antioxidant]

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) plant part	Target inhibited (other targets) / in vivo effects/
Calceolarioside A (phenylethanoid glycoside)	<i>Digitalis purpurea</i> (Scrophulariaceae) [leaf]	PKC α (0.6)
Calceolarioside B (phenylethanoid glycoside)	<i>Digitalis purpurea</i> (Scrophulariaceae) [leaf]	PKC α (5)
(+)-Catechin (= Catechinic acid; Catechuic acid) (flavan-3-ol)	Widespread; <i>Gossypium</i> sp. (Malvaceae), <i>Agrimonia eupatoria</i> (Rosaceae), <i>Salix caprea</i> (willow) (Salicaceae) [flower]	MLCK (440), PKA (13) (AR, COX-1, COX-2, PSTase) [antioxidant, bitter]
Catechin-(7,8-b,c)-4 β -(3,4-dihydroxyphenyl)-dihydro-2(3H)-pyranone (catechin phenylpropanoid lactone)	<i>Phyllocladus trichomanoides</i> (Podocarpaceae) [twig, cladode]	CDPK (200), MLCK (83), PKA (> 200), PKC (rat) (17)
Catechin-(7,8-b,c)-4 β -(3,4-dihydroxyphenyl)-dihydro-2(3H)-pyranone 3-O- β -hydroxy- δ -(3,4-dihydroxyphenyl)-pentanoate (catechin phenylpropanoid lactone ester)	<i>Phyllocladus trichomanoides</i> (Podocarpaceae) [twig, cladode]	CDPK (7), MLCK (148), PKA (12), PKC (3)
Chrysazin (= Danthron; Dantron; 1,8-dihydroxy-9,10-anthraquinone) (anthraquinone)	<i>Rheum palmatum</i> (Polygonaceae) [root], <i>Cinchona ledgeriana</i> (Rubiaceae), <i>Xyris semifuscata</i> (Xyridaceae) [leaf, stem]	CDPK (20), MLCK (160), PKA (14), PKC (25) (AROM, DNA, TOPII) [cathartic, immunosuppressive, purgative]
Chrysophanic acid (= Chrysophanol; 1,8-Dihydroxy-3-methyl-9,10-anthraquinone; 3-Methylchrysazin) (anthraquinone)	<i>Rumex</i> spp., <i>Rheum</i> spp. (rhubarb) (Polygonaceae), <i>Cassia senna</i> [leaf], <i>C. siamea</i> , <i>Senna obtusifolia</i> (Fabaceae), <i>Rhamnus purshiana</i> (Rhamnaceae), <i>Tectona grandis</i> (Verbenaceae) [wood] lichen, Dipterocarpaceae, Guttiferae, Liliaceae, Simaroubaceae	CDPK (56), PKA (5), PKC (32) [dye, anti-termite]
Condensed tannins (condensed catechins)	<i>Phyllocladus trichomanoides</i> (Podocarpaceae), <i>Pseudotsuga menziesii</i> (Pinaceae), <i>Acacia melanoxylon</i> (Fabaceae) [wood]	CDPK, PKA, PKC
Condensed tannins (procyanidin & prodelfphinidin polymers)	Widespread; e.g. <i>Ribes nigrum</i> (Rubiaceae), <i>Vitis vinifera</i> (Vitaceae) [fruit, seed, leaf]	CDPK, MLCK, PKA, PKC
Coumarin (= 2H-1-Benzopyran-2-one; Coumarone) (coumarin)	Widespread, <i>Dipteryx odorata</i> (Fabaceae), <i>Myroxylon balsamum</i> (Flacourtiaceae), Pinaceae, Poaceae, Polypodiaceae (fern), <i>Galium odoratum</i> (Rubiaceae)	MLCK (317) [antifungal, haemorrhagic]
Curcumin (= Diferuloylmethane; turmeric yellow) (phenylpropanoid)	<i>Curcuma longa</i> (turmeric), <i>C. aromatica</i> , <i>C. xanthorrhiza</i> , <i>C. zedoaria</i> , <i>Zingiber officinale</i> (Zingiberaceae) [root]	CDPK (41), IKK, PhosbK [75], PKA (5), PKC (15), p60 ^{c-src} , TK (150) (F ₁ -ATPase, HIV-1-INT) [AI, antioxidant, hypoglycaemic, cytotoxic]

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part/	Target inhibited (other targets) / in vivo effects/
Cyanidin (= 3,5,7,3',4'-Pentahydroxy-flavilium) (anthocyanidin)	Widespread as glycoside [flower, fruit, leaf, tuber]; <i>Asimina triloba</i> (paw paw) (Annonaceae)	EGF-RTK (0.8) [inhibits EGF-induced tumour cell growth (42; 73); 3-galactoside inactive; red pigment]
Cycloheterophyllin (prenylflavone)	<i>Artocarpus heterophyllus</i> (Moraceae)	PKC [inhibits PA (AA induced), COX]
Daidzein (= 4',7-Dihydroxyisoflavone) (isoflavone)	<i>Genista tinctoria</i> , <i>Glycine max</i> (soy), <i>Phaseolus</i> , <i>Psoralea</i> , <i>Pueraria</i> , <i>Sophora</i> , <i>Trifolium</i> , <i>Ulex</i> , <i>Vigna</i> (Fabaceae) spp. [seed]; 7-O-glucoside (Daidzin) in <i>Baptisia</i> spp., <i>Glycine max</i> , <i>Pueraria</i> spp., <i>Trifolium pratense</i> (Fabaceae)	Inactive as TK inhibitor cf. Genistein (CFTR, DNAPOL, EST-R, F ₁ -ATPase, GABAA-R, lipase, TOPII, TPO) [antifungal, phytoestrogen]
Damnacanthal (anthraquinone)	<i>Morinda citrifolia</i> (Rubiaceae)	p56 ^{lck} TK (0.05–0.2), PDGF-RTK (5), erbB2-RTK (2), insulin-RTK (10), p59 ^{lyn} TK (5), p60 ^{src} TK (3), PKA (75), PKC (140) (TOPII)
Delphinidin (= 3,5,7,3',4',5'-Hexahydroxy-flavilium) (anthocyanidin)	Widespread as glycoside [flower, fruit, tuber]; <i>Abrus precatorius</i> , <i>Trifolium pratense</i> (Fabaceae)	EGF-RTK (1) [inhibits EGF-induced tumour cell growth (18; 33); mauve pigment]
Desmal (= 8-Formyl-2,5,7-trihydroxy-6-methylflavanone) (flavanone)	<i>Desmos chinensis</i> (Annonaceae) [leaf, stem]	[A431 cell PM EGF-RTK (8)]
[1,4-Diamino-9,10-anthraquinone] (anthraquinone)	Synthetic anthraquinone (cf. Emodin)	CDPK (>160), MLCK (18), PKA (8), PKC (23)
1,6-Digalloyl-glucoside (galloyl glycoside, hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae) [aerial]	CDPK (42), MLCK (>167), PKA (2), PKC (>167)
[2,3-Dihydroapigenin (= 2,3-Dihydro-5,7,4'-Trihydroxyflavone)] (flavanone)	Cf. Trihydroxyflavanones	CDPK (>160), MLCK (170), PKA (24)
2,3-Dihydrofisetin (= 2,3-Dihydro-3,7,3',4'-tetrahydroxyflavone; Fustin) (dihydroflavonol)	<i>Rhus glabra</i> , <i>R.</i> spp., <i>Schinopsis</i> (Anacardiaceae), <i>Platanus</i> (Platanaceae), <i>Tilia</i> spp. (Tiliaceae); as glycoside in <i>Baptisia</i> spp. (Fabaceae)	MLCK (180), PKA (18)
2,3-Dihydroluteolin (= 2,3-Dihydro-5,7,3',4'-tetrahydroxyflavone; Eriodictyol) (flavanone)	Widespread; <i>Petroselinum crispum</i> (Apiaceae), <i>Silybum marianum</i> (Asteraceae), <i>Eriodictyon californicum</i> (Hydrophyllaceae), <i>Ocimum basilicum</i> , <i>Origanum vulgare</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Citrus paradisi</i> (grapefruit) (Rutaceae)	CDPK (>160), PKA (18)
2,3-Dihydroquercetin (= 2,3-Dihydro-3,5,7,3',4'-pentahydroxyflavone; Taxifolin) (dihydroflavonol)	Widespread; <i>Acacia catechu</i> , <i>Robinia pseudoacacia</i> (Fabaceae), <i>Polygonum nodosum</i> (Polygonaceae), <i>Salix capraea</i> (Salicaceae), Coniferae; glycosides in <i>Astilbe</i> (Saxifragaceae), <i>Rhododendron</i> (Ericaceae) spp.	MLCK (80), PKA (17), PKC (AD-R, LOX, NADH DH, succinate DH) [antibacterial, antifungal, AI, antioxidant]

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part	Target inhibited (other targets) / in vivo effects/
2,2'-Dihydroxychalcone (chalcone)	Plant	MLCK (118)
3',4'-Dihydroxyflavone (flavone)	<i>Camellia sinensis</i> (tea leaf) (Theaceae)	MLCK (262), PKA (19)
5,4'-Dihydroxyflavone (= Ro 09-0179) (flavone)	From a Chinese medicinal herb	MLCK (24), PKA (24)
5,7-Dihydroxyflavone (= Chrysin) (flavone)	Widespread; <i>Passiflora coerulea</i> (Passifloraceae), <i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (Salicaceae), <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	CKII, MLCK, PKA (CBZ-R, EST-R, PBZ-R) [phytoestrogen]
7,8-Dihydroxyflavone (flavone)	Plant	PKA (19)
(3 <i>R</i>)-1,7-bis(3,4-Dihydroxyphenyl)heptan-3-ol (diarylheptanoid)	<i>Pinus flexilis</i> (Pinaceae)	PKC α (5)
(3 <i>R</i>)-1,7-bis(3,4-Dihydroxyphenyl)heptan-3-ol 3- <i>O</i> -glycoside (diarylheptanoid glycoside)	<i>Pinus flexilis</i> (Pinaceae)	PKC α (3)
8- γ -Dimethylallyl-wighteone (prenylated isoflavone)	<i>Derris scandens</i> (Fabaceae) [stem]	PKA (20)
3'- γ -Dimethylallyl-wighteone (prenylated isoflavone)	<i>Derris scandens</i> (Fabaceae) [stem]	PKA (24)
4,4'-Di- <i>O</i> -methyl-scandenin (coumarin)	<i>Derris scandens</i> (Fabaceae) [stem]	PKA (50)
Ellagic acid (= Benzoic acid; Lagistase) (phenolic acid lactone)	Widespread [leaf], ellagitannin product; <i>Psidium guajava</i> (guava) (Myrtaceae), <i>Fragaria</i> spp. (strawberry) (Rosaceae)	MLCK (>167), PKA (2) [4], PKA (0.6), PKC (8) [9], p60 ^{src} TK (0.3) (HIV-1 INT, ITD, PGK) [anti-mutagen, haemostatic]
Emodin (= Archin; Frangula emodin; Frangulic acid; Rheum emodin; 1,3,8-Trihydroxy-6-methyl-9,10-anthraquinone (anthraquinone))	<i>Senna obtusifolia</i> (Fabaceae), <i>Psorospermum glaberrimum</i> (Guttiferae), <i>Myrsine africana</i> (Myrsinaceae), <i>Polygonum cuspidatum</i> , <i>Rumex</i> spp., <i>Rheum palmatum</i> , <i>R.</i> spp. (Polygonaceae), <i>Ventilago calyculata</i> , <i>Rhamnus frangula</i> (Rhamnaceae), lichen; glycosides in <i>Rheum</i> , <i>Polygonum</i> (Polygonaceae), <i>Rhamnus</i> (Rhamnaceae) spp.	CDC2, CKI, CKII, CDPK (>160), MLCK (8), PKA (40), PKC (25), TK (p60src), RTK p56 ^{lck} TK (cow) (DNA, PI3K, TOPII) [cathartic, cytotoxic]
(-)-Epicatechin (= (2 <i>R</i> ,3 <i>R</i>)-5,7,3',4'-Tetrahydroxyflavan-3-ol) (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), Gymnospermac, <i>Pterocarpus</i> spp. (Fabaceae) [bark], <i>Podocarpus nagi</i> (Podocarpaceae), <i>Crataegus monogyna</i> (Rosaceae), <i>Camellia sinensis</i> (Theaceae)	PKA (18) (AR) [antibacterial, AI, antioxidant, bitter]

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part/	Target inhibited (other targets) / in vivo effects/
Epicatechin-(5,6-b,c)-4 β -(3,4-dihydroxyphenyl)-dihydro-2(3H)-pyranone (epicatechin phenylpropanoid lactone)	<i>Phyllocladus trichomanoides</i> (Podocarpaceae) [twig, cladode]	CDPK (17), MLCK (>167), PKA (147), PKC (13)
Epicatechin-(7,8-b,c)-4 β -(3,4-dihydroxyphenyl)-dihydro-2(3H)-pyranone (epicatechin phenylpropanoid lactone)	<i>Phyllocladus trichomanoides</i> (Podocarpaceae) [twig, cladode]	CDPK (24), MLCK (>167), PKA (53), PKC (13)
2,3-cis-3,4-trans-Epicatechin-(4 β \rightarrow 8)-epicatechin (procyanidin condensed tannin)	<i>Pseudotsuga menziesii</i> (Douglas fir) (Pinaceae) [bark]	CDPK (1), PKA (5), PKC (1)
Epicatechin-(4 β \rightarrow 8)-[epicatechin-(4 β \rightarrow 8)] ₂ -epicatechin (procyanidin condensed tannin)	<i>Pseudotsuga menziesii</i> (Douglas fir) (Pinaceae) [bark]	CDPK (0.6), PKA (1), PKC (0.6)
Epicatechin-(4 β \rightarrow 8)-epicatechin-(4 β \rightarrow 8)-catechin (procyanidin condensed tannin)	<i>Pseudotsuga menziesii</i> (Douglas fir) (Pinaceae) [bark]	CDPK (1), PKA (8), PKC (1)
(-)-Epicatechin 3-O-gallate (flavan-3-ol)	<i>Chimaphila umbellata</i> (Ericaceae), <i>Sorbus aucubaria</i> (Rosaceae), <i>Camellia sinensis</i> (tea) (Theaceae)	[Cell-EGF-RTK (<5)] (collagenase, EST-R, F ₁ -ATPase, 5 α R)
Epicatechin-(4 β \rightarrow 2)-phloroglucinol (= Epicatechin-(4 β \rightarrow 2)-1,3,5-trihydroxybenzene) (epicatechin phloroglucinol)	<i>Pseudotsuga menziesii</i> (Pinaceae) [bark]	CDPK (76), PKC (51)
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	CKII (8), EGF-RTK (1), PDGF-RTK (2), FGF-RTK (2), pp60 ^{src} (>22), PKA (>20), PKC (20) (EST-R, F ₁ -ATPase, proteasome, 5 α R, TOPOIB) [cell-EGF-RTK (<5); oxidation products give tea taste]
4-O-Ethyl-isomalacacidin (= 4-O-Ethyl-(2R,3R,4S)-2,3-cis-3,4-trans-3,3',4,4',7,8-hexahydroxyflavan) (leucoanthocyanidin flavan-3,4-diol)	<i>Acacia melanoxylon</i> (Fabaceae) (heartwood)	CDPK (8), PKA (100), PKC (9)
Eturunagarone (prenylated isoflavone)	<i>Derris scandens</i> (Fabaceae)	PKA (248)

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part	Target inhibited (other targets) / in vivo effects/
Eugeniin (= Tellimagrandine II) (ellagitannin)	<i>Coriaria</i> (Coriariaceae), <i>Quercus</i> (Fagaceae), <i>Syzygium</i> (Myrtaceae), <i>Fuchsia</i> (Onagraceae), <i>Rosa</i> (Rosaceae), <i>Tellima</i> (Saxifragaceae) spp.	PKA (80 nM) (SEP)
Fisetin (= 5-Deoxy- quercetin; 3,7,3',4'- Tetrahydroxyflavone) (flavonol)	<i>Rhus cotinus</i> , <i>R. rhodantha</i> (Anacardiaceae), <i>Acacia</i> spp., <i>Glycine max</i> , <i>Robinia pseudoacacia</i> (Fabaceae) [heartwood]; as glycosides in <i>Rhus succedanea</i> (Anacardiaceae) [wood], <i>Dalbergia odorifera</i> [wood], <i>Trifolium subterraneum</i> (Fabaceae)	CDPK (20), MLCK (5), PKA (1), PKC (< 50) (ITDI, HIV-1 INT, LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, succinate DH, TPO) [allergenic, antibacterial, apoptotic, inhibits SM contraction & histamine release]
Flavone (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	EGF-RTK (225) (AROM, COX, EST-R, 17βHSOR, 5-LOX) [allergenic, antibacterial, AI, inhibits histamine release, PAI, phytoestrogen]
Forsythiaside (phenylethanoid glycoside)	<i>Digitalis purpurea</i> (Scrophulariaceae) [leaf]	PKCα (2)
Galangin (= 3,5,7- Trihydroxyflavone) (flavonol)	<i>Escallonia</i> spp. (Saxifrageaceae) [leaf], Betulaceae, Salicaceae [bud], Lamiaceae, ferns [leaf], <i>Alpinia officinarum</i> (Zingiberaceae)	CDPK (>160), MLCK (20), PKA (2) (AROM, COX, Na ⁺ , K ⁺ -ATPase) [antibacterial]
1-Galloyl-2,4-dehydro- hexahydroxy-diphenoyl- glucoside (ellagitannin, hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae) [aerial]	CDPK (46), MLCK (>167), PKA (0.6), PKC (>167)
1-Galloyl-2,4-dehydro- hexahydroxydiphenoyl- 3,6-hexahydroxy- diphenoyl-glucoside (ellagitannin, hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae) [aerial]	CDPK (2), MLCK (56), PKA (0.2), PKC (26)
1-Galloyl-2,4;3,6-bis- dehydro-hexahydroxy- diphenoyl-glucoside (= Amariin) (ellagitannin, hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae) [aerial]	CDPK (4), MLCK (118), PKA (0.4), PKC (26)
1-Galloyl-4,6- hexahydroxydiphenoyl- glucoside (= Corilagin) (ellagitannin, hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae) [aerial]	CDPK (26), MLCK (>167), PKA (0.6), PKC (167)
1-Galloyl-4,6- hexahydroxydiphenoyl-6- (1'-[5,6,7-trihydroxy- benzopyran-1-one-3 carboxy-4-fumaroyl])- glucoside (ellagitannin, hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae) [aerial]	CDPK (42), MLCK (>167), PKA (1), PKC (>167)

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part/	Target inhibited (other targets) / in vivo effects/
Galloylpedunculidin (gallotannin)	<i>Platycara strobilacea</i> (Juglandaceae)	CKII (0.6), PKA (50–300 nM)
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Phaseolus lunatus</i> , <i>Trifolium subterraneum</i> , <i>T. brachycalycinum</i> (Fabaceae); 7- <i>O</i> -glucoside (= Genistin; Genistoside) in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> (Fabaceae); 4'- <i>O</i> -glucoside (= Sophocoroside) in <i>Sophora japonica</i> (Fabaceae) [pod]	EGF-RTK (3; 22), HISK, MLCK (14), PKA (126), pp60 ^{v-src} TK (RSV) (26; 30), pp110 ^{gag-fcs} TK (24), [A431 cell EGF-RTK (4) <i>in vivo</i>] (ADH, AD-R, F ₁ -ATPase, GABAA-R, lipase, peroxidase, Na ⁺ /K ⁺ /Cl ⁻ TR, TOPII, TPO) [antifungal, apoptotic, oestrogenic]
Genistin (= Genistein 7- <i>O</i> -glucoside; Genistoside; 4',5,7-Trihydroxyisoflavone 7- <i>O</i> -glucoside) (isoflavone <i>O</i> -glycoside)	<i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex europaeus</i> , <i>U. nanus</i> (Fabaceae), <i>Prunus cerasus</i> (Rosaceae)	EGF-RTK (> 231) (cf. Genistein) (TOPII) [plant growth inhibitor]
Hesperidin (flavanon <i>O</i> -glycoside)	<i>Citrus limon</i> , <i>C. sinensis</i> , <i>Poncirus trifoliata</i> (Rutaceae), <i>Mentha</i> spp., <i>Hyssopus officinalis</i> (Lamiaceae)	PKA
Hirsutanonol (diarylheptanoid)	<i>Alnus hirsuta</i> (Betulaceae), <i>Pinus flexilis</i> (Pinaceae)	PKCα (18)
Hirsutenone (diarylheptanoid)	<i>Alnus hirsuta</i> (Betulaceae), <i>Pinus flexilis</i> (Pinaceae)	PKCα (4)
Homoplantaginidin (flavonoid glycoside)	<i>Plantago asiatica</i> [leaf], <i>P. media</i> (Plantaginaceae)	EGF-RTK
Hydrolysable tannins (polyphenols)	<i>Phyllanthus amarus</i> (Euphorbiaceae)	CDPK, MLCK, PKA, PKC
2'-Hydroxychalcone (chalcone)	Plant; cf. hydroxychalcones	MLCK (>160) (GST)
7-Hydroxycoumarin (coumarin)	<i>Citrus</i> spp. (Rutaceae); Coumarin metabolite in mammals	MLCK (197)
3-Hydroxyflavone (flavone)	Plant; cf. hydroxyflavones	PKA (4) (17βHSOR)
[5-Hydroxyflavone] (flavone)	Semi-synthetic	CDPK (>160), MLCK (320) (AD-R)
2-(3-Hydroxy-4-methoxyphenyl)-ethyl- <i>O</i> -Rha-Rha-4- <i>O</i> - <i>E</i> -feruloylglucoside (phenylethanoid glycoside)	<i>Digitalis purpurea</i> (Scrophulariaceae)	PKCα (125)
[7-Hydroxy-4-methylcoumarin] (coumarin)	Semi-synthetic	MLCK (167)
Hypericin (bianthraquinone)	<i>Hypericum perforatum</i> , <i>H.</i> spp. (Hypericaceae)	CDPK, EGF-RTK, MLCK, PKA, PKC (HIV-1 INT, HIV-1 RT, PI3K) [photosensitizing, red pigment]
Hypericin-like compound (phenolic)	<i>Fagopyrum esculentum</i> (buckwheat) (Polygonaceae) [herb]	EGF-RTK (PKC) [photosensitizing, red pigment]

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part	Target inhibited (other targets) / in vivo effects/
Isoliquiritigenin (= 2',4',4'-Trihydroxychalcone) (chalcone)	<i>Glycyrrhiza glabra</i> (Fabaceae) [root]; glycoside in <i>Dahlia variabilis</i> (Asteraceae), <i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root, rhizome]	MLCK (111) (AR, COX, EST-R, 5-LOX, MAO, ox. phos. uncoupler) [PAI, yellow pigment]
Isomalacacidin (= (2R,3R,4S)-2,3-cis-3,4-trans-3,3',4,4',7,8-Hexahydroxyflavan) (leucoanthocyanidin flavan-3,4-diol)	<i>Acacia melanoxylon</i> (Fabaceae) (heartwood)	CDPK (4), MLCK (>167), PKA (6), PKC (3)
Isorhamnetin (= 3,5,7,3',4'-Pentahydroxyflavone 3'-methyl ether; (flavonol))	Widespread; aglycone & glycoside in <i>Arnica</i> , <i>Artemisia dracunculus</i> , <i>Haplophappus</i> (Asteraceae) spp.; glycosides in <i>Cotula</i> (Asteraceae), <i>Cactus</i> (Cactaceae), <i>Argemone</i> (Papaveraceae), <i>Taxodium</i> (Taxodiaceae) spp.	PKC (>50)
Juglone (= 5-Hydroxy-1,4-naphthalenedione; Mucin; Natural Brown 7; Regianin) (naphthoquinone)	<i>Juglans cinerea</i> , <i>J. nigra</i> [stem bark], <i>J. regia</i> , <i>Carya ovata</i> , <i>C. illinoensis</i> [leaf, nut] (Juglandaceae), <i>Lomatia</i> spp. (Proteaceae)	MLCK, PKA, PKC (α & β) (2), pp60 ^{c-src} (24) (ECMOX) [antifungal, antiviral, molluscicidal, feeding deterrent, walnut allelopathic]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae) [seed, stem], <i>Pisum sativum</i> (Fabaceae), <i>Thespesia populnea</i> (Malvaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (grapefruit) (Rutaceae), <i>Koeleruteria henryi</i> (Sapindaceae)	CDPK (>160), EGF-RTK (11), MLCK (4), PKA (2; 9), p56 ^{lck} TK (ADH, AROM, CFTR, EST-R, TPO)
Kaempferol 4'-O-methyl ether (= Kaempferide; 3,5,7,4'-Tetrahydroxyflavone 4'-O-methyl ether) (flavonol)	<i>Pityrogramma triangularis</i> (fern) (Adiantaceae), <i>Baccharis</i> spp. (Asteraceae), <i>Prunus</i> spp. (Rosaceae), <i>Linaria dalmatica</i> (Scrophulariaceae) [aerial]; Betulaceae, Salicaceae [leaf], <i>Alpinia galanga</i> (Zingiberaceae)	CDPK (>160), MLCK (8), PKA (9) (BZ-R) [AI (TPA-induced)]
Kievitone (= 2',4',5,7-Tetrahydroxy-8-isoprenylisoflavanone) (isoflavanone)	<i>Dolichos biflorus</i> , <i>Lablab niger</i> , <i>Phaseolus coccineus</i> (Fabaceae)	[EGF-RTK (A431 cells) (28)] [antibacterial, antifungal, oestrogenic]
[Laurylgallate (= Dodecylgallate ester)] (long chain alcohol gallic acid ester)	Semi-synthetic cf. Gallic acid, Gallotannins	PKA (2), PKC (300)
Leucosceptoside A (phenylethanoid glycoside)	<i>Penstemon linarioides</i> (Scrophulariaceae)	PKC- α (19)

(continued)

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Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part/	Target inhibited (other targets) / in vivo effects/
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Ammi</i> , <i>Cuminum</i> , <i>Daucus</i> (Apiaceae), <i>Lavandula</i> , <i>Mentha</i> , <i>Ocimum</i> , <i>Origanum</i> , <i>Rosmarinus</i> , <i>Thymus</i> (Lamiaceae); widespread as glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	CDPK (>160), MLCK (26), PKA (1; 2), PKC (<50) (ACE, AR, AROM, HIV-1 INT, HIV-1 PR, ITDI, NADH DH, Na ⁺ , K ⁺ -ATPase, Nase, NEP, succinate DH, TOPII, TPO) [antibacterial, AI, apoptotic, nodulation signal]
Magnolol (lignan)	<i>Sassafras randaiense</i> (Lauraceae) [root], <i>Magnolia officinalis</i> , <i>M. obovata</i> (Magnoliaceae) [bark]	PKC [blocks PE binding site]
Malacacidin (= (2 <i>R</i> ,3 <i>R</i> ,4 <i>R</i>)-2,3- <i>cis</i> -3,4- <i>trans</i> -3,3',4,4',7,8-Hexahydroxyflavan) (leucoanthocyanidin flavan-3,4-diol)	<i>Acacia melanoxylon</i> (Fabaceae) (heartwood)	CDPK (8), MLCK (>167), PKA (20), PKC (5)
α-Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	CDPK (21; 33), MLCK (120), PKA (13) (Ca ²⁺ ATPase, cAMP PDE, EST-R, HIV-1 PR, HIS-R) [antibacterial, AI, antiulcer]
γ-Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	CDPK (5; 6), MLCK (110), PKA (2) (cAMP PDE, HIV-1 PR, 5HT-R)
[3-Methoxy-2,3-dihydroluteolin (= 3-Methoxy-2,3-dihydro-5,7,3',4'-tetrahydroxyflavone)] (flavanone)	Semi-synthetic	PKA (22)
5-Methoxypsoralen (coumarin)	<i>Petroselinum crispum</i> (parsley) (Apiaceae) [leaf]	PKA (240)
[Methyl-2,5-dihydroxycinnamate] (phenolic acid ester)	Synthetic cinnamic acid derivative	RTK
8-Methyl-juglone (= 5-Hydroxy-8-methyl-1,4-naphthalenedione) (naphthoquinone)	<i>Rumex crispus</i> (yellow dock) (Polygonaceae)	PKC (α & β) (3), pp60 ^{c-src} (68)
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> , <i>Chlorophora tinctoria</i> , <i>Morus alba</i> (mulberry), <i>M. spp.</i> (Moraceae)	CDPK (> 160), MLCK (28), PKA (10; 8) (AR, DNAL, GST, 5-LOX, ITDI, Nase) [antibacterial, antiviral, allergenic, silkworm feeding attractant]

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part	Target inhibited (other targets) / in vivo effects/
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplophragmum canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	CDPK (30), IKK, MLCK (6), PKA (1) (AROM, DNAL, DNAP, F ₁ -ATPase, HIV-1 INT, HIV-1 RT, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, Nase, NEP, PGK, 5αR, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic, apoptotic]
Nallanin (prenylated isoflavone)	<i>Derris scandens</i> (Fabaceae)	PKA (33), PKC (120)
Naphthazarin (naphthoquinone)	<i>Juglans mandshurica</i> (Juglandaceae) [husk], <i>Lomatia obtigua</i> (Proteaceae) [wood, bark]	MLCK, PKA
Naringin (= 2,3-Dihydroapigenin 7-O-rhamnosyl-glucoside) (flavanone O-glycoside)	<i>Adiantum</i> spp., <i>Ceterach officinarum</i> (fern) (Adiantaceae), <i>Origanum vulgare</i> (oregano) (Lamiaceae), <i>Citrus aurantium</i> , <i>C. limon</i> , <i>C. paradisi</i> , <i>C. sinensis</i> (grapefruit) (Rutaceae)	PKA (27) (TPO) [bitter, oviposition stimulant]
Norathyriol (xanthone)	<i>Allanblackia</i> , <i>Cratogeomys</i> , <i>Garcinia</i> , <i>Hypericum</i> , <i>Mammea</i> , <i>Ochrocarpus</i> , <i>Symphonia</i> (Guttiferaceae), <i>Clarisa</i> , <i>Chlorophora</i> , <i>Maclura</i> (Moraceae) spp.; ferns	PKC
Okanin (= 3,4,2',3',4'-Pentahydroxychalcone) (chalcone)	Glycoside in <i>Bidens</i> spp., <i>Coreopsis</i> spp. (Asteraceae) [flower]	CDPK (45), MLCK (55) (ox. phos. uncoupler) [yellow pigment]
Oregonin (diarylheptanoid)	<i>Alnus hirsuta</i> (Betulaceae), <i>Pinus flexilis</i> (Pinaceae)	PKCα (15)
Phloretin (= 2',4,4',6'-Tetrahydroxy-dihydrochalcone) (dihydrochalcone)	<i>Malus domestica</i> (Rosaceae) [leaf]; as 2'-glucoside (Phloridzin) in <i>Kalmia latifolia</i> , <i>Pieris japonica</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>Malus</i> spp. (Rosaceae), <i>Symplocos</i> spp. (Symplocaceae)	PKC (> 50) (ECMOX, EGF-RTK, EST-R, F ₁ -ATPase, ITD, ox. phos. (uncoupler)) [antibacterial, AI, feeding deterrent]
Phylloflavan (= 2R-2,3-trans-Catechin 3-O-β-hydroxy-δ-(3,4-dihydroxyphenyl)-pentanoate) (catechin ester)	<i>Phyllocladus trichomanoides</i> (Podocarpaceae) [twig, cladode]	CDPK (8), MLCK (56), PKA (120), PKC (7)
Piceatannol (= 3,3',4,5'-Tetrahydroxystilbene) (stilbene)	<i>Laburnum anagyroides</i> (Fabaceae) [wood], <i>Morus alba</i> (Moraceae), <i>Picea</i> spp., <i>Pinus</i> spp., <i>Tsuga canadensis</i> (Pinaceae)	CDPK (19), MLCK (12), PKA (3), PKC (8), p56 ^{lck} TK (PM) (~50), p40 TK (15), soluble & membrane TK (F ₁ -ATPase) [antifungal]
Plantainoside (phenylethanoid glycoside)	<i>Digitalis purpurea</i> (Scrophulariaceae) [leaf]	PKCα (15)

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part/	Target inhibited (other targets) / in vivo effects/
Plumbagin (naphthoquinone)	<i>Dionaea muscipula</i> (Venus fly trap; 2 action potential-initiating stimulus events required before trap closure), <i>Drosera</i> (Droseraceae), <i>Aristea</i> , <i>Sisyrinchium</i> , <i>Sparaxis</i> (Iridaceae), <i>Diospyros</i> (Ebenaceae), <i>Pera</i> (Euphorbiaceae) spp.; <i>Plumbago europaea</i> (Plumbaginaceae) [root]	MLCK, PKA (ECMOX, TOPII)
Poliumoside (phenylethanoid glycoside)	<i>Penstemon linarioides</i> (Scrophulariaceae)	PKC α (24)
Procyanidin B-2 3,3'-di-O-gallate (condensed tannin)	<i>Rheum palmatum</i> (rhubarb) (Polygonaceae) [rhizome]	CKII (3) (SEP)
Prunetin (= 5-Hydroxy-7,4'-dimethoxyisoflavone) (isoflavone)	<i>Glycyrrhiza glabra</i> , <i>Dalbergia miscolobium</i> , <i>Pterocarpus angolensis</i> , (Fabaceae), <i>Prunus cerasus</i> (sour cherry), <i>P.</i> spp. (Rosaceae)	EGF-RTK (15) (ADH)
Psoralen (= Ficusin) (coumarin)	<i>Psoralea</i> spp., <i>Coronilla glauca</i> (Fabaceae) [seed], <i>Foeniculum vulgare</i> , <i>Levisticum officinale</i> , <i>Pastinaca sativa</i> , <i>Petroselinum crispum</i> (Apiaceae), <i>Ficus carica</i> (Moraceae), <i>Phebalium agentium</i> [oil], <i>Xanthoxylum flavum</i> (Rutaceae) [wood]	MLCK (267) [photosensitizer, anti-mycobacterial]
Purpurin (anthraquinone)	<i>Asperula odorata</i> , <i>Rebunium hypocarpum</i> , <i>Galium</i> spp., <i>Rubia cordifolia</i> , <i>R. tinctorum</i> , <i>R. cordifolia</i> (Rubiaceae) [root]; glycoside in <i>Rubia tinctorum</i> (madder) (Rubiaceae) [root]	CDPK (14), MLCK (25), PKA (4), PKC (19) (HIV-1 INT) [genotoxic, pigment]
Purpurogallin (bicyclic phenolic)	<i>Dryophanta divisa</i> gall on <i>Quercus pedunculata</i> (Fagaceae)	EGF-RTK (28; 45) [55; 84] (HIV-1 INT, PEP, PGK, XO) [antioxidant, red pigment]
Quercetagetin (= 6-Hydroxyquercetin; 3,5,6,7,3',4'-Hexahydroxyflavone) (flavonol)	<i>Eupatorium gracile</i> (Asteraceae), other Asteraceae [flower]; glycosides in <i>Tagetes erecta</i> (marigold) (Asteraceae) [flower]	CDPK (>160), MLCK (26), PKA (2) (AR, DNAP, F ₁ -ATPase, HIV-1 INT, HIV-1 RT, Na ⁺ , K ⁺ -ATPase, TOPII) [antibacterial, yellow pigment]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	CDPK (14), CKII (0.8), EGF-RTK (17; 27), MLCK (6), PhK (17), PKA (1; 4), PKC (<50), pp60 ^{src} (RSV) (27), p56 ^{lck} TK (AR, cAMP PDE, CFTR, DNAP, F ₁ -ATPase, HIV-1 RT, 11 β HSDH, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, Nase, NEP, NQOR, PS-EF-1 α , TOPII) [allergenic, antibacterial, AI, antiviral]

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part	Target inhibited (other targets) / in vivo effects/
Quercitrin (= Quercetin 3-Rha; 3,5,7,3',4'-Penta-hydroxyflavone-Rha) (flavonol O-glycoside)	Widespread; <i>Acacia catechu</i> , <i>A.</i> spp. (Fabaceae), <i>Quercus tinctoria</i> (Fagaceae) [bark], <i>Polygonum</i> spp. (Polygonaceae)	MLCK (137), PKA (6) (ACE, AR) [antibacterial, antimutagenic, antiviral, feeding deterrent & stimulant]
[Quinalizarin (= 1,2,5,8-Tetrahydroxy-9,10-anthraquinone)] (anthraquinone)	Semi-synthetic from Alizarin	CDPK (65), MLCK (53), PKA (2), PKC (4) (HIV-1 INT)
[Quinizarin (= 1,4-Dihydroxy-9,10-anthraquinone)] (anthraquinone)	Synthetic (cf. Emodin)	MLCK (26), PKA (20), PKC (24)
Resveratrol (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum grandiflorum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae) spp., <i>Vitis vinifera</i> (Vitaceae) [leaf]	p56 ^{lck} TK, soluble & membrane TK (END-R, EST-R, F ₁ -ATPase, TYRase, XO)
Robustic acid (coumarin)	<i>Derris scandens</i> (Fabaceae)	PKA (10)
Rutin (= Quercetin 3-O-rutinoside; Quercetin 3-O-rhamnosyl-glucoside) (flavonol O-glycoside)	Widespread; <i>Sophora japonica</i> (Fabaceae), <i>Morus alba</i> (Moraceae), <i>Fagopyrum esculentum</i> , <i>Polygonum</i> spp. (Polygonaceae), <i>Ruta graveolens</i> (Rutaceae), <i>Viola tricolor</i> (Violaceae)	MLCK (320), PKA (32) (AR, 5-LOX) [antioxidant, feeding attractant, feeding deterrent, oviposition stimulant]
[Secalonic acid D] (dimeric hydroxanthone)	Toxic ergochrome mycotoxin of <i>Penicillium oxalicum</i> (fungus) & <i>Claviceps purpurea</i> (ergot infection fungus on <i>Secale cereale</i> (rye) (Poaceae))	CDPK (67), MLCK (60), PKA (12) [6], PKC (15)
[7,8,3',4'-Tetrahydroxy-flavone] (flavone)	Cf. tetrahydroxyflavones	CDPK (80), MLCK (20), PKA (1)
Theaflavin (condensed tannin)	<i>Camellia sinensis</i> (tea) (Theaceae)	CHII (6)
Tricetin (= 5,7,3',4',5'-Pentahydroxyflavone) (flavone)	<i>Oenanthe aquatica</i> (Apiaceae), <i>Ginkgo biloba</i> (Ginkgoaceae), <i>Camellia sinensis</i> (tea) (Theaceae); glucosides in <i>Thuja occidentalis</i> (Cupressaceae), <i>Metasequoia glyptostroboides</i> (Taxodiaceae)	CDPK (4), MLCK (12), PKA (1)
[Tricetin 3',4',5'-tri-O-methyl ether (= 5,7-Dihydroxy-3',4',5'-trimethoxyflavone)] (flavone)	Semi-synthetic; cf. pentahydroxyflavones	PKA (31)
[3,3',4'-Trihydroxyflavone] (flavonol)	Cf. trihydroxyflavones	CDPK (25), MLCK (10), PKA (2) (Na ⁺ , K ⁺ -ATPase)
[3',4',7-Trihydroxyisoflavone] (isoflavone)	Cf. trihydroxyisoflavones	CKII (0.4)

(continued)

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Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part/	Target inhibited (other targets) / in vivo effects/
Verbascoside (= Acteoside; Kusagin) (phenyl propanoid glycoside)	<i>Echinacea</i> spp. (Asteraceae), <i>Buddleja globosa</i> , <i>B. officinalis</i> , <i>Forsythia suspense</i> , <i>Olea europaea</i> (Oleraceae), <i>Plantago media</i> (Plantaginaceae), <i>Verbascum sinuatum</i> , <i>V. thapsus</i> (Scrophulariaceae); Acanthaceae, Bignoniaceae, Gesneriaceae, Orobanchaceae, Verbenaceae	EGF-RTK (AR, 5-LOX) [AI]
Vanicosides A & B (= Sucrose 1,3,6- <i>p</i> -coumaryl triester 6'-feruloyl ester) (phenylpropanoid coumaryl sugar esters)	<i>Polygonum pennsylvanicum</i> (Polygonaceae)	PKC
Warangalone (prenylated isoflavone)	<i>Derris scandens</i> (Fabaceae)	PKA (4)
Terpenes		8.1t
Abietic acid (abietane diterpenoid)	Widespread in Pinaceae [resin]; <i>Pinus insularis</i> , <i>Pinus kesiya</i> , <i>Pinus strobes</i> , <i>Pinus sylvestris</i> (pinaceae)	CDPK, PKA
α -Amyrin (= α -Amyrenol; Viminalol) (ursane triterpene)	<i>Alstonia boonei</i> (Apocycaceae) [root], <i>Balanophora elongata</i> (Balanophoraceae) [latex], <i>Erythroxylum coca</i> (Erythroxylaceae), <i>Hevea brasiliensis</i> (rubber) (Euphorbiaceae), <i>Ficus variegata</i> (Moraceae)	CDPK (52) [26], PKA (8) [2], PKC (32) [28] (CABPase, CHY, collagenase, HIV-1 PR, TRY) [anti-arthritic, AI, anti-insect]
[α -Amyrin linoleate] (ursane triterpene FA ester)	Semi-synthetic from α -Amyrin	MLCK (>83), PKA (8) [2], PKC (>83) (CABPase, CHY, collagenase, 5-LOX, TRY) [AI]
[α -Amyrin palmitate] (ursane triterpene FA ester)	Semi-synthetic from α -Amyrin	PKA (8) [4], PKC (>83) (CABPase, CHY, collagenase) [AI]
Asiatic acid (ursane triterpene)	<i>Shorea</i> spp. (Dipterocarpaceae), <i>Centella asiatica</i> (Apiaceae), <i>Glechoma hederacea</i> (Lamiaceae), <i>Punica granatum</i> (Punicaceae); triglycoside Asiaticoside in <i>Centella asiatica</i> (Apiaceae)	CDPK (40), PKA (22), PKC (400)
Asiaticoside (= Asiatic acid triglycoside) (ursane triterpene glycoside)	<i>Centella asiatica</i> (Apiaceae)	PKA (190) [promotes wound healing]
Betulin (= Betulinol; Betulol; Trochol) (lupane triterpene)	Widespread; <i>Betula platyphylla</i> , <i>B.</i> spp. (birch) (Betulaceae) [outer bark], <i>Diospyros</i> spp. (Ebenaceae)	CDPK (75), PKA (20), PKC (> 300) [antineoplastic]
Betulinic acid (lupene triterpene)	Widespread; <i>Diospyros perigrina</i> (Ebenaceae), <i>Rhododendron arboreum</i> (Ericaceae) [bark], <i>Psophocarpus tetragonolobus</i> (Fabaceae), <i>Syzygium claviflorum</i> (Myrtaceae) [leaf], <i>Solanum aviculare</i> (Solanaceae)	CDPK (84), PKA (45), PKC (145) (AP, ATP-K ⁺ CH, HIV-1 PR) [antineoplastic]
[5-Cholenic acid-3 β -ol] (triterpene)	Human & animal origin cf. oleanolic acid	PKA (8)

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part	Target inhibited (other targets) / in vivo effects/
Corosolic acid (ursane triterpene)	<i>Crataegus pinnatifida</i> [fruit], <i>Rubus alceaefolius</i> (Rosaceae)	PKC [cytotoxic]
Crocetin (carotenoid)	<i>Bixa orellana</i> (Bixaceae), <i>Crocus sativus</i> (style = saffron), <i>Crocus</i> spp. (Iridaceae) [flower]; digentiobiose ester (= Crocin) in <i>Crocus sativus</i> (style), <i>C.</i> spp. (Iridaceae) [flower], <i>Gardenia</i> spp. (Rubiaceae), <i>Verbascum phlomoides</i> (Scrophulariaceae)	PKA (3), PKC (80) [yellow food colour]
Dipterocarpol (dammarane triterpene)	<i>Dipterocarpus acutangulus</i> , <i>D. draco</i> (dragon's blood) (Dipterocarpaceae), <i>Pistacia terebinthus</i> (Anacardiaceae) [gall]	PKA
Friedelin (friedelane triterpene)	<i>Ceratopetalum petalum</i> (Cunoniaceae), <i>Quercus suber</i> (Fagaceae) [cork], <i>Viola odorata</i> (Violaceae), lichens	PKA
18- α -Glycyrrhetic acid (Glycyrrhetic acid; Glycyrrhetin) (triterpene sapogenin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root, rhizome]	PKA (6), PKC (159) [AI, anti-ulcerogenic, anti-diuretic]
18- β -Glycyrrhetic acid (Glycyrrhetic acid; Glycyrrhetin) (triterpene sapogenin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root, rhizome]	PKA (6), PKC (121) (ALDO-R, CBG, CORT-R, ELA, EST-R, β HSDH, SBG) [AI, anti-ulcerogenic, anti-diuretic]
Glycyrrhizic acid (= Glycyrrhetic acid 3- <i>O</i> -glucuronosyl-glucuronide; Glycyrrhizin; Glycyrrhinic acid; Glycyrrhizinic acid) (triterpene glycoside saponin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root, rhizome]	PKA (360); HMG phosphorylation by CKI & PKC per interaction with HMG (ALDO-R, CBG, CORT-R, EST-R, SBG) [AI, anti-ulcerogenic, sweet taste]
Gossypol (dimeric phenolic sesquiterpenoid)	<i>Gossypium</i> spp. (cotton), <i>Montezuma speciosissima</i> , <i>Thespesia populnea</i> (Malvaceae) [seed]; African slave labour especially for cotton, sugar & coffee plantations in the Americas – about 10–15 million kidnapped & sent to America	CDPK (17), MLCK (144), PKA (10), PKC (50–100) (Ca^{2+} -ATPase, CAMA, DNAP, 11 β HSDH) [antifungal, antitumour, inhibits spermatogenesis]
Helenalin (pseudoguaianolide sesquiterpene lactone)	<i>Anaphalis</i> , <i>Arnica</i> , <i>Balduina</i> , <i>Eupatorium</i> , <i>Gaillardia</i> , <i>Helenium</i> , <i>Inula</i> spp. (Asteraceae)	IKK-NF κ B complex (prevents NF κ B release) (ox. phos.) [antineoplastic, cytotoxic, toxic]
α -Hederin (triterpene saponin)	<i>Hedera helix</i> (Araliaceae) [leaf]	CDPK
Hypoestoxide (diterpene)	<i>Hypoestes rosea</i> (Acanthaceae)	IKK [blocks LPS-induced monocyte iNOS, TNF- α , IL-1 β & IL-6 expression]
[Lithocholic acid methyl ester] (triterpene)	Human & animal origin cf. oleanolic acid	PKA (rat) (9)

(continued)

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Table 8.1 (Continued)

<i>Compound (class)</i>	<i>Plant source (family) / plant part/</i>	<i>Target inhibited (other targets) / in vivo effects/</i>
Lupeol (= Fagasterol; Monogynol B; β -Viscol) (lupane triterpene)	<i>Alstonia boonei</i> (Apocynaceae) [bark, seed], <i>Phyllanthus emblica</i> (Euphorbiaceae), <i>Lupinus luteus</i> (Fabaceae) [seed]; various Asteraceae [flower]	PKA (5) [6; 4], PKC (82) [35], (CABPase, CHY, TOPII, TRY) [anti-arthritic, AI, antitumour]
Lupeol linoleate (= Lupeol-9, <i>cis</i> -12-octadecadienoic acid acid ester) (lupane triterpene FA ester)	Semi-synthetic from Lupeol	PKA (4) [2], PKC (35) [40] (CABPase, CHY, TRY) [AI]
Lupeol palmitate (= Lupeol hexadecanoic acid ester) (lupane triterpene FA ester)	Semi-synthetic from Lupeol	PKA (9) [4] (CABPase, CHY, TRY) [AI]
Oleanolic acid (oleanane triterpene)	<i>Luffa cylindrica</i> (sponge gourd); (Cucurbitaceae), <i>Lavandula latifolia</i> , <i>Rosmarinus officinalis</i> , <i>Salvia triloba</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Syzygium aromaticum</i> (Myrtaceae); 3- <i>O</i> -glucuronide in <i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae)	CDPK (112), PKA (12), PKC (250) (C3-convertase, DNAL, DNAP, ELA, HYAL, TOPI, TOPII) [anti-angiogenic, AI]
Parthenolide (germacranolide sesquiterpene lactone)	<i>Ambrosia</i> spp., <i>Arctotis</i> spp., <i>Chrysanthemum parthenium</i> , <i>Tanacetum parthenium</i> (feverfew), <i>T. vulgare</i> (Asteraceae), <i>Michelia</i> spp. (Magnoliaceae)	IKK β (5HT-R) [antibacterial, antifungal, antitumour, anti-migraine, cytotoxic]
Platanic acid (triterpene) [Retinal] (carotene)	<i>Melaleuca leucadendron</i> , <i>Syzygium claviflorum</i> (Myrtaceae) Oxidation of Vitamin A (Retinol), in turn derived from pro-vitamin A carotenes	PKC [anti-HIV] PKC
α -Tocopherol (= Vitamin E entity) (chromanol)	Widespread esp. in green leaf, green vegetables, grain & plant oils; most active of Vitamin E entities	PKC β [AO/FRS]
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (ursane triterpene)	Widespread; <i>Nerium oleander</i> (Apocynaceae), <i>Vaccinium macrocarpon</i> (cranberry), <i>Arctostaphylos uva-ursi</i> (bearberry) (Ericaceae), <i>Salvia triloba</i> , <i>Prunella vulgaris</i> , <i>Rosmarinus officinalis</i> (Lamiaceae), <i>Malus</i> sp. (apple), <i>Pyrus</i> sp. (pear) (Rosaceae) [fruit surface]	CDPK (71), PKA (9), PKC (106), RTK (ACHe, DNAL, DNAP, ELA, HIV-1 PR, RT, TOPI, TOPII) [anti-angiogenic, AI, cytotoxic, antineoplastic]
Other		8.1o
Aristolochic acid (phenanthrene)	<i>Aristolochia clematis</i> , <i>A. debilis</i> , <i>A. indica</i> , <i>A. longa</i> , <i>Asarum canadense</i> (Aristolochiaceae)	MLCK, PKA, PKC

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part	Target inhibited (other targets) / in vivo effects/
Arsenite (= AsO ₃ ³⁻) (oxidized arsenic); arsenite/arsenate-contamination of W. Bengal & Bangladesh under-ground drinking water	Environmental; arsenic accumulator and hyper-accumulator plants, e.g. <i>Pteris vittata</i> (ladder brake, fern), <i>Pityrogramma calomelanos</i> (silverback fern) (Pteridaceae)	IKK (Arsenite (AsO ₃ ³⁻) toxic due to reaction with thiols) [carcinogenic, cardiovascular disease, hyperkeratosis, peripheral neuropathy, toxic; reacts with vicinal thiols]
14.3.3 proteins (protein)	All plants (& animals, fungi)	PKC [& other regulatory functions]
CaM-binding basic proteins (protein)	All plants	CDPK
CDK inhibitor protein (= Ubiquitin) (protein)	<i>Medicago</i> sp. (Fabaceae); universal in eukaryotes	CDK
10-Hydroxydecanoic acid (fatty acid)	Cf. fatty acids	PKA (138)
12-Hydroxystearic acid (fatty acid)	Cf. fatty acids	PKA (127)
Lithium ion (Li ⁺)	Environmental; used for bipolar mood disorder & manic depression treatment	GSK3β [normal GSK Ser phosphorylation & inhibition by insulin-activated PKB]
15-Pentadecanolide (= 15-Hydroxypentadecanoic acid lactone) (hydroxy fatty acid lactone)	Cf. fatty acids	PKA (20)
PKI (= Protein kinase inhibitor protein) (protein)	<i>Triticum aestivum</i> (wheat), <i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	eIF2αK
PRL1 WD protein (protein)	<i>Arabidopsis thaliana</i> (Brassicaceae); likely to be widespread	SNF1K
Selenic acid (H ₂ SeO ₄) (selenium oxide)	Derives from oxidation of selenocysteine & other selenium metabolites	CDK2, PKC
Selenious acid (H ₂ SeO ₃) (selenium oxide)	Derives from oxidation of selenocysteine & other selenium metabolites	CDK2, PKC
Selenium dioxide (SeO ₂) (selenium oxide)	Derives from oxidation of selenocysteine & other selenium metabolites	CDK2, MLCK, PKC (Ca ²⁺ site [68], phosphatidylserine site [60]) [chemopreventative, pro-apoptotic]
[α-Terthiophene] (polythiophene)	<i>Tagetes erecta</i> (marigold) (Asteraceae) [leaf, root]	Potential metabolites PKC inhibitors Hydroxymethyl-α-terthiophene & α-Terthiophene carboxaldehyde [phototoxic, photodermatitis]
Non-plant reference		8.1n
[Alkyl-lysophospholipid] (phospholipid)	Animal	PKC

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) / plant part/	Target inhibited (other targets) / in vivo effects/
[Anthraflavic acid (= 2,6-Dihydroxy-9,10-anthraquinone)] (anthraquinone)	Synthetic anthraquinone cf. Emodin	MLCK (37), PKA (60), PKC (26)
[Anthrarufin (= 1,5-Dihydroxy-9,10-anthraquinone)] (anthraquinone)	Synthetic (cf. Emodin)	CDPK (>160), MLCK (>160), PKA (2), PKC (4)
[6-Benzylamino-2-thiomorpholinyl-9-isopropylpurine] (purine)	Synthetic	CDK2
[Calphostin C] (perylene quinone)	<i>Cladosporium cladosporioides</i> (fungus)	PKC [anticancer, antiviral]
[Doxorubicin (= Adriamycin)] (anthracycline)	<i>Streptomyces peucetius</i> (fungus) (Actinomycete) cf. Daunomycin; major clinical anticancer drug	PKC (as Fe(III)-adriamycin complex) [1] (DNA, TOPII) [antineoplastic, cytotoxic]
[Erbstatin] (phenolic)	Synthetic	RTK
[Flavopiridol] (N-methylpiperidinyl, chlorophenyl flavone)	Synthetic 5,7-Dihydroxyflavone (Chrysin) derivative	CDK1, CDK2, CDK4 & CDK7
[H7] (isoquinoline sulphamide)	Synthetic	PKA (2), PKC (5) [0.8], TK (4), CaM-PK (80)
[H89] (isoquinoline)	Synthetic	PKA
[Halenaquinone] (polyketide)	Sea sponge	EGF-RTK (19), pp60 ^{src} (2) (PI3K)
[Hydroxymethyl α -terthiophene] (polythiophene)	Synthetic	PKC (0.1)
(10 <i>E</i>)-Hymenialdesine (alkaloid)	<i>Stylissa massa</i> (Philippine sponge)	MAPKK-1 (= MEK-1) (3 nM)
(10 <i>Z</i>)-Hymenialdesine (alkaloid)	<i>Stylissa massa</i> (Philippine sponge)	MAPKK-1 (= MEK-1) (6 nM)
[K252a] (indole)	<i>Streptomyces</i> sp. (fungus)	PKC
[Mitoxantrone (= Mitoxanthrone)] (anthraquinone)	Synthetic anthraquinone (cf. Emodin); clinically used anticancer drug	MLCK (2), PKA (60), PKC (4) [1] (DNA, DNAS, RNAS) [antineoplastic]
[Olomoucine (= 6-(Benzylamino)-2-(2-hydroxyethylamino)-9-methylpurine)] (purine)	Synthetic	CDK2 [antimitotic]
[Purealin] (brominated polycyclic aryl imidazole)	<i>Psammaphysilla purea</i> (sea sponge)	MLCK (CaM, cAMP PDE) [modulates smooth muscle myosin]
[Roscovitine] (purine)	Synthetic	CDK2

(continued)

Table 8.1 (Continued)

Compound (class)	Plant source (family) plant part	Target inhibited (other targets) / in vivo effects/
[Staurosporine] (isoquinoline)	Microbial	PKA (60 nM), PKC (30 nM), TK (19 nM), CAMPK (10 nM)
[Staurosporine] (indole)	<i>Streptomyces</i> sp. (fungus)	IGF-1-RTK, I-RTK, PKA, PKC
[Tamoxifen] (triphenylethylene amine)	Synthetic EST-R antagonist used against breast cancer	PKC (EST-R) [clinical anticancer drug]
[α -Terthiophene carboxaldehyde] (polythiophene)	Synthetic	PKC (0.1)

Table 8.2 Activation of protein kinase C by plant-derived phorbol esters

Compound (class)	Plant (family) part	Effect on PKC / in vivo effects/
Phenolic		8.2p
Daphnoretin (= 3,6-Dihydroxy-7-methoxycoumarin 3-(6'-coumaryl) ether) (dimeric coumarin)	<i>Medicago sativa</i> (Fabaceae), <i>Ruta graveolens</i> (Rutaceae), <i>Daphne mezereum</i> (Thymelaeaceae), <i>Wikstroemia indica</i> (Thymelaeaceae)	Activates cytosolic PKC (rabbit) (EC ₅₀ 12), inhibits PM PKC (rabbit) (IC ₅₀ 45) [induces PA (EC ₅₀ 17); ↑ platelet ATP release]
Decursin (coumarin)	<i>Angelica decursiva</i> , <i>A. gigas</i> (Apiaceae) [root]	PKC activation [cytotoxic]
Decursinol angelate (= structural isomer of decursin) (coumarin)	<i>Angelica gigas</i> , <i>Seseli grandivittatum</i> (Apiaceae) [root]	PKC activation [cytotoxic]
Sanggenon C (flavanone)	<i>Morus mongolica</i> (Moraceae) [root bark]	Inhibits PE binding & PKC activation
Sanggenon D (flavanone)	<i>Morus mongolica</i> (Moraceae) [root bark]	Inhibits PE binding & PKC activation
Terpene		8.2t
<i>cis</i> -Abienol (labdane diterpene)	<i>Abies balsamea</i> (Pinaceae), <i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	Inhibits ODC induction by TPA
Daphnetoxin (daphnane diterpene)	<i>Daphne gnidium</i> , <i>D. mezereum</i> (Thymelaeaceae) [stem bark]	Activates PKC – PKC- α (0.5), γ (0.9), δ (3) [toxic]
28-Deacetylbelamcandal (spiroiridal triterpene)	<i>Iris tectorum</i> (Iridaceae) [rhizome]	PKC activator [induces TNF α release, secondary tumour promoter]
12-Deoxy-5- β -hydroxyphorbol-6 α ,7 α -oxide-13-hexadeca-2,4,6-13-hexadeca-,2,4,6-trienoic acid ester (= irritant factor M3) (tigliane diterpene PE)	<i>Hippomane mancinella</i> (manchineel apple) (Euphorbiaceae) [fruit, leaf latex]; W. Indies arrow poison; fruit poisoned sailors of Christopher Columbus (1493)	Presumed PKC activator [dermatitic, irritant, secondary tumour promoter, toxic]; Horatio Nelson drank <i>Hippomane mancinella</i> leaf-poisoned water in W. Indies (1777)
12-Deoxyphorbol 13-benzoate (phorbol ester; tigliane diterpene)	<i>Sapium sebiferum</i> (Chinese tallow) (Euphorbiaceae) [seed]	Activates PKC (EC ₅₀ 0.18) [inflammatory]

(continued)

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Table 8.2 (Continued)

Compound (class)	Plant (family) part/	Effect on PKC / in vivo effects/
12-Deoxyphorbol 13-phenylacetate (phorbol ester; tiglane diterpene)	<i>Euphorbia poissonii</i> , <i>E. unispina</i> (Euphorbiaceae) [latex]	Activates PKC [inflammatory]
12-Deoxyphorbol 13-phenylacetate-20-acetate (phorbol ester; tiglane diterpene)	<i>Euphorbia poissonii</i> , <i>E. unispina</i> (Euphorbiaceae) [latex]	Activates PKC [inflammatory]
ent-16 α ,17-Dihydroxyatisan-3-one (diterpene)	<i>Euphorbia quinquecostata</i> (Euphorbiaceae) [stem wood]	Inhibits PDB-R (PKC) binding
Faradiol (taraxastane triterpene)	<i>Arnica montana</i> , <i>Calendula officinalis</i> , <i>Helianthus annuus</i> , <i>Taraxacum japonicum</i> , <i>T. officinale</i> , <i>Tussilago farfara</i> , <i>Taraxacum</i> (Asteraceae)	Inhibits TPA co-carcinogenesis (CHY, TRY) [chemopreventive]
Frullanolide (eudesmanolide sesquiterpene lactone)	<i>Frullania tamarisci</i> , <i>F. dilatata</i> (liverworts) (Hepaticae)	Inhibits ODC induction by TPA [dermatitic]
18 β -Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	Inhibits ODC induction by TPA (ALDO-R, CBG, CORT-R, EST-R, 11 β HSDH, Na ⁺ , K ⁺ -ATPase, SBG) [elevated cortisol, hypermineralo-corticoidism]
Gnidamacrin (daphnane diterpene)	<i>Stellera chamaejasme</i> (Thymelaeaceae) [root]	PKC activation [antitumour, PKC activation & downregulation, CDK2 activity suppression, cell cycle arrest]
Huratoxin (daphnane diterpene PE)	<i>Hippomane mancinella</i> (manchineel apple), <i>Hura crepitans</i> (Euphorbiaceae) [fruit, leaf latex], <i>Pimelea simplex</i> , <i>Wikstroemia retusa</i> (Thymelaeaceae)	Presumed PKC activator [dermatitic, irritant, secondary tumour promoter, toxic]
17-Hydroxyingenol 20-hexadecanoate (ingenane diterpene)	<i>Euphorbia quinquecostata</i> (Euphorbiaceae) [stem wood]	Inhibits PDB-R (PKC) binding
Ingenol (ingenane diterpene)	<i>Euphorbia</i> spp. (Euphorbiaceae)	Inactive but esters activate PKC
Ingenol 3-benzoate (ingenane diterpene)	<i>Euphorbia</i> spp. (Euphorbiaceae)	Activates PKC
Ingenol 3,20-dibenzoate (ingenane diterpene)	<i>Euphorbia esula</i> (Euphorbiaceae)	Activates PKC – nPKC, PKC- δ , ϵ , θ & μ [anticancer]
Ingenol 20-hexadecanoate (ingenane diterpene)	<i>Euphorbia quinquecostata</i> (Euphorbiaceae) [stem wood]	Inhibits PDB-R (PKC) binding
Mezerein (daphnane diterpene)	<i>Daphne mezereum</i> (Thymelaeaceae)	Activates PKC – PKC- α (at 1–100 nM), PKC- γ , δ , ζ & η (at 1) [antitumour]
Phorbol (tiglane diterpene)	<i>Croton tiglium</i> (Euphorbiaceae) [seed oil]	Inactive but esters activate PKC
Resiniferonol (daphnane diterpene)	<i>Euphorbia poissonii</i> , <i>E. resinifera</i> (Euphorbiaceae)	Inactive but di- & triesters activate PKC

(continued)

Table 8.2 (Continued)

Compound (class)	Plant (family) part	Effect on PKC / in vivo effects
Resiniferonol 9,13,14-orthophenylacetate (daphnane diterpene triester)	<i>Euphorbia resinifera</i> (Euphorbiaceae)	Activates PKC – PKC- α (at 1–100 nM), PKC- γ , δ , ζ & η (at 0.1–1)
Resiniferatoxin (= <i>Euphorbia</i> factor RL ₉ ; Resiniferol vanillate & phenylacetate diester) (daphnane diterpene diester)	<i>Euphorbia poissonii</i> , <i>E. resinifera</i> , <i>E. unispina</i> (Euphorbiaceae)	Activates PKC – PKC- α (at 1–100 nM), PKC- γ , δ , ζ & η (at 1) (VAN-R) [secondary tumour promoter; irritant, bladder sensory fibre desensitization]
Sapintoxin A (= 4-Deoxyphorbol 12-(2-methylamino)benzoate-13-acetate (phorbol ester; tiglane diterpene)	<i>Sapium indicum</i> [ripe fruit], <i>S. sebiferum</i> (Chinese tallow) (Euphorbiaceae) [seed]	Activates PKC – PKC- α (at 1–100 nM), PKC- γ , δ , ζ & η (at 1) [inflammatory]
Sapintoxin C (= 4-Deoxy-20-deoxy-5-hydroxy phorbol 12-(2-methylamino) benzoate-13-acetate; 20-deoxy-5-hydroxy-sapintoxin A) (phorbol ester; tiglane diterpene)	<i>Sapium sebiferum</i> (Chinese tallow) (Euphorbiaceae) [seed]	Does not activate PKC (EC ₅₀ > 100) [not inflammatory]
Steviol (diterpene)	<i>Stevia rebaudiana</i> (Asteraceae)	Inhibits ODC induction by TPA [GA-like activity]
Taraxasterol (taraxastane triterpene)	<i>Saussurea lappa</i> , <i>Taraxacum japonicum</i> (Asteraceae)	Inhibits TPA co-carcinogenesis [chemopreventive]
Taraxerol (taraxastane triterpene)	<i>Taraxacum japonicum</i> (Asteraceae), <i>Skimmia japonica</i> (Rutaceae), <i>Camellia sinensis</i> (Theaceae)	Inhibits TPA co-carcinogenesis [chemopreventive]
12-Tetradecanoylphorbol 13-acetate (= TPA; Croton factor A1) (phorbol ester; tiglane diterpene)	<i>Croton tiglium</i> (Euphorbiaceae) [seed oil]	Activates PKC – PKC- α , γ , δ , ζ & η (at 1–100 nM) [irritant, inflammatory, secondary tumour promoter]
Thapsigargin (sesquiterpene lactone)	<i>Thapsia garganica</i> (Apiaceae)	Activates PKC (PKC- α) (Ca ²⁺ -ATPase)
Thymeleatoxin (diterpene)	<i>Thymelea hirsuta</i> (Thymelaeaceae) [leaf]	Activates PKC – nPKC, cPKC, PKC- μ
Tinyatoxin (daphnane diterpene)	<i>Euphorbia poissonii</i> (tinya) (Euphorbiaceae) [latex]	Activates PKC (PKC- α) [skin inflammatory]
ent-3 β ,16 α ,17-Trihydroxyatisane (atisane diterpene)	<i>Euphorbia quinquecostata</i> (Euphorbiaceae) [stem wood]	Inhibits PDB-R (PKC) binding
Tubeimoside I (triterpene saponin)	<i>Bolbostenma paniculatum</i> (Cucurbitaceae) [bulb]	Inhibits TPA co-carcinogenesis & oedema [AI]
Tubeimoside III (triterpene saponin)	<i>Bolbostenma paniculatum</i> (Cucurbitaceae) [bulb]	Inhibits TPA co-carcinogenesis & oedema (loses antitumour promotion if ingested) [AI]
Other		8.2o
Ca ²⁺ (calcium ion)	Universal	Activates Ca ²⁺ -dependent PKC isozymes

(continued)

Table 8.2 (Continued)

Compound (class)	Plant (family) part	Effect on PKC / in vivo effects
Diacylglycerol (glycerol diester)	Universal	Activates PKC [PA, ↑ platelet ATP release]
Tricolorin A (= (11S)-Hydroxyhexadecanoic acid 11- <i>O</i> -rhamnosyl-[2- <i>O</i> -(2 <i>S</i> -methylbutyryl)-4- <i>O</i> -(2 <i>S</i> -methylbutyryl)]rhamnosyl-glucosyl-furanoide-(1,3'-lactone) (FA glycoside)	<i>Ipomoea tricolor</i> (Convolvulaceae) [resin]	Inhibits PDB binding to PKC (calf brain) [allelopathic, inhibits seedling growth, cytotoxic]
Non-plant reference		8.2n
[Bryostatin-1] (pyrane macrolide lactone)	Bryozoa (<i>Bugula neretina</i>)	Activates PKC – PKC- α , γ , δ , ζ & η (at 10–100 nM)
[Octanoyl acylglycerol diester (= OAG)] (glycerol diester)	Semi-synthetic	Activates PKC [PA, ↑ platelet ATP release]
[Phorbol 12,13-dibutyrate] (phorbol ester; diterpene ester)	Semi-synthetic	Activates PKC – PKC- α , γ , δ , ζ & η (at 1–100 nM) [PA, ↑ platelet ATP release]

Table 8.3 Receptor tyrosine kinase-mediated signalling

Compound (class)	Plant (family) part	Process inhibited (other targets) / in vivo effects
Brain-derived neurotrophic factor (BDNF) receptor tyrosine kinase (BDNF-RTK)		8.3A
L-BOAA (= β - <i>N</i> -Oxalylamino-L-alanine) (amino acid)	<i>Lathyrus sativus</i> (Fabaceae) [seed]	Induces BDNF expression (Non-NMDA-Glu-R, Norepinephrine transport) [cytotoxic, excitatory, lathyrism (neuronal damage disease) in humans]
L-BMAA (= β - <i>N</i> -Methylamino-L-alanine) (amino acid)	<i>Cycas circinalis</i> (Cycadaceae)	Induces BDNF expression (Non-NMDA-Glu-R agonist, Norepinephrine transport) [excitotoxin, lathyrism (neuronal damage disease) in humans]
Collagen receptor (COLL-R) (cf. 5.7D)		8.3B
[Avicine pseudocyanide] (alkaloid)	<i>Zanthoxylum integrifolia</i> (Rutaceae)	COLL-R antagonist [inhibits collagen-induced PA (47) & platelet adhesion & ATP release]
Frangulin B (anthraquinone glycoside)	<i>Frangula alnus</i> , <i>Rhamnus cathartica</i> , <i>R. frangula</i> (Rhamnaceae) [bark, root, seed]	COLL-R antagonist [inhibits collagen-induced PA & platelet adhesion & ATP release]

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) / part	Process inhibited (other targets) / in vivo effects
Epidermal growth factor (EGF) receptor tyrosine kinase (EGF-RTK)		8.3C
Alkaloid		8.3Ca
Pheophorbide a (pyrrole)	<i>Psychotria acuminata</i> (Rubiaceae)	[Light-dependent inactivation of EGF-R & of complement factor 5 α binding; antitumour, immunosuppressive]
Phenolic		8.3Cp
Acacetin (= Apigenin 4'-methyl ether; 5,7,4'-Trihydroxyflavone 4'-methylether) (flavone)	Fern [leaf exudate], <i>Ammi visnaga</i> (Apiaceae), Asteraceae [leaf], Betulaceae [leaf bud exudate], <i>Ginkgo biloba</i> (Ginkgoaceae), <i>Agastache foeniculum</i> , <i>Mentha aquatica</i> (Lamiaceae); glycosides in <i>Cirsium</i> (Asteraceae), <i>Linaria</i> (Scrophulariaceae), <i>Tilia japonica</i> (Tiliaceae) spp.	EGF-RTK (141) (AR, ITDI) [allergenic, inhibits histamine release]
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	<i>Apium</i> , <i>Daucus</i> (Apiaceae), <i>Achillea</i> , <i>Artemisia</i> (Asteraceae), <i>Mentha</i> , <i>Thymus</i> (Lamiaceae), ferns [leaf surface], <i>Buddleja officinalis</i> (Loganiaceae) [flower], <i>Digitaria exilis</i> (Poaceae); as glycoside in <i>Apium</i> (celery), <i>Petroselinum</i> (parsley) (Apiaceae), <i>Cosmos</i> , <i>Erigeron</i> , <i>Dahlia</i> (Asteraceae), <i>Amorpha</i> (Fabaceae) spp.	EGF-RTK (92) (CDK2, IGF-1-RTK, I-RTK, MAOA, MAOB, MLCK, PKA, PKC) (BZ-R-like R) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
Biochanin A (= 5,7-Dihydroxy-4'-methoxyisoflavone; Pratensol) (isoflavone)	<i>Cicer arietum</i> , <i>Medicago sativa</i> , <i>Trifolium pratense</i> , <i>Baptisia</i> spp., <i>Dalbergia</i> spp. (Fabaceae), <i>Virola cadudifolia</i> (Myristicaceae) [wood], <i>Cotoneaster pannosa</i> (Rosaceae) [fruit]	EGF-RTK (92) (MLCK, PKA) [oestrogenic, hypolipidaemic]
Butein (= 2',4',3,4-Tetrahydroxychalcone) (chalcone)	<i>Vicia faba</i> , <i>Dalbergia odorifera</i> , <i>Robimia pseudoacacia</i> (Fabaceae) [wood]; glycosides in <i>Coreopsis</i> , <i>Bidens</i> (Asteraceae), <i>Butea</i> (Fabaceae) spp.	EGF-RTK (8; 65) (p60 ^{src} TK)
Cyanidin (= 3,5,7,3',4'-Pentahydroxyflavilium) (anthocyanidin)	Widespread as glycoside [flower, fruit, leaf, tuber]	EGF-RTK (0.8) [inhibits EGF-induced tumour cell growth (42; 73); 3-galactoside inactive; red pigment]
Delphinidin (= 3,5,7,3',4',5'-Hexahydroxyflavilium) (anthocyanidin)	Widespread as glycoside [flower, fruit, tuber]	EGF-RTK (1) [inhibits EGF-induced tumour cell growth (18; 33); mauve pigment]
Desmal (= 8-Formyl-2,5,7-trihydroxy-6-methylflavanone) (flavanone)	<i>Desmos chinensis</i> (Annonaceae) [leaf, stem]	[Human A431 cell PM EGF-RTK (8)]

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) part/	Process inhibited (other targets) / in vivo effects/
(-)-Epigallocatechin 3-gallate (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Chimaphila umbellata</i> (Ericaceae), <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Sorbus aucubaria</i> (Rosaceae), <i>Camellia sinensis</i> (tea) (Theaceae)	EGF-RTK (0.2; 1–2) (FGF-RTK, PDGF-RTK, pp60 ^{v-src} , PKA, PKC) [human A431 cell-EGF-RTK (<5); inhibits EGF-induced tumour cell growth (21; 32) & TF AP-1 activation; anticarcinogen, oxidation products give tea taste]
Flavone (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	EGF-RTK (225) (5-LOX, COX) [allergenic, antibacterial, AI, PAI, inhibits histamine release]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Phaseolus lunatus</i> , <i>Trifolium subterraneum</i> , <i>T. brachycalycinum</i> (Fabaceae); 7- <i>O</i> -glucoside (= Genistin; Genistoside) in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> (Fabaceae); 4'- <i>O</i> -glucoside (= Sophocoroside) in <i>Sophora japonica</i> (Fabaceae) [pod]	EGF-RTK (3; 22) (HISK, MLCK, PKA, pp60 ^{v-src} TK, pp110 ^{gag-fts} TK) [human A431 cell EGF-RTK (4) <i>in vivo</i>] (AD-R, GABAA-R, lipase, peroxidase, TOPII) [antifungal, oestrogenic]
Genistin (= Genistein 7- <i>O</i> -glucoside; Genistoside; 4',5,7-Trihydroxyisoflavone 7- <i>O</i> -glucoside) (isoflavone <i>O</i> -glycoside)	<i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> (Fabaceae), <i>Prunus cerasus</i> (Rosaceae)	EGF-RTK (> 231) – cf. Genistein (TOPII) [plant growth inhibitor]
Homoplantagin (flavonoid glycoside)	<i>Plantago asiatica</i> [leaf], <i>P. media</i> (Plantaginaceae)	EGF-RTK [antiproliferative]
Hypericin-like compound (phenolic)	<i>Fagopyrum esculentum</i> (buckwheat) (Polygonaceae) [herb]	EGF-RTK (PKC) [photosensitizing, red pigment]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae) [seed, stem], <i>Pisum sativum</i> (Fabaceae), <i>Thespesia populnea</i> (Malvaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (grapefruit) (Rutaceae), <i>Koelreuteria henryi</i> (Sapindaceae)	EGF-RTK (11) (CDPK, MAOA, MAOB, MLCK, PKA, p56 ^{lck} TK)
Kievitone (= 2',4',5,7-Tetrahydroxy-8-isoprenylisoflavanone) (isoflavanone)	<i>Dolichos biflorus</i> , <i>Lablab niger</i> , <i>Phaseolus</i> spp. (Fabaceae)	EGF-RTK [antibacterial, antifungal, oestrogenic; inhibits EST-R positive breast cancer cell proliferation]
Okanin (= 2',3',4',3,4-Pentahydroxychalcone) (chalcone glucoside)	Aglycone of 4'- <i>O</i> -glycoside (Marein) in <i>Bidens</i> sp., <i>Coreopsis</i> sp. (Asteraceae) [flower]	EGF-RTK (19) (uncoupler)

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) part	Process inhibited (other targets) / in vivo effects/
Phloretin (= 2',4,4',6'-Tetrahydroxy-dihydrochalcone) (dihydrochalcone)	Aglycone of 2'-glucoside (Phloridzin)	EGF-RTK (19) (ECMOX, ITD, ox. phos. (uncoupler), PKC) [antibacterial, AI, feeding deterrent]
Phloridzin (= Phloretin 2'-O-glycoside) (dihydrochalcone O-glycoside)	<i>Kalmia</i> , <i>Pieris</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>Malus</i> spp. (Rosaceae)[apple leaf, fruit skin], <i>Symplocos</i> spp. (Symplocaceae)	EGF-RTK (> 100) (Glc-TR, Glc-R(GIP)) [bitter, feeding deterrent]
Procyanidin B-2 (condensed tannin)	<i>Malus</i> sp. (apple) (Rosaceae), <i>Uncaria sinensis</i> (Rubiaceae)	EGF-RTK via PKC (downstream); promotes hair growth
Procyanidin C-1 (condensed tannin)	<i>Rheum palmatum</i> (rhubarb) (Polygonaceae) [rhizome]	PKC
Prunetin (= 5-Hydroxy-7,4'-dimethoxyisoflavone) (isoflavone)	<i>Pterocarpus angolensis</i> , <i>Dalbergia miscolobium</i> (Fabaceae), <i>Prunus</i> spp. (Rosaceae)	EGF-RTK (15)
Purpurogallin (bicyclic phenolic)	<i>Dryophanta divisa</i> gall on <i>Quercus pedunculata</i> (Fagaceae)	EGF-RTK (28; 45) [55; 84] [antioxidant, red pigment]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	EGF-RTK (AR, cAMP PDE, LOX, NEP, PK, PS-EF-1 α , RTKTOPII) [allergenic, antibacterial, AI, antiviral]
Theaflavin-3,3'-digallate (gallotannin)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	EGF-RTK blocker [inhibits EGF binding & EGF-RTK activation & autophos'n]
Theaflavins (tannin)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	EGF-RTK signalling [inhibit TF AP-1 activation]
Verbascoside (= Acteoside; Kusaginins) (phenyl propanoid glycoside)	<i>Echinacea</i> spp. (Asteraceae), <i>Buddleja globosa</i> , <i>B. officinalis</i> , <i>Forsythia suspense</i> , <i>Olea europaea</i> (Oleraceae), <i>Plantago media</i> (Plantaginaceae), <i>Verbascum sinuatum</i> , <i>V. thapsus</i> (Scrophulariaceae); Acanthaceae, Bignoniaceae, Gesneriaceae, Orobanchaceae, Verbenaceae	EGF-RTK (AR, 5-LOX) [AI, antiproliferative]
Other		8.3Co
<i>Glycine</i> Concanavalin A (lectin; CHO-binding protein)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	EGF-RTK activator [through binding oligosaccharide (CHO) residues]
<i>Oryza</i> EGF-binding proteins (35, 40 & 50 kDa proteins)	<i>Oryza sativa</i> (rice) (Poaceae) [leaf]	[EGF-like regulation in plant?]
<i>Phaseolus</i> Erythroagglutinating phytohaemagglutinin (= E-PHA) (lectin; CHO-binding protein)	<i>Phaseolus vulgaris</i> (bean) (Fabaceae)	EGF-RTK blocker (<i>Phaseolus</i> Leukoagglutinating PHA (L-PHA) isolectin inactive) [possible antitumour agent]

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) part/	Process inhibited (other targets) / in vivo effects/
<i>Solanum</i> Carboxypeptidase Inhibitor (= PCI) (39 aa, 4 kDa, 6 Cys T-knot protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	EGF-RTK antagonist (100 pM) [antitumour]
<i>Triticum</i> wheat germ agglutinin (lectin; CHO-binding protein)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	EGF-RTK activator [through binding oligosaccharide (CHO) residues]
Non-plant reference		8.3Cn
[Calphostin C] (perylene quinone)	<i>Cladosporium cladosporioides</i> (fungus)	PKC (involved downstream in EGF signalling); promotes hair growth
[Chalcone (= 1,3-Diphenyl-2-propen-1-one)] (chalcone)	Synthetic; parent chalcone	PKC (>50) (involved downstream in EGF signalling)
[Epidermal growth factor (= EGF)] (protein)	Animals; endogenous EGF-R ligand; Stanley Cohen (USA, EGF & NGF) (Nobel Prize, Physiology/Medicine, 1986, growth factors)	EGF-RTK agonist (0.6 pM) [induces cell division & epidermal differentiation; stimulates tumour growth]
[Halenaquinone] (polyketide)	Sea sponge	EGF-RTK (19) (PI3K)
[Staurosporine] (indole)	<i>Streptomyces</i> sp. (fungus)	EGF-RTK (I-RTK, PKI)
[Transforming growth factor- α (= TGF- α)] (25 kDa protein)	Animals; endogenous EGF-R ligand	EGF-RTK agonist [induces cell division & epidermal differentiation; stimulates tumour growth]
[Tyrphostin AG1478 (= <i>N</i> -[3-Chlorophenyl]-6,7-dimethoxy-4-quinazolinamine)] (phenyl quinazolinamine)	Synthetic	EGF-RTK (2)
[Tyrphostins 25, 46, 47, 51] (phenolics)	Synthetics	EGF-RTK – Tyrphostin 25 (3), 46 (10), 47 (2), 51 (0.8)
Fibroblast growth factor (FGF) receptor tyrosine kinase (FGF-RTK)		8.3D
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Lamiaceae, ferns [leaf surface]; various glycosides in <i>Apium graveolens</i> (celery), <i>Petroselinum</i> (parsley) (Apiaceae) [leaf, seed], <i>Amorpha fruticosa</i> (Fabaceae), <i>Cosmos bipinnatus</i> [flower], <i>Erigeron annuus</i> [flower], <i>Dahlia variabilis</i> (Asteraceae) [flower]	FGF-RTK (20) (BZ-R-like R, CDK2, EGF-RTK, insulin-RTK, IGF-1-RTK MLCK, PKA, PKC, RTK) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	FGF-RTK (1–2) (EGF-RTK, PDGF-RTK, pp60 ^{v-src} , PKA, PKC) [anticarcinogen, oxidation products give tea taste]

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) [part]	Process inhibited (other targets) / in vivo effects/
[Fibroblast growth factor (=FGF)] (16 kDa protein)	Animals – endogenous FGF-RTK ligand	FGF-RTK agonist [angiogenesis, development, neural tube development]
Glial cell line-derived neurotrophic factor (GDNF) receptor tyrosine kinase (GDNF-RTK)		8.3E
Bilobalide (sesquiterpene)	<i>Ginkgo biloba</i> (Ginkgoaceae) [leaf]	Induces GDNF expression
[Glial cell line-derived neurotrophic factor (= GDNF)] (protein)	Animal; promotes neurite outgrowth; PKA-modulated; activates Ras/Erk (MAPK), PI3K/Akt & PLC γ pathways & Rho, Rac & Cdc42 GTPases	GDNF-RTK (Ret plus co-receptor GDNF family R)
Insulin-like growth factor-1 (IGF-1) receptor tyrosine kinase (IGF-1-RTK)		8.3F
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Lamiaceae, ferns [leaf surface]; various glycosides in <i>Apium graveolens</i> , <i>Petroselinum</i> (Apiaceae), <i>Cosmos bipinnatus</i> , <i>Erigeron annuus</i> , <i>Dahlia variabilis</i> (Asteraceae), <i>Amorpha fruticosa</i> (Fabaceae)	IGF-1-RTK (48) (BZ-R-like R, CDK2, EGF-RTK, I-RTK, MAOA, MAOB, MLCK, PKA, PKC) [antibacterial, AI, diuretic, hypotensive, modulation stimulant]
[Insulin-like growth factor-1 (IGF-1)] (protein)	Animal	IGF-2-RTK agonist
[Staurosporine] (indole)	<i>Streptomyces</i> sp. (fungus)	IGF-1-RTK (6) (I-RTK, PKI)
Insulin-like growth factor-2 (IGF-2) receptor tyrosine kinase (IGF-2-RTK)		8.3G
Torilin (sesquiterpene)	<i>Torilis japonica</i> (Apiaceae) [fruit]	[Anti-angiogenic, down regulates hypoxia-inducible VEGF & IGF-2 expression]
[Insulin-like growth factor-2 (IGF-2)] (8 kDa protein)	Animal	IGF-2-RTK agonist
Insulin receptor tyrosine Kinase (INS-RTK)		8.3H
Phenolic		8.3Hp
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Lamiaceae, ferns [leaf surface]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]; as glycoside in <i>Apium</i> (celery), <i>Petroselinum</i> (parsley) (Apiaceae), <i>Cosmos</i> , <i>Erigeron</i> , <i>Dahlia</i> (Asteraceae), <i>Amorpha</i> (Fabaceae) spp.	INS-RTK (10) (CDK2, EGF-RTK (93), IKK, MLCK, PKA, PKC (>50), RTK (FGF-RTK, insulin-RTK, IGF-1-RTK, TPO) (BZ-R-like R, EST-R, Na ⁺ /K ⁺ /Cl ⁻ TR) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> modulation stimulant]

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) part	Process inhibited (other targets) / in vivo effects/
Damnacanthal (anthraquinone)	<i>Morinda citrifolia</i> (Rubiaceae)	INS-RTK (10) (p56 ^{lck} TK, PDGF-RTK, erbB2-RTK, p59 ^{ltn} TK, p60 ^{src} TK, PKA, PKC, TOPII)
(-)-Epicatechin (= (2 <i>R</i> ,3 <i>R</i>)-5,7,3',4'-Tetrahydroxyflavan-3-ol) (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), Gymnospermae, <i>Pterocarpus marsupium</i> , <i>P. spp.</i> (Fabaceae) [bark], <i>Podocarpus nagi</i> (Podocarpaceae), <i>Crataegus monogyna</i> (Rosaceae)	Does not compete with Insulin-INS-RTK binding [Insulinogenic, Insulin-mimetic – ↑ glycogen, ↓ lipolysis] (AR, PKA) [antibacterial, antidiabetic, AI, antioxidant]
Methylhydroxychalcone polymer (= MHCP polymer) (chalcone)	<i>Cinnamomum zeylanicum</i> (cinnamon) (Lauraceae)	Mimics insulin in activating insulin-RTK autophosphorylation, glycogen synthase and glucose uptake (action inhibited by PI3K inhibitor Wortmannin)
Terpene		8.3Ht
Steviol (kaurane diterpene)	<i>Stevia rebaudiana</i> (Asteraceae) [leaf]	↑ Glc-induced insulin secretion (β cells) [activity like Gibberellin, insulinotropic]
Stevioside (kaurane diterpene glycoside)	<i>Stevia rebaudiana</i> (Asteraceae) [leaf]	↑ Glc-induced insulin secretion (β cells) [sweet (300 × >sucrose), insulinotropic]
Other		8.3Ho
<i>Glycine</i> Concanavalin A (lectin (CHO binding protein); kDa protein)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	[Insulin mimic at nuclear envelope]
<i>Glycine</i> insulin-like protein (= Leginsulin) (4 kDa protein; 6 Cys)	<i>Glycine max</i> (soya bean) (Fabaceae) [germinated seed radicle]	<i>Glycine</i> insulin-binding protein Bg ligand (insulin competes; promotes Bg phosphorylation)
<i>Glycine</i> insulin-binding protein Bg (37 kDa; 2 disulfide-linked subunits)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Leginsulin- & insulin-binding
<i>Glycine</i> insulin-binding proteins (39 kDa; 2 disulfide-linked subunits)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Insulin-binding [4 nM]
<i>Triticum</i> Phytohaemagglutinin (lectin (CHO binding protein); kDa protein)	<i>Triticum aestivum</i> (Poaceae) [seed]	[Insulin mimic at nuclear envelope]
Non-plant reference		8.3Hn
[Demethylasterriquinone B-1 (= DMAQ-B1)] (quinone)	<i>Pseudomassaria</i> sp. (tropical fungus)	INS-RTK agonist [first orally active insulin-mimetic small molecule; induces INS-RTK activation & phos'n, IRS-1 phos'n, PI3K, PKB & glucose uptake activation]

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) part	Process inhibited (other targets) / in vivo effects/
[Insulin] (5 kDa S-S-linked heterodimer; 3 S-S; A 31 aa, B 31 aa); sequence by Fred Sanger (1953) (UK, Nobel Prizes, Chemistry, 1958 [insulin sequence] & 1980 [RNA sequencing]	Animals <i>ex</i> pancreatic β cells; discovery (1922) by Frederick Banting, J.B. Collip, Charles Best, J. Macleod (Canada; Nobel Prize, Medicine, to Banting & MacLeod, 1923); type 2 diabetes mellitus, the most widespread metabolic disease	INS-RTK agonist [promotes anabolic reactions (glycogen, fatty acid & protein synthesis), & glucose uptake; inhibits apoptosis]; type 1 diabetes (lack of insulin production, requires insulin therapy); type 2 diabetes (\downarrow insulin production & insulin resistance)
[Staurosporine] (indole) Interferon-γ (IFNγ) receptor (IFNγ-R) (-)-Epigallocatechin 3-gallate (flavan-3-ol)	<i>Streptomyces</i> sp. (fungus) <i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	INS-RTK (61 nM) (IGF-1-RTK, PKI) 8.3I Blocks TK-mediated STAT-1 activation (EST-R, PKA, PKC, proteasome, 5 α R, RTK, TK) [cell-EGF-RTK (<5); oxidation products give tea taste] [Antiviral defence]
[Interferon- γ (= IFN γ)] (20 kDa protein) Interleukin -1β receptor (IL-1β-R) Sinomenine (morphinan isoquinoline)	Animal <i>Sinomenium acutum</i> (Menispermaceae); Chinese anti-arthritis plant	8.3J Inhibits TGF- β 2-induced synovial fibroblast proliferation [AI, anti-proliferative] IL-1 β -R [pro-inflammatory cytokine, immunomodulatory, T & B cell activation, ACTH activation]
[Interleukin -1 β (IL-1 β)] (17 kDa protein) Interleukin-8-receptor (IL-8-R) Pheophorbide a (pyrrole)	Animals <i>ex</i> mononuclear immune- & inflammation-stimulated phagocytes <i>Psychotria acuminata</i> (Rubiaceae)	8.3K Non-specific light-dependent inactivation of IL-8 binding to IL-8-R [antitumour, immunosuppressive] [Immunomodulatory, chemotactic chemokine (C-X-C family)]
[Interleukin-8 (= IL-8-R)] (8 kDa protein) Leptin receptor (LEP-R) Green tea High GI starchy diet	Animal <i>Camellia sinensis</i> (tea) (Theaceae) [leaf] <i>Zea mays</i> (Poaceae)	8.3L \downarrow Leptin (JAK/STAT signalling) \downarrow Leptin (JAK/STAT signalling) LEP-R agonist (JAK/STAT signalling)
[Leptin] (16 kDa protein)	Animals <i>ex</i> adipocytes; reports fat storage status, \downarrow orexigenic, \uparrow anorexigenic hormones	

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) part	Process inhibited (other targets) / in vivo effects/
Nerve growth factor (NGF) receptor tyrosine kinase (NGF-RTK)		8.3M
L-BOAA (= β - <i>N</i> -Oxalylamino-L-alanine) (amino acid)	<i>Lathyrus sativus</i> (Fabaceae) [seed]	[Induces NGF expression] (Non-NMDA Glu-R, Norepinephrine transport) [cytotoxic, excitatory, lathyrism (neuronal damage disease) in humans]
L-BMAA (= β - <i>N</i> -Methylamino-L-alanine) (amino acid)	<i>Cycas circinalis</i> (Cycadaceae)	[Induces NGF expression] (Non-NMDA-Glu-R agonist, Norepinephrine transport) [excitotoxin, lathyrism (neuronal damage disease) in humans]
Ginsenoside Rb1 (triterpene glycoside saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	[Potentiates NGF-mediated neurite outgrowth]
Isodunnianin (sesquiterpene)	<i>Illicium tahiroid</i> (Illiciaceae)	[Enhances NGF-mediated neurite outgrowth]
Malonylginsenoside Rb1 (triterpene glycoside saponin)	<i>Panax ginseng</i> (Araliaceae) [root]	[Potentiates NGF-mediated neurite outgrowth (at 30)]
4-Methylcatechol (phenolic)	<i>Picea abies</i> (Pinaceae) [wood]	Induces NGF expression [antifungal, phytoalexin]
Nardosinone (sesquiterpene)	<i>Nardostachys chinensis</i> (Valerianaceae) [rhizome, root]	Enhances NGF-induced neurite outgrowth
[Nerve growth factor (= β -NGF)] (27 kDa homodimeric protein)	Animal; Stanley Cohen (USA, EGF & NGF) & Rita Levi-Montalcini (Italy, NGF) (Nobel Prize, Physiology/Medicine, 1986, growth factors)	NGF-RTK agonist [promotes growth & survival of peripheral sympathetic & sensory neurons & brain cholinergic neurons]
Picroside I (iridoid monoterpene lactone)	<i>Picrorhiza scrophulariiflora</i> (Scrophulariaceae) [rhizome]	Enhances NGF-induced neurite outgrowth
Picroside II (iridoid monoterpene lactone)	<i>Picrorhiza scrophulariiflora</i> (Scrophulariaceae) [rhizome]	Enhances NGF-induced neurite outgrowth
Platelet-derived growth factor (PDGF) receptor tyrosine kinase (PDGF-RTK)		8.3N
(+)-Catechin (= Catechinic acid; Catechuic acid; (+)-Cyanidanol; (2R,3S)-5,7,3',4'-Tetrahydroxyflavan-3-ol) (flavan-3-ol)	Widespread; <i>Salix caprea</i> (willow) (Salicaceae) [flower]	[Inhibits PDGF-BB-induced PDGF-RTK β autophos'n (at 50)] (AR, COX-1, COX-2, MLCK, PKA) [anticancer, antioxidant]
(-)-Epicatechin 3-gallate (= ECG) (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	[Inhibits PDGF-BB-induced PDGF-RTK β autophos'n (at 50)] (collagenase) [human A431 cell-EGF-RTK (< 5)]

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) part	Process inhibited (other targets) / in vivo effects/
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf], <i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark]	PDGF-RTK (1-2) [inhibits PDGF-RTK β autophosphorylation (at 50)] (PK, RTK) [anticarcinogen, oxidation products give tea taste]
[Platelet-derived growth factor (= PDGF)] (30 kDa glycoprotein)	Animal – endogenous ligand for PDGF-RTK	PDGF-RTK agonist [attractant & mitogen for fibroblasts, smooth muscle & glial cells]
Theaflavin-3,3'-digallate (gallotannin)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	PDGF-RTK blocker [inhibits PDGF binding]
[Tyrphostin AG1296 (= 6,7-Dimethoxy-2-phenylquinoxaline)] (phenyl quinoxaline)	Synthetic	PDGF-RTK (selective inhibitor)
Prolactin		8.30
[Bromocryptine (= 2-Bromoergocryptine)] (indole)	Semi-synthetic from Ergocryptine	Inhibits prolactin release (D2-R agonist, \oplus D-REL) [anti-Parkinsonian]
Ergine (= Lysergic acid amide; Lysergamide) (indole)	<i>Ipomoea argyrophylla</i> , <i>I. tricolor</i> , <i>I. violacea</i> , <i>Rivea corymbosa</i> (Convolvulaceae); from hydrolysis of ergot (<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals)	Inhibits prolactin release (D2-R agonist) [depressant, hallucinogenic]
[Ergocornine] (indole)	<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals e.g. <i>Secale</i> (rye); ergot inspiration of apocalyptic paintings of Hieronymus Bosch?	Inhibits prolactin release (D2-R agonist) [ergotism (hallucinogenic , convulsant), haemostatic, vasoconstrictor]
[Ergocristine] (indole)	<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals e.g. <i>Secale</i> (rye); ergot-induced hallucination = St Anthony's fire, addressed by Mandrake root extract	Inhibits prolactin release (D2-R agonist (\oplus D-REL)) [ergotism (hallucinogenic , convulsant), haemostatic, vasoconstrictor]
[α -Ergocryptine (= Ergokryptine)] (indole)	<i>Claviceps purpurea</i> , <i>C. spp.</i> (ergot fungus) on cereals e.g. <i>Secale</i> (rye); European "witch killing" because ergotism gives "devil possession" symptoms	Inhibits prolactin release (D2-R agonist, \oplus D-REL) [anti-Parkinson's, ergotism (hallucinogenic , convulsant), haemostatic, vasoconstrictor]
[Ergonovine] (indole)	<i>Claviceps purpurea</i> , <i>C. paspali</i> (ergot fungus) on cereals & <i>Acremonium</i> -infected <i>Stipa robusta</i> (Poaceae); cattle & horse stupor after eating infected grass	Inhibits prolactin release (D2-R agonist) [ergotism (hallucinogenic , convulsant), haemostatic, oxytocic, vasoconstrictor]
[Ergotamine] (indole)	<i>Claviceps purpurea</i> , <i>C. paspali</i> (ergot fungus) on cereals e.g. <i>Secale</i> sp. (rye) (Poaceae)	Inhibits prolactin release (D2-R agonist) [anti-migraine, ergotism , haemostatic, vasoconstrictor]
[Ergovaline] (indole)	<i>Claviceps purpurea</i> , <i>C. paspali</i> (ergot fungus) on grasses & cereals e.g. <i>Secale</i> sp. (rye), <i>Festuca arundinacea</i> (tall fescue) (Poaceae)	Inhibits prolactin release (D2-R agonist) [ergotism (hallucinogenic , convulsant), haemostatic, vasoconstrictor]

(continued)

Table 8.3 (Continued)

Compound (class)	Plant (family) / part/	Process inhibited (other targets) / in vivo effects/
[Prolactin] (23 kDa protein)	Animals <i>ex</i> anterior pituitary	Prolactin R (JAK/STAT-linked receptor)
Tumour necrosis factor-α (TNF-α) receptor (TNF-α-RTK)		8.3P
Pheophorbide a (pyrrole)	<i>Psychotria acuminata</i> (Rubiaceae)	[Non-specific light-dependent inactivation of TNF- α -R \rightarrow blocks NF κ B activation]
Methyl pheophorbides a & b (porphyrins, pyrroles)	Porphyrin-related	Inhibit TGF- α -R binding & TGF- α -induced cell proliferation
[Tumour necrosis factor- α (TNF- α)] (17 kDa trimeric protein)	Animals <i>ex</i> leucocytes	PM Rs [NF κ B activation & pro-inflammatory cytokine, COX-2 & iNOS expression; activates apoptosis]
Transforming growth factor β (TGF-β) receptor (TGF-β-Rs; I, II – TGF-β-RS/TKs, III – proteoglycan)		8.3Q
Sinomenine (morphinan isoquinoline)	<i>Sinomenium acutum</i> (Menispermaceae); Chinese anti-arthritis plant	Inhibits TGF- β 2-induced synovial fibroblast proliferation [AI, anti-proliferative]
[Transforming growth factor β (TGF- β)] (25 kDa homodimeric protein)	Animals	Ser/ThrPK receptor
Vascular endothelial growth factor (VEGF) receptor tyrosine kinase (VEGF-RTK) (e.g. Flk-1)		8.3R
Bilobalide (sesquiterpene)	<i>Ginkgo biloba</i> (Ginkgoaceae) [leaf]	Induces VEGF expression
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae), <i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark]	Inhibits VEGF expression induced by serum starvation (EGF-RTK, FGF-RTK, PDGF-RTK, pp60 ^{v-src} , PKA, PKC) [anti-angiogenic, anticancer, anti-carcinogen]
Torilin (sesquiterpene)	<i>Torilis japonica</i> (Apiaceae) [fruit]	[Anti-angiogenic, down regulates hypoxia-inducible VEGF & IGF-II expression]
[Vascular endothelial growth factor (= VEGF)] (46 kDa dimeric glycoprotein)	Animals	VEGF-RTK [VEGF induced by ischaemia & hypoxia; VEGF induces angiogenesis]

Table 8.4 Phosphatidylinositol 3-kinase

Compound (class)	Plant (family)	Target (other targets) / in vivo effects/
Phosphatidylinositol-3-kinase (PI3K)		8.4
Phenolic		8.4p
Emodin (= Archin; Frangula emodin; Frangulic acid; Rheum emodin; 1,3,8-Trihydroxy-6-methyl-9,10-anthraquinone (anthraquinone))	<i>Senna obtusifolia</i> (Fabaceae), <i>Psorospermum glaberrimum</i> (Guttiferae), <i>Myrsine africana</i> (Myrsinaceae), <i>Polygonum cuspidatum</i> , <i>Rumex</i> spp., <i>Rheum palmatum</i> , <i>R.</i> spp. (Polygonaceae), <i>Ventilago calyculata</i> , <i>Rhamnus frangula</i> (Rhamnaceae), lichen; glycosides in <i>Rheum</i> , <i>Polygonum</i> (Polygonaceae), <i>Rhamnus</i> (Rhamnaceae) spp.	PI3K (3) (CDC2, CKI, CKII, CDPK, MLCK, PKA, PKC, p60 ^{src} , RTK p56 ^{lck} TK (DNA, TOPII) [cathartic, cytotoxic]
Hypericin (bianthraquinone)	<i>Hypericum perforatum</i> , <i>H.</i> spp. (Hypericaceae)	PI3K (0.2) (CDPK, EGF-RTK, MLCK, PKA, PKC) [photosensitizing, red pigment]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	PI3K (GST, LOX, PK, RTK) [AI, feeding stimulant]
Terpene		8.4t
Asperuloside (= Asperulin; Rubichloric acid) (iridoid monoterpene lactone)	<i>Daphniphyllum macropodium</i> (Daphniphyllaceae), <i>Plantago major</i> (Plantaginaceae) <i>Asperula odorata</i> , <i>Galium aparine</i> , <i>G. odoratum</i> (Rubiaceae), <i>Escallonia</i> spp. (Saxifragaceae)	PI3K (2) [laxative]
Other		8.4o
Inositol hexaphosphate (cyclheanol hexaphosphate)	Widespread in grain; e.g. <i>Oryza sativa</i> (rice) (Poaceae) [seed]	PI3K
Non-plant reference		8.4n
[5'- <i>p</i> -Fluorosulphonyl-benzoyl-adenosine (= FSBA)] (nucleoside)	Synthetic	Alkylates PI3K ATP-binding site (ATP- & ADP-like alkylating agent)
[Halenaquinone] (polyketide)	Sea sponge	PI3K (3) (EGF-RTK)
[Wortmannin] (indenobenzopyran)	<i>Penicillium wortmanni</i> (fungus)	PI3K [1–10]

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Table 8.5 Phosphoprotein phosphatases

Compound (class)	Plant (family) / part/	Process affected (other targets) / in vivo effects/
Phosphoprotein phosphatase (PP)	Phillip Cohen (UK)	8.5A
Other		8.5Ao
Calmodulin (= CaM) (18 kDa protein)	Universal in eukaryotes & evolutionarily highly conserved	Activates PP2B (calcineurin) (activates CaM-PKs, MLCK & other CaM-dependent enzymes)
Non-plant reference		8.5An
[Vanadate (= VO ₃) (oxidized vanadium)]	Environmental	PP
[Cantharidic acid] (hexahydro-epoxybenzofuranone)	Active component of Cantharides (Spanish fly) from <i>Cantharis vesicatoria</i> (blister beetles) & other insects; reputed aphrosidiac	PP1 & PP2A (53 nM) [extreme irritant, causes priapism, rubefacient, vesicant]
[Cantharidin] (hexahydro-epoxybenzofuranone)	Active component of Cantharides (Spanish fly) from <i>Cantharis vesicatoria</i> (blister beetles) & other insects; reputed aphrosidiac	PP1 & PP2A [extreme irritant, causes priapism, rubefacient, vesicant]
[Microcystins LR & RR] (cyclic heptapeptide)	<i>Microcystis aeruginosa</i> (blue-green alga)	PP1 (at 1 nM), PP2A (at 10 nM), PP2B (at 10 nM) [hepatotoxic, secondary tumour promoter, toxic]
CaM antagonists (various – see Table 7.1)	Various – see Table 7.1	PP2B (Calcineurin, Ca ²⁺ -dependent PP)
[Okadaic acid] (ionophoric polyether)	<i>Prorocentrum concavum</i> (dinoflagellate); contributes to ciguatera poisoning due to consumption of toxin-contaminated fish	PP1, PP2A [hepatotoxic, secondary tumour, promoter toxic]; ~50,000 ciguatera cases reported each year

9 Gene expression, cell division and apoptosis

9.1 Introduction

Cells respond to changing environments by signalling-induced reversible modification of proteins, notably via phosphorylation and dephosphorylation. Such regulatory processes maintain homeostasis as illustrated by the hormonal control of blood glucose, which involves various hormones, hormone receptors, signal transducing proteins, second messenger-regulated protein kinases and phosphoprotein phosphatases (Chapters 5–8). Such processes that regulate metabolism can also involve expression of particular proteins required for special circumstances. Thus, the hormone glucagon signals a “fasting” state. Glucagon elevates levels of the second messenger cAMP, which (via PKA-catalysed phosphorylation of the CRE-binding CREB protein) induces the expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK), which enables synthesis of the requisite glucose from lactate and amino acids. Conversely, the “plenty” hormone insulin initiates signalling pathways resulting in expression of anabolic enzymes such as fatty acid synthase and inhibition of cAMP-induced gene expression.

However, in addition to metabolic homeostasis, cells can also be involved in cell division (multiplication of cells) and differentiation (generation of new types of cells expressing a particular type of protein complement e.g. in haematopoiesis from precursor stem cells). In embryological development, tissue regeneration and tissue re-modelling, new, differentiated cells have to occupy the “space” of superfluous cells that are disposed of through “apoptosis” or programmed cell death. Such apoptosis, division and differentiation processes are described as “developmental processes”. Developmental processes such as cell division and cell differentiation variously require expression of particular proteins at particular times and such “gene expression” is exquisitely regulated.

We have already seen how various plant-derived defensive compounds can interfere with the cell signalling machinery involved in second messenger-mediated or cytosolic hormone receptor-mediated induction of specific gene expression. This chapter is concerned with plant compounds interfering with DNA unwinding, DNA replication, transcription (DNA-dependent RNA synthesis), RNA processing, translation (protein synthesis on ribosomes), pro-protein (protein precursor) processing, protein targeting and protein folding. Plant compounds that interfere with viral (notably HIV-1) replication are also considered in this chapter. While a huge variety of compounds can be cytotoxic or more specifically, induce caspase-mediated apoptosis, some consideration is also given to plant defensive compounds shown to be apoptotic.

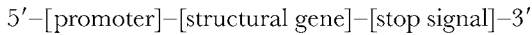
9.2 Regulation of gene expression in prokaryotes

The process of DNA-dependent RNA synthesis (transcription) has been outlined in Chapter 2. RNA polymerase catalyses this reaction in which there is a 5′ to 3′ direction of synthesis

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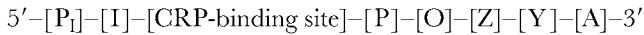
and an RNA copy is made of the coding DNA sense strand. Base-pairing of the incoming nucleotides with the bases of the complementary DNA anti-sense strand means that the DNA strands have to unwind in the process of transcription. In the first step of protein expression the DNA actually being transcribed is that of the gene encoding a protein. However, this structural DNA can be prefaced and followed by non-coding DNA that is involved (together with regulatory proteins) in the regulation of the process.

This regulatory arrangement is most simply illustrated by bacterial transcription in which the structural gene is prefaced by a regulatory region including “promoters” that bind regulatory proteins:



The bacterial RNA polymerase has a subunit composition of $\alpha\beta\beta'\sigma$, the σ subunit being involved in correct initiation of transcription. Appropriate regulatory protein binding to the promoter region permits correct RNA polymerase binding, double-stranded DNA (dsDNA) unwinding and correct initiation of transcription. The dsDNA unwinds and the nascent RNA forms a transient RNA–DNA hybrid in the “transcription bubble” of unwound DNA that moves down the DNA.

The regulation of bacterial transcription is well illustrated by the lactose operon (*lac* operon) of the colon bacterium *Escherichia coli* in which the “upstream” region successively (from the 5' end of the “sense” strand) includes a promoter (P_I) for the gene (I) coding for a repressor protein (the *lac* repressor), a “CRP binding site”, the promoter for the *lac* operon (P), and finally an “operator” site (O) that prefaces the Z, Y and A structural genes of the operon:



The Z, Y and A genes respectively code for a β -galactosidase (that hydrolyses the β -galactoside lactose), a β -galactoside permease (that transports lactose into the bacterium) and a thiogalactoside transacetylase. The *lac* repressor protein binds to the operator (O) and blocks transcription but in the presence of the “esoteric” sugar lactose, an inducer allolactose (derived from lactose) binds to the repressor and prevents *lac* repressor binding. However, a “positive control” mechanism is also involved in transcription regulation: a dimeric cAMP receptor protein (CRP) must bind cAMP in order to bind to the CRP-binding site and permit transcription to occur.

In the absence of lactose, the *lac* repressor binds to the operator (O) and transcription is blocked. In the presence of lactose as the sugar to be oxidized (catabolized), allolactose is formed, the *lac* repressor–alloactose complex does not bind to O and the cAMP–CRP binds to the promoter (P) with resultant transcription to ultimately yield the encoded proteins after mRNA translation on ribosomes. However, in the presence of the “normal” sugar glucose, cAMP levels fall, there is no cAMP–CRP complex and transcription of the *lac* operon does not occur. This so-called “catabolite repression” ensures that the normally expressed (constitutive) enzymes use the available normal sugar source (glucose) when it is available. As in higher organisms, cAMP acts as “hunger signal” and is elevated in the absence of glucose thus permitting cAMP–CRP-dependent expression of “specialized catabolic enzymes” when lactose (and indeed other “esoteric” sugars) are present.

9.3 Regulation of transcription in eukaryotes

Transcription and transcriptional regulation is more complicated in eukaryotes than in prokaryotes. The very much larger amount of DNA in eukaryotes is organized with histones

into the complex nucleosome-based chromatin structure (Chapter 2) and signal-induced modification of this structure is a prerequisite for transcriptional activation. A multiplicity of multi-subunit RNA polymerases (RNAPs) are involved. Thus RNAPI catalyses transcription of ribosomal RNA genes in the nuclear zone called the nucleolus. RNAPIII makes transfer RNA (tRNA), small nuclear RNA (snRNA) and 5S rRNA. Genes encoding proteins are transcribed by RNAPII. Unlike the situation in prokaryotes, the RNA transcript has to be transported to the cytosol for translation on ribosomes to yield the encoded pro-protein (precursor protein). Further, the regulation of transcription is much more complicated and generally involves positive rather than negative control by transcription factors and other regulatory factors.

Transcription requires chromatin modification and indeed transcriptionally active areas are hypersensitive to deoxyribonuclease (DNase) digestion. Acetylation of histones by histone acetyltransferases (HATs), ubiquitination of histones and “chromatin remodelling” by ATP-dependent enzyme complexes (such as the SWI/SNF complex) permit access of RNAPII and associated transcription-regulating proteins to the genes to be transcribed and associated regulatory DNA. The DNA organization successively involves upstream enhancer regions (some –10 kilobases (kb) to –50 kb “upstream”), further control elements (some 200 bases upstream), the so-called TATA box, the initiation region (Inr), the protein-encoding structural gene(s) and then “downstream” enhancer elements (some +10 to +50 kb downstream). This can be summarized thus (the 5′ → 3′ polarity of the “sense” strand being indicated):

$$5' - [\text{enhancer}] \cdots [\text{intervening DNA}] \cdots [\text{further control elements}] - [\text{TATA box}] - [\text{Inr}] - [\text{genes}] - [\text{intervening DNA}] \cdots [\text{downstream enhancer}] - 3'$$

The enhancers (or “upstream activator sequences” in yeast) are activated by DNA-binding transactivators. Intervening DNA is associated with high mobility group (HMG) proteins. Specific regulatory proteins interact with the further control elements to permit transcription. The RNAPII binds to the TATA-box-Inr region and is associated with a TATA box-binding protein (TBD) and a multiplicity of RNAPII “basal transcription factors” (e.g. TFIIA, B, D, E, F and H).

The upstream (and downstream) enhancer elements bind DNA-binding transactivators and can be in close proximity to the other regulatory regions through DNA “looping” and mutual interactions with coactivators (such as TFIID) that link the RNAPII–basal transcription factor complex with the enhancer–transactivator complex. Once DNA unwinding is initiated at the Inr promoter sequence, the RNAPII is phosphorylated (via protein kinases), leaves the promoter region and commences transcription with displacement of transcription factors. Elongation of the RNA is promoted by elongation factors, and when termination sequences are encountered, elongation factors are released, the RNAPII is dephosphorylated (via phosphoprotein phosphatases) and re-initiation occurs.

As indicated in Chapters 5, 7 and 8, transcription can be switched on by a variety of signalling pathways. Thus, cAMP-mediated pathways generate phosphorylated CREB proteins that activate expression of particular proteins by binding to promoters called cAMP response elements (CREs). Similarly, Ca^{2+} -dependent PKC activation results in phosphorylation of transcription factors that bind to and activate tetradecanoylphorbol ester response element (TRE) promoters. In the immune response bacterial lipopolysaccharide (LPS) and particular cytokines can switch on signalling pathways resulting in activation of transcription factors such as NF κ B (Chapter 7) with resultant expression of proteins such as cytokines,

COX-2 and iNOS. Some steroid hormone receptors complexed with their specific hormone ligand act as DNA-binding transactivators to switch on transcription of particular genes. However, in the hormone-free state these proteins can act as repressors and block initiation of transcription of these genes. DNA and associated transcription, translation and replication processes are similar in plants and non-plant eukaryotes. Nevertheless, some plants elaborate DNA binding compounds or compounds that otherwise interfere with gene expression and DNA replication (Tables 9.1–9.4).

9.4 RNA processing and translation

The eukaryote RNA “primary transcript” contains exons (coding for protein) and introns (non-coding sequences between exons). The primary transcript has to be processed by removal of the non-coding introns. Type I introns (found in some nuclear, mitochondrial and chloroplast genes variously encoding rRNA, tRNA and some mRNAs) and type II introns (found in organelle mRNAs of plants, algae and fungi) are self-splicing, that is, the RNA is catalytic in performing this excision and re-ligation. Type III intron splicing requires the participation of snRNA–protein complexes called small nuclear ribonucleoproteins (snRNPs). ATP is required for the assembly of intron and snRNP to form a spliceosome complex but the excision and re-ligation is ATP-independent. Type IV introns are found in certain tRNAs and an endonuclease and ATP are required for cleavage and re-ligation, respectively.

A “cap” involving 7-methylguanosine is added to the 5′-end of the mRNA that may assist ribosomal interactions. A polyadenylate (i.e. (AMP)_n) or “polyA” tail of 80 to 250 residues is added to the 3′-end of the mRNA by a polyadenylate polymerase in a process successively involving transcriptional extension past a conserved (5′)AAUAA sequence and a subsequent cleavage sequence, cleavage of much of this extension and then addition of the “tail”. These final additions increase the longevity of the mRNA through specific protein interactions. Alternative splicing of the primary transcript can yield more than one mRNA for translation from the initial primary transcript. Thus, in the thyroid, a calcitonin gene transcript encoding calcitonin (exon 4) and calcitonin-gene-related peptide (CGRP) (exon 5) are cleaved, polyadenylated at a particular site and processed to yield a processed mRNA, which ultimately yields calcitonin after translation and pro-protein processing. However, in the brain, differential processing of the same primary transcript involving polyadenylation at a “later” site yields a different mRNA, which ultimately yields CGRP after translation and pro-protein processing. Similar differential RNA splicing involving “poly(A) site choice” generates immunoglobulin heavy chain variable domain diversity at the post-transcriptional level.

9.5 Control of translation

Translation can be regulated by phosphorylation. Thus, eukaryote initiation factor 2 (eIF2) is phosphorylated by dsRNA-dependent protein kinase (activated by viral dsRNA as a consequence of viral infection), by hemin-inhibited protein kinase (activated in the absence of hemin in reticulocytes) and by GCN2 (general control non-derepressible) kinase (activated by amino acid starvation and excess free tRNA). Phospho-eIF-2 inhibits the exchange factor eIF-2B that is required to recycle eIF-2-GDP to the eIF-2-GTP form, required for translation. Signalling by the anti-apoptotic, anabolic and growth-promoting hormone insulin results in the phosphorylation of an eIF4E binding protein (eIF4E-BP) that inhibits translation through binding eIF4E. However, the phosphorylated form (P-eIF4E-BP) no longer binds eIF4E and thus translation (and hence cell growth) is stimulated.

9.6 Protein processing and post-translational modification

Proteins are typically made as pro-proteins and are then subsequently modified by “post-translational processing” involving selective proteolysis (“trimming”) and addition of other groups. Thus, nascent polypeptides commence with N-formylmethionine (bacteria) or methionine (eukaryotes). However, N-terminal sequences are often removed in proteolytic processing. In many eukaryote proteins, the final N-terminal amino acid of the processed protein is N-acetylated. The C-terminus may also be changed by peptide cleavage and other covalent modification.

Post-translational modification of amino acid R groups can occur, examples being the hydroxylation of prolines (notably in collagen by a process requiring vitamin C (ascorbate)), methylation of lysines (cytochrome *c*), carboxy group methylation (calmodulin) and phosphorylation (notably in the casein of mammalian milk and in cell signalling cascades). Vitamin K-dependent generation of γ -carboxyglutamate on prothrombin is required for the blood clotting cascade (this process being antagonized by the plant-derived coumarin dicoumarol and related haemorrhagic anticoagulants). Other covalent modifications include: formation of farnesyl thioethers (C_{10} -S-X) and myristoylation (which enable membrane association via the added hydrophobic group); formation of disulfide bonds (S-S links) (notably in ectoproteins that function in the oxidizing extracellular environment); attachment of asparagine (Asn)-linked N-linked oligosaccharides and Ser- or Thr-linked (O-linked) oligosaccharides as in mucous membrane proteoglycans and other glycoproteins (notably outwardly facing membrane proteins and ectoproteins); and addition of prosthetic groups (such as the biotin of acetylCoA carboxylase).

Just as differential splicing can occur at the mRNA level, so differential processing can occur at the pro-protein level. Thus, the glucose-induced insulin secretagogue glucagon-like peptide-1 (GLP-1) is produced in the brain and in intestinal cells by specific proteolysis of the same pro-protein that gives rise (through different processing) to the “fasting” hormone glucagon in α -cells of the pancreas. A further subtlety involves inteins, which are “in-frame” intervening sequences within a gene that at the expressed protein level are excised (with re-ligation) by a self-catalytic protein splicing mechanism to yield the “extein” from the “intein” protein.

9.7 Protein targeting

Proteins are targeted to various locations after synthesis by “signal” sequences. Thus, proteins destined for the ER, the mitochondria and chloroplasts have particular kinds of signal sequences at the N-terminus. ER-targeted proteins enter the ER directly off “rough ER” ribosomes via a “signal recognition particle” (SRP) complex that is linked to an SRP receptor and a ribosome receptor–transmembrane peptide translocation complex associated with the ER membrane. Within, the ER polypeptides are processed and folded and S-S links are formed.

Proteins with a C-terminal KDEL sequence are retained by the ER but other proteins enter the Golgi network (Chapter 2) for glycosylation via transfer of a core oligosaccharide from a polyisoprenoid dolicholphosphate donor catalysed by a transferase. The oligosaccharide moiety on these secretory proteins is appropriately trimmed and the glycoprotein then exported by exocytosis. Integral plasma membrane proteins are anchored into the ER membrane and follow a similar route of glycosylation, trimming and exocytosis to end up on the PM with the oligosaccharide moiety facing outwards. Proteins targeted to the lysosomes (notably hydrolytic enzymes) are phosphorylated in the *cis*-Golgi system to yield mannose-6-phosphate residues that are recognized by a mannose-6-phosphate receptor. Vesicles

containing these receptor-bound complexes bud off into acidic sorting vesicles on the *trans* side of the Golgi complex in which the mannose residues are dephosphorylated by a phosphatase. These vesicles then fuse with lysosomes in a process involving fusion-mediating membrane proteins called v-snares (v for vesicle) and t-snares (t for target membrane) and the mannose-6-phosphate receptor is recycled.

Most mitochondrial proteins are encoded by the nucleus. After synthesis the precursor protein (pro-protein) destined for mitochondrial “import” is kept unfolded by association with the chaperone protein called hsp70. The positively charged N-terminal signal sequence directs the entry of the protein through a general insertion pore spanning both the outer and inner mitochondrial membranes. The respiratory chain-generated mitochondrial transmembrane potential (negative, inside with respect to outside) “drags” the positively charged polypeptide inside. In the mitochondrial matrix the polypeptide is “chaperoned” by a mitochondrial hsp70 and then folded by a mitochondrial cpn10–cpn60 complex with proteolytic cleavage of the signal sequence. Nuclear-targeted proteins are directed through the nuclear pore by a basic nuclear localization signal. A C-terminal Ser-Lys-Leu (SKL) signal marks proteins for peroxisomal import. Plant amino acid analogues such as canaline (a lysine analogue) and canavaine (an arginine analogue) are incorporated into protein and cause protein mis-folding (Table 9.6).

9.8 Cell division and apoptosis

Cell division (mitosis) involves passage of cells through a “cell cycle” having various successive steps, namely G₁ (in which growth occurs until a point is reached at which the cell irreversibly commits to division), an S stage (in which DNA synthesis occurs), G₂, M (in which mitosis occurs) and thence G₁. Progression through the various stages requires activation of cell cycle stage-specific cell division PKs (CDKs) and the synthesis of stage-specific cyclins (substrate-specifying proteins required for CDK activity that are newly synthesized and then destroyed). As outlined in Chapter 8, CDK activation requires the appropriate cyclin and a particular pattern of phosphorylation and dephosphorylation that is determined by a number of signal-regulated protein kinases, phosphatases and other regulatory proteins. The flavone-derived synthetic anti-mitotic flavopiridol is a CDK inhibitor (Table 8.1).

The final mitosis stage involves separation of two sets of chromosomes via microtubules that are filamentous polymers of tubulin monomers. Compounds that interfere with tubulin polymerization such as the plant-derived compounds colchicine, taxol, vinblastine and vincristine are cell division inhibitors (Table 9.6). The cytokinesis of the daughter cells requires equal division of cytoplasm and an actin-myosin-based contractile ring provides the force to make this separation. Accordingly, compounds such as cytochalasin B that interfere with actin will also interfere with cell division (Table 9.6).

Apoptosis or programmed cell death is a highly regulated process required in developmental events such as embryological tissue remodelling and the endometrial changes of the menstrual cycle. The cell complement in particular tissues of metazoans derives from a balance between apoptosis and cell division and an imbalance in favour of cell multiplication is associated with cancer.

Apoptosis in viral-infected cells is induced by cytotoxic T_C cells bound (via both the cell surface T cell receptor and CD8 protein) to the target cell MHC I complex (which presents a virus-derived peptide). This process is assisted by interleukin-2 (IL-2) (acting via the PM IL-2 receptor on T_C cells), the IL-2 having been generated by “helper” T_H cells complexed (via both the cell surface T cell receptor and CD4 protein) to a macrophage MHC II complex

(which presents viral peptides derived from the ingestion of antibody-coated viruses by the macrophage). Antibodies to viruses derive from clones of B cells stimulated to divide by virus particles binding to PM surface antibodies on the B cells. Antibody-coated viruses bind via the Fc portion of the IgGs to IgG Fc receptors on the surface of macrophages and are subsequently ingested (phagocytosed). The Fc portion of a Y-shaped IgG immunoglobulin molecule is the S–S-linked part of the two heavy (H) chains farthest away from the two IgG arms (these involving light chains (L chains) S–S-linked to the heavy chains). The antibody Fc portion is involved in activation of the complement cascade resulting in the lysis of target cells.

Signalling for apoptosis can involve a plasma Fas ligand which binds to the PM Fas receptor with resultant activation of an associated cytosol-side Fas death domain of Fas and activation of caspase 8. Caspase 8 is a thiol protease and once activated initiates a so-called “caspase cascade” leading to activation of further caspases (with consequent proteolysis) and activation of a DNase (leading to DNA destruction with formation of a characteristic “DNA fragment ladder”). Caspase 8 acts on mitochondria with resultant release of cytochrome *c*, which promotes caspase 3 activation by caspase 8 and hence the “caspase cascade”. Another signalling pathway for apoptosis involves tumour necrosis factor (TNF) binding to the TNF receptor with consequent activation of a cytosolic-side TNF receptor-associated death domain (TRADD) and resultant activation of the caspase cascade and cell death.

A large number of plant-derived compounds are apoptotic, having been variously shown to activate caspases, cause membrane blebbing or induce formation of a “ladder” of fragmented DNA. Such compounds are cytotoxic and have potential as anti-neoplastic agents (Table 9.7).

9.9 HIV-1 infection and HIV-1 replication

Because of the continuing impact of HIV-1 on human societies there has been great interest in synthetic and plant-derived compounds that may interfere with infection and replication of the virus. HIV-1 is an RNA retrovirus that targets T_H cells and is integrated into the human genome through the successive action of HIV-1 reverse transcriptase (which generates DNA from the viral RNA template) and HIV-1 integrase (which incorporates this DNA into the host cell genome). HIV-1 RNA translation yields a polypeptide product that must be cleaved specifically by HIV-1 protease to yield separate active proteins. HIV-1 reverse transcriptase, HIV-1 integrase and HIV-1 protease have been targets for potential anti-HIV-1 drugs. HIV-1 protease inhibitors and membrane-permeant nucleoside analogues such as AZT (3'-azido-2',3'-dideoxythymidine) are clinically employed as anti-HIV-1 drugs. AZT 5'-triphosphate inhibits HIV-1 reverse transcriptase by causing chain termination because of the absence of a 3'-hydroxyl. A number of inhibitors of HIV-1 protease (Chapter 13) are used in combination drug therapy against HIV-1 infection. A variety of plant compounds have been found, which inhibit HIV-1 protease (Chapter 13), HIV-1 reverse transcriptase and HIV-1 integrase (Table 9.5).

9.10 Plant compounds interfering with gene expression

The most toxic plant compounds interfering with gene expression are toxic ribosome-inactivating proteins (RIPs) that are introduced into the target cells with the help of an associated lectin (carbohydrate-binding protein). The RIPs are N-glycosidases and remove adenines from ribosomal RNA, thus impairing ribosomal function and blocking protein synthesis (Table 9.1). A number of plant alkaloids are potent and selective inhibitors of eukaryote

protein synthesis including harringtonine, the isoquinolines cephaeline and emetine, the phenanthrene indolizidines tylocrebrine and tylophorine (Section 1, Appendix) and the phenanthroquinolizidine cryptopleurine (Table 9.2). Some plant antifungal proteins of the γ -thionin (defensin) class inhibit protein synthesis (Table 9.2).

A variety of plant compounds bind to DNA and as a consequence variously impair DNA-dependent reactions such as those catalysed by enzymes such as RNA polymerases, DNA polymerases, DNA ligase, DNA helicase and topoisomerases types I and II. Such compounds include the planar, aromatic, polycyclic alkaloids, ellipticine and emetine, and phenolics such as ellagic acid and various anthraquinones. Psoralen and related furanocoumarins bind to DNA and form cross-links in a light-dependent process and are consequently mutagenic and phototoxic (Table 9.3). The quinoline camptothecin is a topoisomerase I inhibitor that has been the lead compound for some related synthetic anti-neoplastic topoisomerase I inhibitors (Table 9.3). Reversible histone acetylation is required for opening up the chromatin to permit gene expression, and inhibition of histone deacetylase interferes with proper control of gene expression. Thus, some fungal histone deacetylase inhibitors are anti-mitotic. Butyric acid (produced from roughage digestion by colonic bacteria) inhibits histone deacetylase and is anti-mitotic and chemopreventive (Table 9.6).

Table 9.1 Ribosome-inactivating polynucleotide aminoglycosidases

<i>Protein name</i> (molecular mass; other properties)	<i>Plant species (family) plant part </i>	<i>In vitro effects in vivo effects </i>
Type I ribosome-inactivating protein (RIP)/ polynucleotide aminoglycosidase (PAG)	Ribosome structure: Masayasu Nomura, Ira Wool, Peter Moore, Thomas Steitz	9.1A
<i>Agrostemma</i> Agrostin (~30kDa)	<i>Agrostemma githago</i> (Caryophyllaceae) [seed]	PAG (apoptotic)
<i>Amaranthus</i> Amaranthin (30kDa; basic)	<i>Amaranthus viridis</i> (Amaranthaceae) [leaf]	PAG (animal rRNA); PSI (25pM) [antiviral (TMV)]
<i>Asparagus</i> Asparin 1 (30kDa; basic)	<i>Asparagus officinalis</i> (Asparagaceae) [seed]	PAG (rRNA); PSI – RRL
<i>Asparagus</i> Asparin 2 (30kDa; basic)	<i>Asparagus officinalis</i> (Asparagaceae) [seed]	PAG (rRNA); PSI – RRL
<i>Basella</i> RIP 1 (~30kDa)	<i>Basella rubra</i> (Basellaceae) [seed]	PAG (<i>E. coli</i> rRNA, polyA, DNA, viral RNA); PSI (~100pM) [toxic (mouse); antiviral (AMCV); PSI]
<i>Basella</i> RIP 2 (~30kDa)	<i>Basella rubra</i> (Basellaceae) [seed]	PAG (<i>E. coli</i> rRNA, polyA, DNA, viral RNA); PSI (~100pM) [toxic (mouse); antiviral (AMCV); PSI]
<i>Beta</i> Betavulgin (~30kDa)	<i>Beta vulgaris</i> (beet) (Chenopodiaceae) [seedling]	PAG (tobacco rRNA)
<i>Bougainvillea</i> RIP (~30kDa)	<i>Bougainvillea spectabilis</i> (Nictaginaceae) [leaf]	PAG (<i>E. coli</i> rRNA, polyA, DNA, viral RNA); PSI (~100pM) [toxic (mouse); antiviral (AMCV); PSI]
<i>Bryonia</i> Bryodin-L (30kDa; basic; glycoprotein)	<i>Bryonia dioica</i> (Cucurbitaceae) [leaf]	PAG (rRNA); PSI – RRL

(continued)

Table 9.1 (Continued)

Protein name (molecular mass; other properties)	Plant species (family) / plant part/	In vitro effects / in vivo effects/
<i>Chenopodium</i> RIP (30 kDa)	<i>Chenopodium amaranticolor</i> (Chenopodiaceae)	PAG (animal, yeast, <i>E. coli</i> & plant rRNA)
<i>Cinnamomum</i> Camphorin (~30 kDa)	<i>Cinnamomum camphora</i> (Lauraceae) [seed]	PAG (RNA), DNA supercoil- dependent endonuclease [selectively cytotoxic]
<i>Citrullus</i> Colocin 1 (30 kDa; basic; glycoprotein)	<i>Citrullus colocynthis</i> (Cucurbitaceae) [seed]	PAG (rRNA); PSI – RRL
<i>Citrullus</i> Colocin 2 (30 kDa; basic; glycoprotein)	<i>Citrullus colocynthis</i> (Cucurbitaceae) [seed]	PAG (rRNA); PSI – RRL
<i>Cucurbita</i> Pepocin (26 kDa; basic; located in sarcocarp & leaf intercellular spaces)	<i>Cucurbita pepo</i> (Cucurbitaceae) [fruit]	PAG (rat, wheat, <i>E. coli</i> 28S rRNA) (at position 4324 of rat 28S rRNA); PSI (RRL) (15 pM)
<i>Dianthus</i> Dianthin 30 (30 kDa)	<i>Dianthus caryophyllus</i> (carnation) (Caryophyllaceae)	PAG (animal, yeast, <i>E. coli</i> & plant rRNA) [PSI (~1 nM)]
<i>Dianthus</i> DAP 30 (30 kDa)	<i>Dianthus caryophyllus</i> (carnation) (Caryophyllaceae) [leaf]	RI (3 nM) [inhibits PS (at 0.3), anti-HIV-1 (1 nM)]
<i>Dianthus</i> DAP 32 (32 kDa)	<i>Dianthus caryophyllus</i> (carnation) (Caryophyllaceae) [leaf]	RI (2 nM) [inhibits DNAs (at 0.3), PS (at 0.3), anti-HIV-1 (1 nM)]
[GAP 31 V5-K42] (~4 kDa)	Synthetic peptide from <i>Gelonium</i> <i>multiflorum</i> GAP 31	RI (at 20) (DNA, RNA, RT) [anti-HIV1 (21–35)]
[[C[GAP 31 V5-K42]] ₂] (~4 kDa; disulfide- linked dimer)	Synthetic peptide from <i>Gelonium</i> <i>multiflorum</i> GAP 31	RI (at 20) (DNA, RNA, RT) [anti-HIV-1 (19–36)]
[GAP 31 K10-K42] (~4 kDa)	Synthetic peptide from <i>Gelonium</i> <i>multiflorum</i> GAP 31	RI (at 20) (DNA, RNA, RT) [anti-HIV-1 (22–36)]
[GAP 31 K10-N33] (~3 kDa)	Synthetic peptide from <i>Gelonium</i> <i>multiflorum</i> GAP 31	RI (at 20) (DNA, RNA, RT) [anti-HIV-1 (700)]
[GAP 31 E23-K42] (~2 kDa)	Synthetic peptide from <i>Gelonium</i> <i>multiflorum</i> GAP 31	RI (at 20)
[GAP 31 Y17-K42] (~3 kDa)	Synthetic peptide from <i>Gelonium</i> <i>multiflorum</i> GAP 31	RI (at 20)
<i>Gelonium</i> Gelonin (30 kDa)	<i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	PAG (rRNA) (mammalian tRNA(Trp) stimulates); DNA GAAL (SS DNA) [relatively non-toxic]
<i>Gelonium</i> GAP 31 (31 kDa)	<i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	RI (4 nM) (HIV-1 INT) [anti-HIV-1 (0.3 nM); not cytotoxic]
<i>Gypsophila</i> Gypsophilin (28 kDa; basic; intercellular & vacuolar localization)	<i>Gypsophila elegans</i> (Caryophyllaceae) [leaf]	PAG (rat 28S rRNA); PSI (RRL)
<i>Hordeum</i> (barley) toxin (RIP) (~30 kDa)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	PAG (rRNA); PSI
<i>Hordeum</i> (barley) jasmonate-induced putative RIP (JIP60) (60 kDa)	<i>Hordeum vulgare</i> (barley) Poaceae [seed]	PAG (tobacco & barley 25S rRNA); PSI

(continued)

Table 9.1 (Continued)

Protein name (molecular mass; other properties)	Plant species (family) / plant part/	In vitro effects / in vivo effects/
<i>Iris</i> IRIP (~30kDa monomer; disulfide linked ~60kDa dimer)	<i>Iris hollandica</i> (Iridaceae) [bulb]	PAG (rRNA)
<i>Luffa</i> Luffin (~30kDa)	<i>Luffa cylindrica</i> (Cucurbitaceae)	PAG (rRNA) (HIV-1 INT)
<i>Lychnis</i> Lychnin (30kDa; basic; glycoprotein)	<i>Lychnis chalconica</i> (Caryophyllaceae) [seed]	PAG (wheat, rat, <i>E. coli</i> rRNA); PSI – RRL
<i>Manihot</i> Mapalmin (30kDa; basic; glycoprotein)	<i>Manihot palmata</i> (Euphorbiaceae) [seed]	PAG (rRNA); PSI – RRL
<i>Mesembryanthemum</i> RIP1 (33kDa [reading frame])	<i>Mesembryanthemum crystallinum</i> (Aizoaceae) [plant]	PAG (rabbit & <i>M. crystallinum</i> rRNA)
<i>Mirabilis</i> MAP, MAP30 (30kDa)	<i>Mirabilis jalapa</i> (Nyctaginaceae)	PAG (RNA, DNA, wheat, <i>M. jalapa</i> , prokaryote & eukaryote 28S-like rRNA); DNA GAAL [antivirus per suicide]
<i>Momordica</i> α - Momorcharin (α -MMC) (30kDa; basic)	<i>Momordica charantia</i> (Cucurbitaceae) [seed]	PAG (rRNA); PSI – RRL
<i>Momordica</i> β - Momorcharin (β -MMC) (29kDa; basic; glycoprotein)	<i>Momordica charantia</i> (Cucurbitaceae) [seed]	PAG (rRNA); PSI – RRL
<i>Momordica</i> γ - Momorcharin (γ -MMC) (11.5kDa; basic)	<i>Momordica charantia</i> (Cucurbitaceae) [seed]	PAG (rRNA); PSI – RRL (55nM)
<i>Momordica</i> Momorcochin-S (30kDa; basic; glycoprotein)	<i>Momordica cochinchinensis</i> (Cucurbitaceae) [seed]	PAG (rRNA); PSI – RRL (HIV-1 INT)
<i>Momordica</i> Momorcochin-S isoform (30kDa; basic; glycoprotein)	<i>Momordica cochinchinensis</i> (Cucurbitaceae) [root]	PAG (rRNA); PSI – RRL
<i>Petrocoptis</i> Petroglauclin 1 (30kDa)	<i>Petrocoptis grandiflora</i> (Caryophyllaceae) [plant]	PSI – RRL (nM); inactive on bacterial PS
<i>Petrocoptis</i> Petroglauclin 2 (30kDa)	<i>Petrocoptis grandiflora</i> (Caryophyllaceae) [plant]	PSI – RRL (nM)
<i>Petrocoptis</i> Petrograndin (30kDa)	<i>Petrocoptis grandiflora</i> (Caryophyllaceae) [plant]	PSI – RRL (nM); inactive on bacterial PS
<i>Phytolacca</i> antiviral protein (PIP) (~30kDa)	<i>Phytolacca insularis</i> (Phytolaccaceae) [leaf]	rPIP: PAG (rRNA), PSI (RRL) [antiviral (potato virus X, potato virus Y & potato leafroll virus)]

(continued)

Table 9.1 (Continued)

Protein name (molecular mass; other properties)	Plant species (family) / plant part/	In vitro effects / in vivo effects/
<i>Phytolacca</i> PAP (pokeweed antiviral protein) (30 kDa; basic)	<i>Phytolacca americana</i> (Phytolaccaceae) [leaf]	PAG (animal, yeast, <i>E. coli</i> & plant rRNA); deguanlylates HIV-1 RNA; PSI (RRL); depurinates & cleaves SS DNA
<i>Phytolacca</i> PAP-R (pokeweed antiviral protein from roots) (30 kDa; basic)	<i>Phytolacca americana</i> (Phytolaccaceae) [root]	PAG (animal, yeast, <i>E. coli</i> & plant rRNA; rat liver rRNA at multiple sites); PSI (RRL); depurinates & cleaves SS DNA
<i>Phytolacca</i> PAP-S (pokeweed antiviral proteins from seed) (30 kDa; basic)	<i>Phytolacca americana</i> (Phytolaccaceae) [seed]	PAG (<i>E. coli</i> rRNA, wheat 25S rRNA)
<i>Phytolacca</i> PAP-S' (pokeweed antiviral proteins from seed) (~30 kDa)	<i>Phytolacca americana</i> (Phytolaccaceae) [seed]	PAG (wheat 25S rRNA)
<i>Phytolacca</i> PD-L1 (33 kDa; basic; glycoprotein)	<i>Phytolacca dioica</i> (Phytolaccaceae) [leaf]	PAG (yeast rRNA); PSI – RRL (pM)
<i>Phytolacca</i> PD-L2 (31.542 kDa; basic; glycoprotein)	<i>Phytolacca dioica</i> (Phytolaccaceae) [leaf]	PAG (yeast rRNA); PSI – RRL (pM)
<i>Phytolacca</i> PD-L3 (30 kDa; basic; glycoprotein)	<i>Phytolacca dioica</i> (Phytolaccaceae) [leaf]	PAG (yeast rRNA); PSI – RRL (pM)
<i>Phytolacca</i> PD-L4 (29 kDa; basic; aglycone of PD-L3)	<i>Phytolacca dioica</i> (Phytolaccaceae) [leaf]	PAG (yeast rRNA); PSI – RRL (pM)
<i>Phytolacca</i> PD-S2 (29 kDa; basic)	<i>Phytolacca dioica</i> (Phytolaccaceae) [root]	PAG (rRNA); PSI – RRL (pM)
<i>Pisum</i> α -Pisavin (20.5 kDa; basic)	<i>Pisum sativum</i> (pea) (Fabaceae) [seed]	PAG (rRNA); PSI – RRL (pM); linearizes circular & supercoiled DNA
<i>Pisum</i> β -Pisavin (18.7 kDa; basic)	<i>Pisum sativum</i> (pea) (Fabaceae) [seed]	PAG (rRNA); PSI – RRL (pM); linearizes circular & supercoiled DNA
<i>Pisum</i> Sativin (basic)	<i>Pisum sativum</i> (pea) (Fabaceae) [seed]	PSI (14) (weak) [related to RIP Pisavin & sweet Miraculin; antifungal]
<i>Sambucus</i> Nigritin fl (24 kDa; basic; constitutive in fruit)	<i>Sambucus nigra</i> (Caprifoliaceae) [fruit]	PSI (RRL; inactive against plant ribosomes)
<i>Sambucus</i> Nigritin f2 (24 kDa; basic; inducible in maturing fruit)	<i>Sambucus nigra</i> (Caprifoliaceae) [fruit]	PSI (RRL; inactive against plant ribosomes)
<i>Saponaria</i> <i>ocymoides</i> RIP (30 kDa; basic)	<i>Saponaria ocymoides</i> (Caryophyllaceae) [seed]	PAG (rRNA); PSI – RRL (pM); rat liver ribosomes (1 nM) [PSI, intact cells, (4 nM – > 3000 nM)]
<i>Saponaria</i> Saporin-L1 (~30 kDa)	<i>Saponaria officinalis</i> (Caryophyllaceae) [leaf]	PAG (rRNA, DNA, polyA)
<i>Saponaria</i> Saporin 6 (~30 kDa)	<i>Saponaria officinalis</i> (Caryophyllaceae) [leaf]	PAG (rRNA); (DNA nuclease or contaminant activity?)
<i>Saponaria</i> Saporin-R1 (~30 kDa; glycoprotein)	<i>Saponaria officinalis</i> (Caryophyllaceae) [root]	PAG (28S rRNA); PSI (RRL, plant > <i>E. coli</i>)

(continued)

Table 9.1 (Continued)

Protein name (molecular mass; other properties)	Plant species (family) / plant part/	In vitro effects / in vivo effects/
<i>Saponaria</i> Saporin-R3 (~30kDa; glycoprotein)	<i>Saponaria officinalis</i> (Caryophyllaceae) [root]	PAG (28S rRNA); PSI (RRL, insect, plant; weak versus <i>E. coli</i>)
<i>Sechium</i> Sechiumin (27kDa)	<i>Sechium edule</i> (Cucurbitaceae) [seed]	PAG (28S rRNA; PSI – RRL (0.7 nM); [PSI, intact HeLa cells (5000nM)])
<i>Spinacia</i> RIP (30kDa)	<i>Spinacia oleracea</i> (Chenopodiaceae)	PAG (animal, yeast, <i>E. coli</i> & plant rRNA)
<i>Trichosanthes</i> Neotrichosanthin (~30kDa)	<i>Trichosanthes kirillowii</i> (Cucurbitaceae) [seed]	PAG (rRNA); PSI
<i>Trichosanthes</i> Trichoanguin (35kDa; basic; glycoprotein; 2 cysteines)	<i>Trichosanthes anguina</i> (Cucurbitaceae) [tuber]	PAG (A4324 site of rat 28S rRNA); PSI – RRL (10 nM) [weak PSI, HeLa cells]
<i>Trichosanthes</i> Trichokirin (~30kDa)	<i>Trichosanthes kirillowii</i> (Cucurbitaceae) [seed]	PAG (rat rRNA at many sites); PSI
<i>Trichosanthes</i> α -Trichosanthin (~30kDa)	<i>Trichosanthes kirillowii</i> (Cucurbitaceae) [seed]	PAG (rat rRNA at many sites); PSI (HIV-1 RT)
<i>Trichosanthes</i> Trichomaglin (25kDa)	<i>Trichosanthes lepiniata</i> (Cucurbitaceae) [tuber]	PAG (rRNA); PSI – RRL (10nM) [abortifacient]
<i>Triticum</i> Tritin-S (~30kDa; requires ATP for action)	<i>Triticum aestivum</i> (Poaceae) [seed]	PAG (A3024 of yeast 26S rRNA); PSI (rabbit, yeast; inactive on wheat, tobacco & <i>E. coli</i> rRNA)
<i>Triticum</i> Tritin-L (~30kDa; does not require ATP for action)	<i>Triticum aestivum</i> (Gramineae) [leaf]	PAG (A3024 of yeast 26S rRNA); PSI (rabbit, yeast, wheat, tobacco & <i>E. coli</i> rRNA)
<i>Vaccaria</i> RIP (28kDa)	<i>Vaccaria pyramidata</i> (Caryophyllaceae) [seed]	PAG (rRNA); PSI – RRL (0.1 nM; rat liver ribosomes (1 nM) [PSI, intact cells (4 nM – > 3000 nM)])
Non-plant reference		9.1An
[Volvarin] (29kDa)	<i>Volvariella volvaceae</i> (Volvariellaceae) – edible mushroom (Basidiomycetae)	PAG (rabbit rRNA); PSI – RRL (0.5 nM); (DNase on supercoiled DNA?) [abortefacient (mouse)]
Type II ribosome- inactivating protein (RIP)/ polynucleotide aminoglycosidase (PAG)		9.1B
<i>Abrus</i> Abrin-a (~60kDa; A[~30kDa PAG]–S–S–B[~30kDa lectin])	<i>Abrus precatorius</i> (Fabaceae); toxic	A: PAG (rat rRNA A4324 in R/S domain; not <i>E. coli</i> ribosomes); B: galactose binding [toxic; PSI]

(continued)

Table 9.1 (Continued)

Protein name (molecular mass; other properties)	Plant species (family) / plant part/	In vitro effects / in vivo effects/
<i>Cinnamomum</i> Cinnamomin (~60 kDa; A[30 kDa PAG]-S-S-B[~30 kDa lectin])	<i>Cinnamomum camphora</i> (Lauraceae) [seed]	A: PAG (RNA, adenine nucleotides except 5'-ATP), DNA supercoil- dependent endonuclease) B: lectin A-B: PSI (14 nM) [toxic (insect larvae)]
<i>Cinnamomum</i> Porrectin (64.5 kDa; A[30.5 kDa PAG]-S-S-B[33.5 kDa glycoprotein lectin])	<i>Cinnamomum porrectum</i> (Lauraceae) [seed]	A: PAG (rat rRNA A4324 in R/S domain); PSI (RRL) [toxic; cytotoxic; PSI]
<i>Phoradendron</i> <i>californicum</i> lectin (PCL) (~60 kDa; A[~30 kDa PAG]-S-S-B[~30 kDa lectin])	<i>Phoradendron californicum</i> (Viscaceae) [plant]	PAG (rat liver 28S rRNA A4324)
<i>Polygonatum</i> RIP monomer (PMRIPm) (~60 kDa; A[~30 kDa PAG]-S-S-B[~30 kDa lectin])	<i>Polygonatum multiflorum</i> (Liliaceae) [leaf]	A: PAG (rRNA) B: Gal/GalNAc-specific lectin [low toxicity for human, animal cells]
<i>Polygonatum</i> RIP tetramer (PMRIPt) (~240 kDa; [A[~30 kDa PAG]-S-S-B[~30 kDa lectin]] ₄ ; ricin-like structure)	<i>Polygonatum multiflorum</i> (Liliaceae) [leaf]	A: PAG (rRNA) B: GalNAc-specific lectin [low toxicity for human, animal cells]
<i>Ricinus</i> Ricin (65 kDa; A[~30 kDa PAG]-S-S-B[~30 kDa glycoprotein lectin])	<i>Ricinus communis</i> (Euphorbiaceae) [seed]; Bulgarian dissident defector Georgi Markov murdered in London, stabbed in thigh by ricin- tipped umbrella (1978)	PAG (rat 28S rRNA A4324 in R/S domain; not <i>E. coli</i> ribosomes); DNA GAAL (ssDNA); PSI; galactose- specific [toxic; cytotoxic, PSI]
<i>Sambucus</i> Ebulin 1 (56 kDa; A[26 kDa PAG]-S-S-B[30 kDa lectin])	<i>Sambucus ebulus</i> (Caprifoliaceae) [leaf]	PAG (rRNA); PSI (RRL, rat brain & liver) [non-toxic (mice, NHC human epithelial cells)]
<i>Sambucus</i> Ebulin r1 (56 kDa; A[26 kDa PAG]-S-S-B[30 kDa lectin])	<i>Sambucus ebulus</i> (Caprifoliaceae) [bark]	PAG (rRNA); PSI (mammalian not plant)
<i>Sambucus</i> Ebulin r2 (56 kDa; A[26 kDa PAG]-S-S-B[30 kDa lectin])	<i>Sambucus ebulus</i> (Caprifoliaceae) [bark]	PAG (rRNA); PSI (mammalian not plant)
<i>Sambucus</i> Nigrin b (58 kDa; A[26 kDa PAG]-S-S-B[32 kDa lectin])	<i>Sambucus nigra</i> (Caprifoliaceae) [leaf]	PAG (rRNA); PSI (mammalian; not plant or bacterial)

(continued)

Table 9.1 (Continued)

Protein name (molecular mass; other properties)	Plant species (family) / plant part/	In vitro effects / in vivo effects/
<i>Sambucus Nigrin</i> 1 (63 kDa; A[26 kDa PAG]-S-S-B[32 kDa inactive lectin])	<i>Sambucus nigra</i> (Caprifoliaceae) [bark]	PAG (rRNA); PSI (RRL; not plant or HeLa cell); no carbohydrate binding activity
<i>Sambucus Sieboldin</i> -b (60 kDa; A[27 kDa PAG]-S-S-B[33 kDa lectin])	<i>Sambucus sieboldiana</i> (Caprifoliaceae) [bark]	PAG (rRNA); PSI (mammalian; not plant or bacterial) [not toxic]
<i>Viscum</i> lectin MLI (pML) (~60 kDa; A[~30 kDa PAG]-S-S-B[~30 kDa lectin])	<i>Viscum album</i> (mistletoe) (Viscaceae)	PAG (rRNA); PSI [cytotoxic]

Table 9.2 Protein synthesis

Compound (class)	Plant (family) / part/	Process inhibited (other targets) / in vivo effects/
Protein synthesis (PS)	Paul Zamecnic, Mahlon Hoagland (ribosomes, aminoacyl-tRNA); Gobind Khorana, Robert Holley & Marshall Nirenberg (genetic code & protein synthesis, Nobel Prize, 1968, medicine)	9.2
Alkaloid		9.2a
Bouvardin (macrocylic)	<i>Bouvardia ternifolia</i> (Rubiaceae)	PS (80S, EF1- & EF2-interacting site) [cytotoxic]
Cephalotaxine (pentacyclic)	<i>Cephalotaxus drupacea</i> , <i>C. harringtonia</i> , <i>C. fortunei</i> , <i>C. wilsoniana</i> , <i>C. spp.</i> (Cephalotaxaceae)	PS (no PS elongation inhibition cf. Homoharringtonine) [antileukaemic, antitumour]
Cephaeline (emetine isoquinoline)	<i>Alangium lamarekii</i> (Alangiaceae), <i>Cephaelis ipecacuanha</i> (ipecaquanha) (Rubiaceae)	PS – ribosomal inhibition [amoebicide, emetic, expectorant]
Cryptopleurine (phenanthro- quinolizidine)	<i>Cryptocarpa pleurosperma</i> (Lauraceae), <i>Boehmeria cylindrica</i> (Urticaceae), <i>Cissus rheifolia</i> (Vitidaceae)	80S PS – 40S subunit site (blocks translocation) (at 10) [antiviral, cytotoxic]
Digoxin (= Digoxigenin 3- <i>O</i> -tridigitoxoside) (cardenolide, steroid triterpene glycoside)	<i>Digitalis lanata</i> , <i>D. orientalis</i> , (Scrophulariaceae)	PS (Na ⁺ , K ⁺ -ATPase) [50 nM] [cardiotonic, cytotoxic (< 0.1), toxic]
Dihydrolycorine (galanthan Amaryllidaceae alkaloid)	<i>Lycoris radiata</i> (Amaryllidaceae)	80S PS – cell-free HeLa PS (~1000), PT (> 1000); yeast 60S ribosomal subunit binding (Narciclasine displacement) (> 1000)

(continued)

Table 9.2 (Continued)

Compound (class)	Plant (family) / part/	Process inhibited (other targets) / in vivo effects/
<i>cis</i> -[1,10b] Dihydronarciclasine (= <i>cis</i> -[1,10b] Dihydrolycoricidinol) (phenanthridine Amaryllidaceae alkaloid)	<i>Hymenocallis littoralis</i> (spider lily) (Amaryllidaceae) [bulb]; cf. <i>trans</i> -[1,10b]Dihydronarciclasine (= <i>trans</i> -[1,10b] Dihydrolycoricidinol)	80S PS – cell-free yeast PS (~1000), PT (~100), 60S ribosomal subunit (Narciclasine displacement) (inactive) [antitumour, insect antifeedant, cytotoxic]
<i>trans</i> -[1,10b] Dihydronarciclasine (= <i>trans</i> -[1,10b] Dihydrolycoricidinol) (phenanthridine Amaryllidaceae alkaloid)	<i>Hymenocallis littoralis</i> (spider lily) (Amaryllidaceae) [bulb]	80S PS – cell-free yeast PS (<100), PT (<1), 60S ribosomal subunit (Narciclasine displacement) (<10)
[<i>trans</i> -[1,10b]Dihydro- narciclasine acetone (= <i>trans</i> -[1,10b]Dihydro- lycoricidinol)] (phenanthridine)	Semi-synthetic from <i>trans</i> - [1,10b]Dihydronarciclasine (= <i>trans</i> -[1,10b] Dihydrolycoricidinol)	80S PS – cell-free yeast PS (<100), PT (1–10), 60S ribosomal subunit (Narciclasine displacement) (<10)
Emetine (= Cephaeline methyl ether) (emetine isoquinoline)	<i>Hedera helix</i> (Araliaceae), <i>Cephaelis</i> (= <i>Uragoga acuminata</i> , <i>C. ipecacuanha</i> (ipecacuanha) (Rubiaceae)	80S PS – 40S subunit site (cf. Cryptopleurine, Tubulosine & Tylocrebrine); rabbit reticulocyte PS (at 1–100) [antiamoebic, anticancer, antiviral, cytotoxic, emetic, expectorant]
Haemanthamine (= 3-Epicrinamine; Haemanthidine; Natalensine) (Amaryllidaceae crinane)	<i>Haemanthus</i> sp. (Amaryllidaceae) [bulb]	80S PS – cell-free HeLa PS (<100), PT (<100); 60S ribosomal subunit binding (Narciclasine displacement) (>1000) [hypotensive]
Harringtonine (cephalotaxine ester)	<i>Cephalotaxus harringtonia</i> , <i>C. fortunei</i> , <i>C. hainensis</i> (Cephalotaxaceae)	PS – 80S ribosomal 60S subunit PT at or near A site (binds at Anisomycin site) [antileukaemic, antitumour]
Homoharringtonine (cephalotaxine ester)	<i>Cephalotaxus drupaceae</i> , <i>C. fortunei</i> , <i>C. harringtonia</i> , <i>C. spp.</i> (Cephalotaxaceae)	PS – 80S ribosomal 60S subunit PT at or near A site (binds at Anisomycin site) [antileukaemic, antitumour, apoptotic, hypotensive, myelosuppressive]
Isoharringtonine (cephalotaxine ester)	<i>Cephalotaxus drupaceae</i> , <i>C. fortunei</i> , <i>C. hainensis</i> , <i>C. harringtonia</i> , <i>C. wilsonia</i> , <i>C. spp.</i> (Cephalotaxaceae)	PS – 80S ribosomal 60S subunit PT at or near A site (binds at Anisomycin site) [antileukaemic, antitumour]
Isonarciclasine (Amaryllidaceae phenanthridine)	cf. Narciclasine (= Lycoricidinol)	80S PS – cell-free yeast PS (<100), PT (1–10), 60S ribosomal subunit binding (Narciclasine displacement) (100–1000)
(–)-Lycorine (= Narcissine; Galanthidine) (Amaryllidaceae galanthan)	<i>Polygonum tuberosum</i> (Agavaceae), <i>Ammodramis coronica</i> , <i>Brunsvigia</i>	80S PS – cell-free HeLa PS (<700), PT (<70); yeast 60S

(continued)

Table 9.2 (Continued)

Compound (class)	Plant (family) / part/	Process inhibited (other targets) / in vivo effects/
	<i>littoralis</i> , <i>Crinum amabile</i> , <i>Lycoris radiata</i> , <i>Narcissus</i> spp. (Amaryllidaceae) [bulb], <i>Hippeastrum vittatum</i> (Liliaceae); also as glycoside, FA ester, acetic acid ester	ribosomal subunit binding (Narciclasine displacement) (~1000) [antiviral, cytotoxic, highly toxic]
2- <i>O</i> -Methylnarciclasine (= <i>O</i> -Methyllycoricidinol) (Amaryllidaceae phenanthridine)	cf. Narciclasine (= Lycoricidinol)	80S PS – cell-free yeast PS (~100), PT (10–100), 60S ribosomal subunit binding (Narciclasine displacement) (> 1000)
Narciclasine (= Lycoricidinol) (Amaryllidaceae phenanthridine)	<i>Haemanthus kalbreyeri</i> , <i>Hymenocallis littoralis</i> (spider lily) [bulb], <i>Lycoris longituba</i> , <i>Narcissus tazetta</i> (Amaryllidaceae)	80S PS – cell-free HeLa PS (< 0.2), PT (< 0.2); cell-free yeast PS (< 100), PT (< 0.1), 60S ribosomal subunit [< 0.1] [antitumour, insect antifeedant, cytotoxic]
Pancreatistatin (Amaryllidaceae alkaloid)	<i>Hymenocallis littoralis</i> (spider lily) [bulb], <i>H.</i> spp., <i>Pancratium littorale</i> , <i>P.</i> spp. (Amaryllidaceae)	80S PS [anticancer, antiviral]
Pretazettine (= Isotazettine) (Amaryllidaceae tazettine)	<i>Leucopum aestivum</i> , <i>Lycoris radiata</i> , <i>Narcissus tazetta</i> , <i>Pancratium biflorum</i> , <i>Zephyranthes carinatus</i> (Amaryllidaceae)	80S PS – cell-free HeLa PS (< 30), PT (< 30); yeast 60S ribosomal subunit binding (Narciclasine displacement) (30–300) [antitumour, antiviral, cytotoxic]
Pseudolycorine (Amaryllidaceae galanthan)	<i>Lycoris radiata</i> , <i>Lycoris squamigera</i> , <i>Narcissus tazetta</i> , <i>Narcissus</i> spp. (Amaryllidaceae, Liliaceae);	80S PS – cell-free HeLa PS (~100), PT (~100); yeast 60S ribosomal subunit binding (Narciclasine displacement) (> 1000) [cytotoxic]
Tubulosine (benzylquinolizidine, isoquinoline)	<i>Pogonopus tubulosus</i> , <i>Psychotria granadensis</i> , <i>Cephaelis ipecacuanha</i> (Rubiaceae)	80S PS – 40S subunit site (cf. Cryptopleurine, Emetine & Tylocrebrine) [amoebicidal, antitumour, toxic]
(–)-Tylocrebrine (phenanthrene indolizidine)	<i>Tylophora crebriflora</i> (Asclepiadaceae)	80S PS – 40S subunit site (cf. Cryptopleurine, Emetine & Tubulosine) [antitumour, toxic, vesicant]
(–)-Tylophorine (phenanthrene indolizidine)	<i>Tylophora asthmatica</i> , <i>Cynanchum vincetoxicum</i> , <i>Pergularia pallida</i> , <i>Vincetoxicum officinale</i> (Asclepiadaceae), <i>Ficus septica</i> (Moraceae)	80S PS – 40S subunit site (cf. Cryptopleurine, Emetine & Tubulosine) [antitumour, toxic, vesicant]
Phenolic		9.2p
Aloe-emodin (= Rhabarberone) (anthraquinone)	<i>Oroxylum indicum</i> (Bignoniaceae), <i>Cassia senna</i> (Fabaceae), <i>Aloe vera</i> , <i>A.</i> spp., <i>Asphodelus microcarpus</i> , <i>Xanthorrhoea australis</i> (Liliaceae), <i>Rheum</i> spp. (Polygonaceae), <i>Tectona grandis</i> (Verbenaceae)	PS – eEF-2 (DNA, TOPII)

(continued)

Table 9.2 (Continued)

Compound (class)	Plant (family) part	Process inhibited (other targets) / in vivo effects
Aloin (= Barbaloin) (anthrone glycoside)	<i>Aloe ferox</i> , <i>A. perryi</i> , <i>A. vera</i> (Liliaceae) [leaf], <i>Frangula alnus</i> , <i>Frangula purshiana</i> (Rhamnaceae)	PS – eEF-2 [purgative]
Caffeic acid (= 3,4-Dihydroxycinnamic acid) (phenylpropanoid)	<i>Artemisia rubripes</i> , <i>Taraxacum officinale</i> , <i>Anthemis nobilis</i> , <i>Achillea millefolium</i> [flower] (Asteraceae), <i>Ipomoea purga</i> (Convolvulaceae), <i>Olea europaea</i> (Oleaceae), <i>Papaver somniferum</i> (Papaveraceae), <i>Coffea arabica</i> , <i>Cinchona cuprea</i> (Rubiaceae), <i>Digitalis purpurea</i> (Scrophulariaceae), <i>Conium maculatum</i> (Umbelliferae)	eEF-2 (5-LOX, 12-LOX) [AI, PAI, 5-LOX & LTB ₄ generation inhibited (weak)]
Polyproanthocyanidin (condensed tannin)	<i>Alhagi kirgisorum</i> (Fabaceae)	PS – eIF-2 [blocks eIF-Met-tRNA-GTP ternary complex formation]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	PS – EF-1 α (AR, cAMP PDE, EGF-RTK, LOX, PK, TK) [allergenic, antibacterial, AI, antiviral]
Terpene		9.2t
Ailanthinone (quassinoid nortriterpene)	<i>Ailanthus altissima</i> , <i>Pierreodendron kerstingii</i> (Simaroubaceae)	80S PS [amoebocidal, antimalarial, antineoplastic]
Brusatol (quassinoid nortriterpene)	<i>Brucea javanica</i> (Simaroubaceae)	80S PS
Bruceantin (quassinoid nortriterpene)	<i>Brucea antidysenterica</i> (Simaroubaceae)	80S PS, 80S PT – yeast PS (10), PT (0.4), 80S ribosome PT centre (Trichodermin displacement) [0.3], polysome PT centre (stabilizes polysomes) [557] [amoebocidal, antileukaemic, cytotoxic]
Digoxin (= Cordioxil; Davoxin; Digacin; Digoxigenin 3-O-tridigitoxoside) (cardenolide)	<i>Digitalis lanata</i> , <i>D. orientalis</i> (Scrophulariaceae)	PS – ribosomal inhibition (Na ⁺ K ⁺ -ATPase) [cardiotonic, toxic]
Genkwadaphnin (diterpene)	<i>Daphne genkwa</i> (Thymelaceae)	PS – PT, chain elongation [antileukaemic, inhibits DNA synthesis]
Tingenone (friedlane triterpene)	<i>Crossopetalum uragoga</i> , <i>Maytenus</i> spp., <i>Schaefferia cuneifolia</i> (Celastraceae)	PS (DNA, DNAs, RNAs)
Yuanhuacine (diterpene)	<i>Daphne genkwa</i> (Thymelaeaceae)	PS – PT, chain elongation [antileukaemic, inhibits DNA synthesis]

(continued)

Table 9.2 (Continued)

Compound (class)	Plant (family) / part	Process inhibited (other targets) / in vivo effects
Other		
<i>Hordeum</i> α-Hordothionin (=α-H) (defensin, α-thionin; 6 kDa; 8 Cys)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	9.2o PS (elongation) – cell-free <i>Artemia</i> (15), rabbit reticulocyte (3)
<i>Hordeum</i> β-Hordothionin (=β-H) (defensin, β-thionin; 6 kDa; 8 Cys)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	PS (elongation) – cell-free <i>Artemia</i> (15), mouse liver (8), rabbit reticulocyte (5)
<i>Hordeum</i> γ-Hordothionin (=γ-H) (defensin, γ-thionin; 6 kDa; 8 Cys)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	PS (elongation) – cell-free <i>Artemia</i> (8), barley (> 76), <i>E. coli</i> (76), mouse liver (8), rabbit reticulocyte (10), rat liver (24), wheat (31)
<i>Hordeum</i> ω-Hordothionin (=ω-H) (defensin, γ-thionin; 6 kDa; 8 Cys)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	PS (elongation) – cell free <i>E. coli</i> (68), rabbit reticulocyte (54), rat liver (32)
<i>Triticum</i> α1-, α2- & β-Purothionin mixture (α- & β-thionins; 5 kDa; 8 Cys)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	PS – cell-free wheat (6), rabbit reticulocyte (7) [baby hamster kidney cell PS inhibition (0.04–0.4)]
RIPs (Type 1: ~30 kDa monomers; Type 2: ~60 kDa S–S-linked RIP-lectin heterodimers)	For RIP details see Table 9.1	PS (ribosomal inactivation)
Non-plant reference		
[3-Acetyldeoxynivalenol] (tricothecane sesquiterpene)	<i>Fusarium</i> spp. (fungus) [on grain] (Deuteromycete)	9.2n PS – 80S ribosomal 60S subunit PT (at 10) [caspase-3 & JNK1 activation (at 10)]
[Anisomycin (= (2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i>)-2-[(4-Methoxyphenyl)methyl]-3,4-pyrrolidinediol-3-acetate)] (aryl pyrrolidine)	<i>Streptomyces griseolus</i> (fungus) (Actinomycete)	PS – non-competitive 80S ribosomal 60S subunit PT, competes with Tricothecin (triggers ribotoxic stress response activating JNK1)
[Diacetylverrucarol] (tricothecane sesquiterpene)	<i>Fusarium</i> sp. (fungus)	PS – 80S ribosomal 60S subunit PT (at 10) [caspase-3 & JNK1 activation (at 10)]
[Diacetoxyscirpenol (= Anguidine)] (tricothecane sesquiterpene)	<i>Fusarium diversisporum</i> , <i>F. sambusinum</i> (fungus)	PS – 80S ribosomal 60S subunit PT (triggers ribotoxic stress response activating JNK1) (at 10) [caspase-3 activation (at 10)]
[Chloramphenicol (= D-threo-N ² (1,1'-dihydroxy-1- <i>p</i> -nitrophenyl-isopropyl)-dichloroacetamide)] (aryl chloroamide)	<i>Streptomyces venezuelae</i> (soil fungus) (Actinomycete)	70S PS (inhibits elongation, the amide moiety competing with the PT complex as a peptide analogue) [antibacterial]
[Cycloheximide] (alicyclic piperidinedione)	<i>Streptomyces griseus</i> (fungus) (Actinomycete)	80S PS (inhibits PT) [apoptotic, fungicide]

(continued)

Table 9.2 (Continued)

Compound (class)	Plant (family) part	Process inhibited (other targets) / in vivo effects
[Erythromycin] (alicyclic glycoside)	<i>Streptomyces erythreus</i> (soil fungus) (Actinomycete)	Binds to 70S ribosomal 50S subunit 23S rRNA & inhibits translocation of the peptidyl tRNA from the A site to the P site [antibacterial]
[Gougerotin (= 1-[4-Deoxy-4-(sarcosyl-D-seryl)amino-β-D-glucopyranuramide]cytosine)] (pyrimidine glycoside)	<i>Streptomyces gougerotii</i> (fungus) (Actinomycete)	70S & 80S PS – ribosomal large subunit (polypeptide elongation) [antibacterial, antineoplastic]
[Griseoviridin]	<i>Streptomyces albolongus</i>	70S & 80S PS – inhibits PT [antibacterial]
[HT-2 toxin] (tricothecane sesquiterpene)	<i>Fusarium</i> spp. (fungus) [on grain] (Deuteromycete)	PS – 80S ribosomal 60S subunit PT (triggers ribotoxic stress response activating JNK1) (at 10) [caspase-3 activation (at 10)]
[Nivalenol] (tricothecane sesquiterpene)	<i>Fusarium nivale</i> , <i>F.</i> spp. (fungus) [on grain] (Deuteromycete)	PS – 80S ribosomal 60S subunit PT (~10) (triggers ribotoxic stress response activating JNK1) (at 10) [caspase-3 activation (at 10); apoptotic, cytotoxic]
[Oxytetracycline] (naphthacene carboxamide); structure determined (1952) by R. B. Woodward (USA, chemist; Nobel Prize, 1965)	<i>Streptomyces</i> spp. (fungus) (Actinomycete)	PS (inhibits aminoacyl tRNA binding to ribosome) [antibacterial]
[Puromycin] (adenosine amide derivative)	<i>Streptomyces alboniger</i> (fungus) (Actinomycete); enters A site as aminoacyl tRNA mimetic & PT catalyses transfer to growing chain → chain termination & release	PS – chain termination [anti-neoplastic, antiprotozoal]
[Roridin A] (trichothecane sesquiterpene)	<i>Myrothecium roridum</i> (fungus)	PS – 80S ribosomal 60S subunit PT [antifungal, apoptotic, cytotoxic, emetic, toxic]
[Satratoxin F] (trichothecane sesquiterpene)	<i>Stachybotrys</i> sp. (fungus)	PS – 80S ribosomal 60S subunit PT [apoptotic, cytotoxic, toxic]
[Satratoxin G] (trichothecane sesquiterpene)	<i>Stachybotrys</i> sp. (fungus)	PS – 80S ribosomal 60S subunit PT [apoptotic, cytotoxic, toxic]
[Scirpentriol] (trichothecane sesquiterpene)	<i>Fusarium</i> spp. (fungus) [on grain] (Deuteromycete)	PS – 80S ribosomal 60S subunit PT (at 10) [caspase-3 & JNK1 activation (at 10)]
[(-)-Sparsomycin] (pyrimidine amide sulphinyl)	<i>Streptomyces sparsogenes</i> (fungus) (Actinomycete)	PS [antibiotic, antitumour]
[Streptomycin] (aminoiminomethylaminoglycoside)	<i>Streptomyces griseus</i> (fungus) (Actinomycete)	Impairs proper aminoacyl tRNA anticodon–codon pairing → misreading → aberrant product [antibacterial]
[Tetracycline] (naphthacene carboxamide)	<i>Streptomyces</i> spp. (fungus) (Actinomycete)	PS (inhibits aminoacyl tRNA binding to ribosome) [antibacterial]

(continued)

Table 9.2 (Continued)

Compound (class)	Plant (family) part	Process inhibited (other targets) in vivo effects
[T-2 Toxin (= Fusariotoxin T-2; Insariotoxin; Mycotoxin T-2)] (tricothecane sesquiterpene)	<i>Fusarium tricinctum</i> (fungus) (Deuteromycete) [on cereal grain]	PS – 80S ribosomal 60S subunit PT (at 10) [caspase-3 activation (at 10); apoptotic, cytotoxic]
[Trichodermin] (sesquiterpene)	<i>Myrothecium roridum</i> , <i>Trichoderma viride</i> (fungi) (Deuteromycetes)	80S PS, 80S PT [1], yeast ribosome binding [0.7–2nM]
[Trichothecin] (tricothecane sesquiterpene)	<i>Trichothecium roseum</i> (fungus) (Deuteromycete)	PS, 80S ribosomal 60S subunit PT (triggers ribotoxic stress response activating JNK1) [antibacterial, mycotoxin, toxic]
[Verrucaric acid] (tricothecane sesquiterpene)	<i>Myrothecium verrucaria</i> , (fungus) (Deuteromycete)	PS – 80S ribosomal 60S subunit PT (at 10) [caspase-3 activation (at 10); apoptotic, cytotoxic]
[Vomitoxin (= 4-Deoxynivalenol)] (sesquiterpene)	<i>Fusarium graminearum</i> , <i>F. roseum</i> (fungus) [on grain] (Deuteromycete)	PS – 80S ribosomal 60S subunit PT [3] [apoptotic, cytotoxic, emetic]

Table 9.3 DNA-dependent RNA and DNA synthesis and topoisomerases

Compound (class)	Plant (family) part	Enzyme inhibited/macromolecular target (other targets) in vivo effects
DNA, RNA & DNA-dependent DNA synthesis (DNAS) & RNA synthesis (RNAS) Lord Todd (UK, Nobel Prize, Chemistry, 1957, nucleotides); Francis Crick (UK), Maurice Wilkins (UK) & James Watson (USA) (Nobel Prize, Medicine, 1962, DNA double helix)	Severo Ochoa (Spain/USA) (polynucleotide phosphorylase) & Arthur Kornberg (USA) (DNA polymerase) (Nobel Prize, Medicine, 1959); Paul Berg (USA, recombinant DNA), Walter Gilbert (USA, DNA sequencing) & Fred Sanger (UK, RNA sequencing) (Nobel Prize, Chemistry, 1980); Kary Mullis (USA, PCR) & M. Smith (site-directed mutagenesis) (Nobel Prize, Chemistry, 1993)	9.3A Gobind Khorana (India/USA), Robert Holley (USA) & Marshall Nirenberg (USA) (Nobel Prize, Medicine, 1968, genetic code & protein synthesis); Sidney Altman & Thomas Cech (USA, Nobel Prize, Chemistry, 1989, catalytic RNA)
Alkaloid Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> sp. (Annonaceae), <i>Berberis vulgaris</i> , <i>B. sp.</i> , <i>Hydrastis canadensis</i> , <i>Mahonia</i> sp., <i>Nandina</i> sp. (Berberidaceae), <i>Archangelica</i> sp. (Menispermaceae), <i>Argemone</i> sp., <i>Chelidonium</i> sp., <i>Corydalis</i> sp. (Papaveraceae), <i>Coptis chinensis</i> , <i>C. japonica</i> , <i>Thalictrum</i> sp. (Ranunculaceae), <i>Evodia</i> sp., <i>Toddalia</i> sp., <i>Zanthoxylum</i> sp. (Rutaceae)	9.3Aa DNA ligand (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA, 5HT ₂ -R, mACh-R, nACh-R, MLCK, PKA, PKC, RT) [antibacterial, antimalarial, anti-pyretic, bitter stomachic, cytotoxic]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) part/	Enzyme inhibited / macromolecular target (other targets) / in vivo effects/
[Berberrubine] (protoberberine isoquinoline)	Generated during herbal medicinal processing of <i>Coptis chinensis</i> (goldthread) (Ranunculaceae)	DNA (intercalation) (TOPII)
Cephaeline (emetine isoquinoline)	<i>Alangium lamarekii</i> (Alangiaceae), <i>Cephaelis ipecacuanha</i> (Rubiaceae) [root]	DNA [antiamoebic, emetic, expectorant]
Cryptolepine (pyridoindole)	<i>Cryptolepis sanguinolenta</i> , <i>C. triangularis</i> (Asclepiadaceae)	DNA (intercalation) (TOPII) [hypotensive]
Dicentrine (aporphine isoquinoline)	<i>Hordeum vulgare</i> (barley) (Poaceae)	DNA (unwinds) (TOPII)
Ellipticine (indole)	<i>Aspidosperma williansii</i> , <i>A. subincarnum</i> , <i>Bleekeria vitiensis</i> , <i>Ochrosia elliptica</i> (Apocynaceae)	DNA (intercalation), DNAS, RNAS (AChE, DNAH, TOPII) [antitrypanosomal, antitumour]
Emetine (= Cephaeline methyl ether) (emetine isoquinoline)	<i>Hedera helix</i> (Araliaceae), <i>Cephaelis ipecacuanha</i> , <i>C. acuminata</i> (Rubiaceae)	DNA, PS [antiamoebic, anticancer, antiviral, cytotoxic, emetic, expectorant]
Matadine (pyridoindole)	<i>Strychnos gossweileri</i> (Loganiaceae)	DNA (intercalation) (TOPII)
Neocryptolepine (indole)	<i>Cryptolepis sanguinolenta</i> (Asclepiadaceae)	DNA (intercalation) (TOPII)
Palmatine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Jateorrhiza palmata</i> (Menispermaceae), <i>Berberis</i> spp., <i>Mahonia</i> spp. (Berberidaceae), Papaveraceae	DNA ligand (α 1A-R, α 2A-R, AChE, ATPase, BChE, ChAT, diamine oxidase, 5HT2-R, mACh-R, nACh-R, PK, TOPI) [antibacterial, AI]
Pithecolobine (macrocylic, peptide, polyamine)	<i>Pithecolobium saman</i> (Fabaceae)	DNA, DNAS & RNAS
Sanguinarine (=Pseudochelerythrine) (benzophenanthridine)	<i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> , <i>Sanguinaria canadensis</i> (Papaveraceae), <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	DNA ligand (intercalation) (α 1A-R, α 2A-R, AChE, ATPase, BChE, ChAT, diamine oxidase DNAL, 5HT2-R, mACh-R, nACh-R, PK, RT) [antibacterial, AI]
Serpentine (pyridoindole)	<i>Catharanthus roseus</i> , <i>Rauwolfia serpentina</i> , <i>R. tetraphylla</i> (Apocynaceae)	DNA (intercalation) (nAChR, TOPII) [antihypertensive, antitumour]
Strychnopentamine	<i>Strychnos usambarensis</i> (Loganiaceae) [root]	DNA (intercalation), RNA synthesis [antiplasmodial, cytotoxic]
Tubulosine (indole)	<i>Cephaelis ipecacuanha</i> , <i>Pogonopus tubulosus</i> , <i>Psychotria granadensis</i> (Rubiaceae)	[amoebicidal, antitumour, cytotoxic, very toxic]
Usambarensine (indole)	<i>Strychnos usambarensis</i> (Loganiaceae) [root]	DNA (intercalation) (mAChR, nAChR, RNA synthesis) [antiamoebic, anticancer, antiplasmodial, poison, apoptotic, toxic]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited/macromolecular target (other targets) in vivo effects
Phenolic		9.3Ap
Aloe-emodin (= 1,8-Dihydroxy-3-(hydroxymethyl)-9,10-anthracenedione; Rhabarberone) (anthraquinone)	<i>Oroxylum indicum</i> [leaf] (Bignoniaceae), <i>Cassia senna</i> (Fabaceae), <i>Aloe vera</i> , <i>A. spp.</i> , <i>Asphodelus microcarpus</i> [tuber], <i>Xanthorrhoea australis</i> [flower] (Liliaceae), <i>Rheum</i> spp. (Polygonaceae), <i>Tectona grandis</i> [teak wood] (Verbenaceae)	DNA (cEF-2, TOPII)
Angelicin (= Isopsoralen) (furanocoumarin)	<i>Angelica archangelica</i> [root], <i>Heracleum</i> spp., <i>Pastinaca sativa</i> , <i>Selinum vaginatum</i> (Apiaceae), <i>Psoralea coryfolia</i> (Fabaceae), <i>Castanopsis indica</i> (Fagaceae), <i>Ficus nitida</i> (Moraceae)	DNA (intercalation) (photosensitive yielding monoadduct) [photosensitizing, spasmolytic]
Chrysazin (= Dantron; Danthron; 1,8-Dihydroxy-9,10-anthracenedione) (anthraquinone)	<i>Rheum palmatum</i> (Polygonaceae) [root], <i>Cinchona ledgeriana</i> (Rubiaceae), <i>Xyris semifusca</i> (Xyridaceae) [leaf, stem]	DNA (CDPK, MLCK, PKA, PKC, TOPII) [cathartic, genotoxic, immunosuppressive, mutagenic, purgative]
Ellagic acid (= Benzoic acid; Lagistase) (phenolic acid lactone)	Widespread; hydrolysis product of ellagitannins e.g. Sanguin H-6; <i>Fragaria</i> spp. (strawberry) (Rosaceae)	DNA (intercalation) (TOPI, TOPII) [anticarcinogen, haemostatic]
Emodin (= Archin; Frangula emodin; Frangulic acid; Rheum emodin; 1,3,8-Trihydroxy-6-methyl-9,10-anthracenedione) (anthraquinone)	<i>Senna obtusifolia</i> (Fabaceae), <i>Polygonum cuspidatum</i> (Polygonaceae), <i>Rumex</i> spp., <i>Rheum palmatum</i> , <i>R. spp.</i> (Polygonaceae), <i>Ventilago calyculata</i> , <i>Rhamnus frangula</i> (Rhamnaceae), <i>Myrsine africana</i> (Myrsinaceae), <i>Psorospermum glaberrimum</i> (Guttiferae), lichen; glycosides in <i>Rheum moorcroftianum</i> , <i>Polygonum cuspidatum</i> (Polygonaceae), <i>Rhamnus cathartica</i> , <i>R. frangula</i> , <i>R. purshiana</i> (Rhamnaceae)	DNA (CDC2, CKI, CKII, CDPK, MLCK, PKA, PKC, p60src TK, RTK p56 ^{lck} , TOPII) [cathartic, cytotoxic, genotoxic, mutagenic]
5-Methoxypsoralen (= Bergapten; Bergaptene; Heraclin; Majudin) (furanocoumarin)	<i>Ficus carica</i> (Moraceae), <i>Citrus bergamia</i> , <i>Fagara</i> spp., <i>Ruta graveolens</i> (Rutaceae), <i>Lycopersicon esculentum</i> (Solanaceae), <i>Ammi</i> sp., <i>Levisticum</i> sp., <i>Angelica</i> sp., <i>Petroselinum</i> sp., <i>Pimpinella</i> sp., <i>Seseli</i> sp. (Umbelliferae)	DNA (intercalation) (photosensitive yielding cross-links) [dermatitic, mutagenic, phototoxic, PUVA therapy for leucoderma & psoriasis]
8-Methoxypsoralen (= Ammoidin, Methoxsalen; Xanthotoxin) (furanocoumarin)	<i>Fagara</i> spp., <i>Ruta graveolens</i> (Rutaceae), <i>Ammi majus</i> , <i>Levisticum</i> sp., <i>Angelica archangelica</i> , <i>A. officinalis</i> , <i>Apium graveolens</i> [phytoalexin], <i>Heracleum Pastinaca sphondylium</i> , <i>sativa</i> (Apiaceae)	DNA (intercalation) (photosensitive yielding cross-links) [dermatitic, mutagenic, phototoxic, PUVA therapy for leukoderma & psoriasis]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited / macromolecular target (other targets) / in vivo effects/
2-Methyl-1,4-naphthoquinone (naphthoquinone)	<i>Juglans regia</i> (walnut)	DNA (intercalation) (Juglandaceae)
Plumbagin (= 5-Hydroxy-2-methyl-1,4-naphthoquinone) (naphthoquinone)	<i>Dionaea muscipula</i> , <i>Drosera rotundifolia</i> , <i>D.</i> spp. (Droseraceae), <i>Diospyros</i> spp. (Ebenaceae), <i>Pera ferruginea</i> (Euphorbiaceae) [bark], <i>Aristea</i> spp., <i>Sisyrychium</i> spp., <i>Sparaxis</i> spp. (Iridaceae), <i>Plumbago europaea</i> (Plumbaginaceae)	DNA (intercalation) (DNA, MLCK, PKA, TOPI, TOPII) [anticancer, molluscicidal]
Psoralen (= Ficusin) (furanocoumarin)	<i>Pastinaca sativa</i> , <i>Petroselinum crispum</i> (Apiaceae), <i>Coronilla glauca</i> , <i>Psoralea</i> spp. (Fabaceae) [seed], <i>Ficus carica</i> (Moraceae), <i>Phebalium argenteum</i> [oil], <i>Xanthoxylum flavum</i> [wood] (Rutaceae)	DNA (intercalation) (photosensitive yielding cross-links) [antimycobacterial, photosensitizing]
Psorospermin (xanthone)	<i>Psorospermum</i> spp. (Guttiferae) [root]	DNA (intercalation) (TOPII) [antileukaemic, antitumour]
Swertifrancheside (= 1,5,8-Trihydroxy-3-methoxy-7-(5',7',3'',4''-tetrahydroxy-6'-C- β -D-glucopyranosyl-4'-oxy-8'-flavyl)-xanthone) Flavone-xanthone C-glycoside)	<i>Swertia franchetiana</i> (Gentianaceae)	DNA (RT)
4,5',8-Trimethylpsoralen (= TMP; Trioxsale; Trioxalen) HMT] (furanocoumarin)	<i>Apium graveolens</i> (celery) (Apiaceae) [fungal infection-induced phytoalexin]	DNA (intercalation) (photosensitive yielding cross-links) [dermatitic]
Terpene		9.3At
Tingenone (friedelane triterpene)	<i>Crossopetalum uragoga</i> , <i>Maytenus</i> spp., <i>Schaefferia cuneifolia</i> (Celastraceae)	DNA, DNAs, RNAs, PS
Other		9.3Ao
GAP 31 (polypeptide)	<i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (a RIP) [anti-HIV-1 (0.3 nM), antitumour]
GAP 31 K10-K42) (polypeptide)	Synthetic peptide based on GAP 31 (RIP) from <i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (RI; potent protein precipitant) [anti-HIV-1 (22–36)]
GAP 31 K10-N33 (polypeptide)	Synthetic peptide based on GAP 31 (RIP) from <i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (weak) (RI) [anti-HIV-1 (700)]
GAP 31 V5-K42 (polypeptide)	Synthetic peptide based on GAP 31 (RIP) from <i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (RI) [anti-HIV-1 (21–35)]
(C[GAP 31 V5-K42]) ₂ (disulfide-linked dimer) (polypeptide)	Synthetic peptide based on GAP 31 (RIP) from <i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (RI) [anti-HIV-1 (19–36)]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited / macromolecular target (other targets) / in vivo effects
Mimosine (= Leucaenol) (pyridinone amino acid)	<i>Leucaena leucocephala</i> (jumbie bean), <i>Mimosa pudica</i> (Fabaceae) [leaf, seed]	DNA – binding & breakage by Mimosine – (Fe(II) (FR formation) [depilatory, goitrogenic, teratogenic]
Non-plant reference		
[Actinomycin C1] (cyclic peptide)	<i>Streptomyces chrysomallus</i> (fungus) (Actinomycete)	9.3An DNA (intercalation), DNAS, RNAS (DNAH) [antineoplastic]
[Actinomycin D] (cyclic peptide)	<i>Streptomyces chrysomallus</i> (fungus) (Actinomycete)	DNA (intercalation), DNAS, RNAS (TOPII) [antineoplastic, apoptotic]
[α -Amanitin] (0.9 kDa cyclic peptide)	<i>Amanita bisporigera</i> , <i>A. phalloides</i> (death cap mushroom), <i>A. ocreata</i> , <i>A. verna</i> , <i>A. virosa</i> (destroying angel mushroom) (Agaricaceae)	Eukaryote RNAPOL II, III (not RNAPOL I, bacterial RNAPOL (PS) [toxic; major toxin of <i>Amanita</i>]
[β -Amanitin] (0.9 kDa cyclic peptide)	<i>Amanita phalloides</i> (death cap mushroom) (Agaricaceae)	Eukaryote RNAPOL II, III (not RNAPOL I, bacterial RNAPOL (PS) [toxic; major toxin of <i>Amanita</i>]
[Amsacrine (= 4'-(9-Acridinylamino)methanesulfon- <i>m</i> -anisidine; m-AMSA) (arylsulfonamide aminoacridine)]	Synthetic	DNA (intercalation), DNAS, RNAS (TOPII) [anti-neoplastic, antiviral, cytostatic, cytotoxic, immunosuppressive]
[Coralyne] (protoberberine alkaloid)	Synthetic	DNA (TOPI) [antileukaemic, cytotoxic]
[Daunomycin (= Daunorubicin; Daunomycinone daunosamine)] (anthracycline)	<i>Streptomyces peucetius</i> (fungus) (Actinomycete) cf. Doxorubicin	DNA (major groove intercalation), DNAS, RNAS (DNAH, TOPII) [anti-neoplastic, cytotoxic]
[Doxorubicin (= Adriamycin; Adriamycinone daunosamine)] (anthracycline)	<i>Streptomyces peucetius</i> (fungus) (Actinomycete) cf. Daunomycin	DNA (intercalation) (TOPII) [anti-neoplastic, cytotoxic]
[Ethidium bromide (= 2,7-Diamino-10-ethyl-9-phenylphenanthridinium bromide)] (phenanthridinium)	Synthetic	DNA, DNAS, RNAS (intercalation) (DNAH, RT)
[Heliquinomycin] (glycosylated rubromycin)	<i>Streptomyces</i> sp. (fungus) (Actinomycete)	DNAS, RNAS (DNAH (TOPI, TOPII)
[4'-Hydroxymethyl-4,5',8-trimethylpsoralen = HMT] (furanocoumarin)	Semi-synthetic cf. 4,5',8-Trimethylpsoralen	DNA (intercalation), RNA (intercalation) (photosensitive yielding cross-links)
[Mitoxantrone] [anthraquinone]	Synthetic anthraquinone (cf. Emodin)	DNA (intercalation), DNAS, RNAS (MLCK, PKA, PKC) [antineoplastic]
[Netropsin] (guanidinoacetamido pyrrole)	<i>Streptomyces netropsis</i> (fungus) (Actinomycete)	DNA (non-intercalative)

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited / macromolecular target (other targets) / in vivo effects/
[Nogalamycin] (glycosylated anthraquinone)	<i>Streptomyces nogalater</i> (fungus) (Actinomycete)	DNA (intercalation), RNAS (DNAH)
[Quinacrine = Mepacrine] (aminoacridine)	Synthetic	DNA ligand [anthelmintic, antimalarial, teniacide]
DNA helicase (DNAH)		9.3B
Alkaloid		9.3Ba
Ellipticine (indole)	<i>Aspidosperma williamsii</i> , <i>A. subincarnum</i> , <i>Bleekeria vitiensis</i> , <i>Ochrosia elliptica</i> (Apocynaceae)	DNAH (<i>E. coli</i>) (AChE, DNA, DNAS, RNAS, TOPII) [antitrypanosomal, antitumour]
Non-plant reference		9.3Bn
[Actinomycin C1] (cyclic peptide)	<i>Streptomyces chrysomallus</i> (fungus) (Actinomycete)	DNAH (pea chloroplast [3], human DNAH II) (DNA, DNAS, RNAS) [anti-neoplastic]
[Daunomycin (=Daunorubicin; Daunomycinone daunosamine)] (anthracycline)	<i>Streptomyces peucetius</i> (fungus) (Actinomycete) cf. Doxorubicin	DNAH (pea chloroplast [1], <i>E. coli</i> DNAH II, human DNAH II) (DNA, DNAS, RNAS, TOPII) [anti-neoplastic, cytotoxic]
[Ethidium bromide (= 2,7-Diamino-10-ethyl-9-phenyl-phenanthridinium bromide)] (phenanthridinium)	Synthetic	DNAH (pea chloroplast [3], <i>E. coli</i> DNAH II, human DNAH II) (DNA, DNAS, RNAS)
[Heliquinomycin] (glycosylated rubromycin)	<i>Streptomyces</i> sp. (fungus) (Actinomycete)	DNAH (human [7]) (DNAS, TOPI, TOPII, RNAS)
[Nogalamycin] (glycosylated anthraquinone)	<i>Streptomyces nogalater</i> (fungus) (Actinomycete)	DNAH (pea chloroplast [1], <i>E. coli</i> DNAH I, II & IV, human DNAH) (DNA, RNAS)
DNA ligase (DNAL)	Key DNA ligating enzyme in DNA replication & molecular biology – Paul Berg (USA, Nobel Prize, Chemistry, 1980, recombinant DNA)	9.3C
Alkaloid		9.3Ca
Chelerythrine (benzophenanthridine)	<i>Argemone mexicana</i> , <i>Bocconia</i> spp., <i>Chelidonium majus</i> [root], <i>Eschscholtzia californica</i> [cell culture] (Papaveraceae)	DNAL (226) (CAMPK, GABAA-R, PKA, PKC, TPK, V-R)
Fagaronine (benzophenanthridine)	<i>Zanthoxylum zanthoxyloides</i> (<i>Fagara xanthoxylum</i>) (Rutaceae)	DNAL – DNAL I [27] (RT) [antibacterial, antitumour]
Nitidine (benzophenanthridine)	<i>Zanthoxylum americanum</i> , <i>Z.</i> spp. (Rutaceae)	DNAL (69)
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> , <i>Sanguinaria canadensis</i> , (Papaveraceae), <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	DNAL (322) (α 1A-R, α 2A-R, AChE, ATPase, BchE, CDPK, ChAT, diamine oxidase, DNAL, 5HT2-R, mACh-R, nACh-R, MLCK, PKA, PKC, RT) [antibacterial, AI]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited / macromolecular target (other targets) / in vivo effects
Phenolic		
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Morus alba</i> (mulberry), <i>M.</i> spp., <i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> , <i>Chlorophora tinctoria</i> (Moraceae)	9.3Cp DNAL (236) (AR, CDPK, DNAL, 5-LOX, ITDI, MLCK, PKA) [antibacterial, antiviral, allergenic, silkworm feeding attractant]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Haplophappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Azadirachta indica</i> , <i>Soymidia febrifuga</i> (Meliaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	DNAL (91) (wheat) (30), (hen) (6), PKA (rat) (1) (CDPK, DNAL, F ₁ -ATPase, IKK, iNOS, MLCK, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, 5αR, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic]
Swertifrancheside (flavanoxanthone glucoside)	<i>Swertia franchetiana</i> (Gentianaceae)	DNAL – DNAL I (11) (HIV-1 RT)
Terpene		
Aleuritic acid (triterpene)	<i>Maprounea africana</i> (Euphorbiaceae) [root]	9.3Ct DNAL – DNAL I (205)
Fulvoplumierin (iridoid monoterpene)	<i>Plumeria rubra</i> (frangipani) (Apocynaceae)	DNAL – DNAL I (357)
Oleanolic acid (oleanane triterpene)	<i>Luffa cylindrica</i> (sponge gourd); (Cucurbitaceae), <i>Lavandula latifolia</i> , <i>Rosmarinus officinalis</i> , <i>Thymus vulgaris</i> , <i>Salvia triloba</i> , (Lamiaceae), <i>Syzygium aromaticum</i> (Myrtaceae); 3- <i>O</i> -glucuronide in <i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae)	DNAL – DNAL I (216) (C3-convertase, CDPK, DNAP, ELA, PKA, PKC) [AI]
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (ursane triterpene)	Widespread; <i>Vaccinium macrocarpon</i> (cranberry), <i>Arctostaphylos uva-ursi</i> (bearberry) (Ericaceae), <i>Lavandula latifolia</i> , <i>Prunella vulgaris</i> , <i>Rosmarinus officinalis</i> , <i>Salvia triloba</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Malus</i> sp. (apple), <i>Pyrus</i> sp. (pear) (Rosaceae) [fruit surface]	DNAL (216) CDPK, DNAP, ELA, HIV-1 PR, PKA, PKC, RT, TOPI, TOPII [AI, cytotoxic, anti-neoplastic]
Other		
Protolichesterinic acid (aliphatic α-methylene-γ-lactone)	<i>Cetraria islandica</i> (lichen)	9.3Co DNAL – DNAL I [20] (HIV-1 RT)
DNA-dependent DNA polymerase (DNAP)	Arthur Kornberg (USA, Nobel Prize, medicine, 1959, DNA polymerase)	9.3D
Phenolic		
Bakuchiol (stilbene)	<i>Psoralea corylifolia</i> (Fabaceae)	9.3Dp DNAP

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited / macromolecular target (other targets) / in vivo effects/
Corylifolin (stilbene)	<i>Psoralea corylifolia</i> (Fabaceae)	DNAP
Daidzein (= 4',7-Dihydroxyisoflavone) (isoflavone)	<i>Glycine max</i> , <i>Psoralea corylifolia</i> , <i>Trifolium repens</i> (clover), <i>Ulex europaeus</i> (gorse) (Fabaceae)	DNAP (GABAA-R, TOPII)
Digallic acid (phenolic)	<i>Phyllanthus emblica</i> (Euphorbiaceae) [fruit], <i>Oenothera biennis</i> (Onagraceae)	DNAP α , DNAP β
Eugeniflorin D1 (tannin)	<i>Eugenia uniflora</i> (Myrtaceae)	DNAP (Epstein–Barr Virus) (3)
Eugeniflorin D2 (tannin)	<i>Eugenia uniflora</i> (Myrtaceae)	DNAP (Epstein–Barr Virus) (4)
Gallocatechin (gallotannin)	<i>Gossypium</i> sp. (Malvaceae), <i>Eugenia uniflora</i> (Myrtaceae)	DNAP (Epstein–Barr Virus) (27) (β -A R ligand)
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Haplophappus canescens</i> (Asteraceae); glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Azadirachta indica</i> , <i>Soymidia febrifuga</i> (Meliaceae), <i>Myrica rubra</i> (Myricaceae), <i>Primula sinensis</i> (Primulaceae), <i>Camellia sinensis</i> (Theaceae)	DNAP α , DNAPI (DNAL, F1 ATPase, HIV-1 RT, IKK, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, 5 α R, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic, apoptotic]
Neobavaisoflavone (isoflavone)	<i>Psoralea corylifolia</i> (Fabaceae)	DNAP
Oenothain B (tannin)	<i>Eugenia uniflora</i> (Myrtaceae)	DNAP (Epstein–Barr Virus) (62)
Quercetagetin (= 6-Hydroxyquercetin; 3,5,6,7,3',4'-Hexahydroxyflavone) (flavonol)	<i>Eupatorium gracile</i> , <i>Tagetes erecta</i> , <i>T. patula</i> (Asteraceae), other Asteraceae [flower], <i>Acacia catechu</i> (Fabaceae); glycosides in <i>Tagetes erecta</i> (marigold) (Asteraceae) [flower]	DNAPI (AR, F1 ATPase, HIV-1 INT, HIV-1 RT, Na ⁺ , K ⁺ -ATPase, PK, TOPII) [antibacterial, yellow pigment]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	DNAP β (AR, cAMP PDE, CFTR, F ₁ -ATPase, HIV-1 RT, 11 β HSDH, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, NEP, PK, PS - EF-1 α , RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
Repandusinic acid (tannin)	<i>Mallotus repandus</i> , <i>Phyllanthus niruri</i> (Euphorbiaceae)	DNAPOL α (0.6) (HIV-1 RT) [anti-HIV-1 (at 10)]
Resveratrol (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum grandiflorum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis vinifera</i> (Vitaceae) spp.	DNAP (END-R, EST-R, F ₁ -ATPase, RTK, TK, TYRase, XO)
3,4,5-Tri-O-galloylquinic acid (polyphenolic)	<i>Guiera senegalensis</i> (Combretaceae)	DNAP - α [0.3], β [44], γ [8]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited / macromolecular target (other targets) / in vivo effects
Terpene		
Betulinic acid (lupene triterpene)	Widespread; <i>Tetracera boiviniiana</i> (Dilleniaceae), <i>Rhododendron arboreum</i> (Ericaceae) [bark], <i>Psophocarpus tetragonolobus</i> (Fabaceae), <i>Syzygium claviflorum</i> (Myrtaceae) [leaf]	9.3Dt DNAP β (7) (AP, ATP-K ⁺ CH, CDPK, HIV-1 PR, PKA, PKC) [antineoplastic, apoptotic]
3- <i>cis-p</i> -Coumarylmaslinic acid (triterpene)	<i>Tetracera boiviniiana</i> (Dilleniaceae)	DNAP β (8)
3- <i>trans-p</i> -Coumarylmaslinic acid (triterpene)	<i>Tetracera boiviniiana</i> (Dilleniaceae)	DNAP β (2)
Gossypol (dimeric phenolic sesquiterpenoid)	<i>Gossypium</i> spp. (cotton), <i>Montezuma speciosissima</i> , <i>Thespesia populnea</i> (Malvaceae) [seed]; African slave labour to North America especially for cotton	DNAP α (Ca ²⁺ -ATPase, CAMA, CDPK, DNAP, 11 β HSDH, MLCK, PKA, PKC) [antifungal, antimutagenic, antitumour, inhibits spermatogenesis]
Harbinatic acid (= 3 α - <i>O</i> - <i>trans-p</i> -Coumaroyl-7-labden-15-oic acid) (labdene diterpenoid)	<i>Hardwickia binata</i> (Fabaceae)	DNAP β (3)
β -Hydroxy-urs-12,19(29)-dien-28-oic acid (ursane triterpene)	<i>Baeckea gunniana</i> (Myrtaceae)	DNAP β (7)
β -Hydroxy-urs-18,20(30)-dien-28-oic acid (ursane triterpene)	<i>Baeckea gunniana</i> (Myrtaceae)	DNAP β (7)
Oleanolic acid (oleanane triterpene)	<i>Luffa cylindrica</i> (sponge gourd); (Cucurbitaceae), <i>Lavandula latifolia</i> , <i>Rosmarinus officinalis</i> , <i>Thymus vulgaris</i> , <i>Salvia triloba</i> , (Lamiaceae), <i>Syzygium aromaticum</i> (Myrtaceae); 3- <i>O</i> -glucuronide in <i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae), <i>Baeckea gunniana</i> (Myrtaceae)	DNAP β (7) (CDPK, PKA, PKC) [AI]
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (ursane triterpene)	Widespread; <i>Vaccinium macrocarpon</i> (cranberry), <i>Arctostaphylos uva-ursi</i> (bearberry) (Ericaceae), <i>Lavandula latifolia</i> , <i>Prunella vulgaris</i> , <i>Rosmarinus officinalis</i> , <i>Salvia triloba</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Malus</i> sp. (apple), <i>Pyrus</i> sp. (pear) (Rosaceae) [fruit surface]	DNAP α , DNAP β (7) (CDPK, PKA, PKC, RT, TOPI, TOPII) [AI, cytotoxic, antineoplastic]
Other		
Cardiolipin (= Diphosphatidylglycerol) (phospholipid)	Eukaryote mitochondrial inner membrane	9.3Do DNAP – α (< 40), δ (> 40), ϵ (< 40) [membrane bilayer component]
Lysophosphatidic acid (= 2-Deacylphosphatidic acid) (phospholipid)	Universal	DNAP – α (> 40), δ (> 40), ϵ (< 40) [membrane bilayer component]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited / macromolecular target (other targets) / in vivo effects/
Lysophosphatidylinositol (= 2-Deacylphosphatidylinositol) (phospholipid)	Universal	DNAP – α (> 40), δ (> 40), ϵ (> 40) [membrane bilayer component]
Phosphatidic acid (= 1,2-Diacylglycerol-3-phosphate) (phospholipid)	Universal	DNAP – α (> 40), δ (> 40), ϵ (< 40) [membrane bilayer component]
Phosphatidylinositol (= PI) (phospholipid)	PIs are universal in biological membranes	DNAP – α [> 1000], δ [> 1000], ϵ [16] [membrane bilayer component; phosphate ester signal transducers]
Phosphatidylinositol-4-phosphate (phospholipid)	PI metabolite	DNAP – α (< 40), δ (< 40), ϵ (< 40) [membrane component]
Phosphatidylserine (phospholipid)	Universal	DNAP – α (> 40), δ (> 40), ϵ (< 40) [membrane bilayer component]
Prunasin (= D-Mandelonitrile- β -D-glucoside) (cyanogenic glycoside)	<i>Artemisia vulgaris</i> (Asteraceae), <i>Perilla frutescens</i> (Lamiaceae), <i>Prunus</i> spp. (Rosaceae); <i>Pteridium aquilinum</i> , <i>Cystopteris</i> spp. (ferns); Fabaceae, Myoporaceae, Myrtaceae, Scrophulariaceae	DNAP β (98)
Non-plant reference		9.3Dn
[Aphidicolin] (tetracyclic diterpene)	<i>Cephalosporium aphidicola</i> (fungus)	DNAP – α (calf) [0.2], δ (calf) [0.1], ϵ (calf) [0.1], DNAP α (competitive with dCTP) [1]
[Bredinin] (nucleoside analogue)	Synthetic; metabolically converted to Bredinin 5'-monophosphate	Bredinin 5'-monophosphate inhibits mammalian DNAP α & DNAP β
[N ² -(<i>p</i> -n-Butylphenyl)-2'-deoxyguanosine 5'-triphosphate] (nucleoside triphosphate)	Synthetic	DNAP (competitive) – α (calf) [24 nM], δ (calf) [90 nM], ϵ (calf) [1]
[Fomitelic acid A] (triterpene)	<i>Fomitella fraxinea</i> (fungus) (Basidiomycete)	DNAP α (< 100), DNAP β (rat), DNAPII (plant) (at 100) (RT, TOPI, TOPII) [inhibits NUGC cancer cell growth (38)]
[Fomitelic acid B] (triterpene)	<i>Fomitella fraxinea</i> (fungus) (Basidiomycete)	DNAP α (< 100), DNAP β (rat), DNAPII (plant) (at 100) (RT, TOPI, TOPII)
[Phosphonoacetic acid] (carboxylic acid)	Synthetic	Epstein-Barr DNAP (16), eukaryote DNAP
[Phosphonoformate] (carboxylic acid)	Synthetic	Eukaryote DNAP

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited / macromolecular target (other targets) / in vivo effects
DNA-dependent RNA polymerase (RNAP)	S.B. Weiss & J. Hurwitz (DNA-dependent RNA polymerase)	9.3E
Non-plant reference		9.3En
[α -Amanitin] (cyclic peptide); Heinrich Otto Wieland (Germany, Nobel Prize, 1927, bile acids)	<i>Amanita phalloides</i> (poisonous mushroom)	RNAP (eukaryote RNAP II & RNAP III) [highly toxic]
[β -Amanitin] (cyclic peptide)	<i>Amanita phalloides</i> (poisonous mushroom)	RNAP (eukaryote RNAP II & RNAP III) [highly toxic]
[Cordycepin (= 3'-Deoxyadenosine)] (nucleoside)	<i>Condyceps militaris</i> (fungus); Metabolite Cordycepin-5'-triphosphate yields 3'-Deoxyadenosine-5-monophosphate (3'-dAMP)	Deoxyadenosine-5-monophosphate (3'-dAMP) incorporation into RNA by RNAP causes chain termination (no free 3'-hydroxyl & therefore no further elongation possible)
[Rifamycins B, O, S and X] (aliphatic bridge-spanned naphthohydroquinones)	<i>Streptomyces mediterranei</i> (fungus)	RNAP (bacterial RNAP) [antibacterial]
[Rifamycin SV] (aliphatic bridge-spanned naphthohydroquinones)	Semi-synthetic from Rifamycin S	RNAP (bacterial RNAP) [antibacterial]
[Rifampin (= Rifampicin)] (aliphatic bridge-spanned naphthohydroquinones)	Semi-synthetic from Rifamycin SV	RNAP (bacterial RNAP) [antibacterial, antimycobacterial, tuberculostatic]
DNA topoisomerase I (TOPI)		9.3F
Alkaloid		9.3Fa
[9-Aminocamptothecin (= 9-Aminocamptothecine)] (quinoline)	Semi-synthetic from Camptothecin	TOPI [antitumour, cytotoxic]
Camptothecin (= Camptothecine) (quinoline)	<i>Mappia foetida</i> (Icacinaceae), <i>Camptotheca acuminata</i> (Nyssaceae) [bark, fruit, wood]	TOPI (nuclear & mitochondrial; stabilizes covalent DNA-TOPI intermediate yielding DNA lesions through inhibition of reclosure) (20 nM; 0.7) [antileukaemic, antitumour, cytotoxic]
Dicentrinone (aporphine isoquinoline alkaloid)	<i>Guatteria scadens</i> (Annonaceae), <i>Ocotea leucoxydon</i> (Lauraceae)	TOPI [weakly cytotoxic]
Epiberberine (protoberberine isoquinoline)	<i>Coptis chinensis</i> (goldthread) (Ranunculaceae)	TOPI (stabilizes cleavable DNA complex with TOPI & yields DNA cleavage)
Groenlandicine (protoberberine isoquinoline)	<i>Coptis chinensis</i> (goldthread) (Ranunculaceae)	TOPI (stabilizes cleavable DNA complex with TOPI & yields DNA cleavage)
[Irinotecan (= Camptosar; CPT-11)] (quinoline)	Semi-synthetic from Camptothecin	TOPI [antileukaemic, antitumour, cytotoxic]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited / macromolecular target (other targets) / in vivo effects/
Mahanimbine (carbazole)	<i>Murraya koenigii</i> (curryleaf) (Rutaceae) [leaf]	TOPI (AO/FRS, TOPII) [antimicrobial, mosquitocidal]
Mahanine (carbazole)	<i>Murraya koenigii</i> (curryleaf) (Rutaceae) [leaf]	TOPI (AO/FRS, TOPII) [antimicrobial, mosquitocidal]
Murrayanol (carbazole)	<i>Murraya koenigii</i> (curryleaf) (Rutaceae) [leaf]	TOPI (TOPII) [antimicrobial, mosquitocidal]
Palmatine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Jateorrhiza palmata</i> (Menispermaceae), <i>Berberis</i> spp., <i>Mahonia</i> spp. (Berberidaceae), Papaveraceae	TOPI (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA, 5HT2-R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]
[Topotecan (= 9-[(Dimethylamino)methyl]-10-hydroxy(20S)-camptothecin] (quinoline)	Semi-synthetic from Camptothecin	TOPI [antineoplastic, cytotoxic]
Phenolic		9.3Fp
[1'-Acetylshikonin] (quinone)	Semi-synthetic from Shikonin	TOPI (45)
Alkannin (naphthoquinone)	<i>Alkanna tinctoria</i> , <i>Arnebia nobilis</i> , <i>Macrotomia cephalotes</i> , <i>Plagiobothrys arizonicus</i> (Boraginaceae)	TOPI
Chebularic acid (ellagitannin)	<i>Terminalia chebula</i> (Combretaceae)	TOPI [enhances ACTH-induced adipocyte lipolysis; cytotoxic]
Curcumin I (phenol)	<i>Curcuma longa</i> (curcumin) (Zingiberaceae) [rhizome]	TOPI (at 140) (TOPII)
Curcumin II (phenol)	<i>Curcuma longa</i> (curcumin) (Zingiberaceae) [rhizome]	TOPI (at 140) (TOPII)
Curcumin III (phenol)	<i>Curcuma longa</i> (curcumin) (Zingiberaceae) [rhizome]	TOPI (at 70) (TOPII)
Diospyrin (= Euclein) (bisnaphthoquinone)	<i>Diospyros</i> spp., <i>Euclea</i> spp. (Ebenaceae) [bark, leaf, root, wood]	TOPI (<i>Leishmania donovani</i>), TOPI (calf thymus, weaker) [anti- <i>Leishmania</i> , antitumour, cytotoxic]
Ellagic acid (= Benzoaric acid; Lagistase) (phenolic acid lactone)	Widespread; hydrolysis product of ellagitannins e.g. Sanguin H-6; <i>Psidium guajava</i> (Myrtaceae) <i>Fragaria</i> spp. (Rosaceae)	TOPI (2) (DNA, PGK, TOPII) [anticarcinogen, haemostatic]
(-)-Epigallocatechin 3-gallate(= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	TOPOIB (26 nM) (EST-R, PK, proteosome, 5 α R, RTK) [cell-EGF-RTK (< 5); oxidation products give tea taste]
[Flavellagic acid] (phenolic acid lactone)	Oxidation product of polyhydroxyphenolic Gallic acid	TOPI (10) (TOPII)
β -Lapachone (α -naphthoquinone)	<i>Haplophragma adenophyllum</i> , <i>Phyllarthron comorense</i> [wood], <i>Tabebuia avellaneda</i> [wood] (Bignoniaceae), <i>Tectona grandis</i> (Verbenaceae) [root]	TOPI (directly inhibits TOPI) (iNOS, RT) [AI, antimicrobial, antitumour, apoptotic, cytotoxic]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited/macromolecular target (other targets) in vivo effects
4-Nerolidylcatechol (catechol)	<i>Pothomorphe peltata</i> (Piperaceae) [leaf]	TOPI (64) [cytotoxic (human KB cells) (4)]
[1'-(4-Pentenoyl)shikonin] (quinone)	Semi-synthetic from Shikonin	TOPI (40)
[1'-Propanoylshikonin] (quinone)	Semi-synthetic from Shikonin	TOPI (44)
Sanguin H-6 (dimeric ellagitannin)	<i>Sanguisorba officinalis</i> (Rosaceae)	TOPI (direct enzyme inhibition) (1) (TOPII)
Shikonin (= 1' R-isomer of Alkamin) (naphthoquinone)	<i>Echium lycopsis</i> , <i>Lithospermum erythrorhizon</i> [root], <i>Onosma caucasicum</i> (Boraginaceae)	TOPI (TOPII) [red colour]
7,3',5'-Tri-O-methylricetin (= 5,4'-Dihydroxy-7,3',5'-Trimethoxyflavone) (flavone)	<i>Lethedon tannaensis</i> (Thymelaeaceae)	TOPI (calf thymus) [cytotoxic – human nasopharynx carcinoma KB cells (22)]
Velutin (flavone)	<i>Lethedon tannaensis</i> (Thymelaeaceae)	TOPI (calf thymus) [cytotoxic – human nasopharynx carcinoma KB cells (5)]
Terpene		9.3Ft
Acetylboswellic acid (triterpene)	<i>Boswellia serrata</i> (frankincense) (Burseraceae) [gum resin]; magi gift for infant Jesus	TOPI (TOPII α)
Acetylboswellic acid (immobilized) (triterpene)	<i>Boswellia serrata</i> (frankincense) (Burseraceae) [gum resin]	TOPI [71 nM] (TOPII)
Acetyl-11-keto- β -boswellic acid (pentacyclic triterpene)	<i>Boswellia serrata</i> (Burseraceae) [gum resin]	TOPI (5-LOX) [LTB ₄ , LTC ₄ release inhibitor; AI in EAE]
Amarogentin (secoiridoid glycoside)	<i>Gentiana lutea</i> , <i>G.</i> spp. (gentian), <i>Swertia chirata</i> , <i>Swertia</i> spp. (Gentianaceae) [root]	TOPI (<i>Leishmania donovani</i> , enzyme ligand) [very bitter]
Betulinic acid (lupene triterpene)	Widespread; <i>Syzygium claviflorum</i> (Myrtaceae) [leaf], <i>Rhododendron arboreum</i> (Ericaceae) [bark]	TOPI (CDPK, HIV-1 PR, PKA, PKC, TOPII) [antineoplastic]
Deca-2,4-diene-4-hydroxy-6-yn-1,4-olide (sesquiterpene)	<i>Conyza albida</i> (fleabane) (Asteraceae)	TOPI [cytotoxic (human KB cells) (118)]
Oleanolic acid (oleanane triterpene)	<i>Luffa cylindrica</i> (sponge gourd); (Cucurbitaceae), <i>Lavandula latifolia</i> , <i>Rosmarinus officinalis</i> , <i>Thymus vulgaris</i> , <i>Salvia triloba</i> , (Lamiaceae), <i>Syzygium aromaticum</i> (Myrtaceae); 3-O-glucuronide in <i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae), <i>Baeckea gunniana</i> (Myrtaceae)	TOPI (C3-convertase, CDPK, DNAL, DNAP, ELA, PKA, PKC, TOPII α) [AI]
Spathulenol (sesquiterpene)	<i>Conyza albida</i> (fleabane) (Asteraceae)	TOPI [cytotoxic (human KB cells) (84)]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited/macromolecular target (other targets) / in vivo effects/
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (triterpene)	Widespread; <i>Vaccinium macrocarpon</i> (cranberry), <i>Arctostaphylos uva-ursi</i> (bearberry) (Ericaceae), <i>Lavandula latifolia</i> <i>Prunella vulgaris</i> , <i>Rosmarinus officinalis</i> , <i>Salvia triloba</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Malus</i> sp. (apple), <i>Pyrus</i> sp. (pear) (Rosaceae) [fruit surface]	TOPI (CDPK, DNAPOL, PKA, PKC, RT, TOPII α) [AI, cytotoxic, antineoplastic]
Non-plant reference		9.3Fn
[Coralyne] (protoberberine alkaloid)	Synthetic	TOPI (DNA, RT)
[Fomitelic acid A] (triterpene)	<i>Fomitella fraxinea</i> (fungus) (Basidiomycete)	TOPI (DNAPOL, RT, TOPII) [inhibits NUGC cancer cell growth (38)]
[Fomitelic acid B] (triterpene)	<i>Fomitella fraxinea</i> (fungus) (Basidiomycete)	TOPI (DNAPOL, RT, TOPII)
[Heliquinomycin] (glycosylated rubromycin)	<i>Streptomyces</i> sp. (fungus) (Actinomycete)	TOPI (at 140) (DNAH, DNAS, TOPII, RNAS)
DNA topoisomerase II (TOPII)		9.3G
Alkaloid		9.3Ga
[Berberrubine] (protoberberine isoquinoline)	Generated during herbal medicinal processing of <i>Coptis chinensis</i> (goldthread) (Ranunculaceae)	TOPII (yields DNA cleavage) (DNA)
Cryptolepine (indole)	<i>Cryptolepis sanguinolenta</i> , <i>C. triangularis</i> (Asclepiadaceae)	TOPII (formation of cleavable TOPII-DNA complex) (DNA) [hypotensive]
Dicentrine (aporphine isoquinoline)	<i>Hordeum vulgare</i> (barley) (Poaceae)	TOPII (formation of cleavable TOPII-DNA complex) (DNA)
Ellipticine (indole)	<i>Aspidosperma williamsii</i> , <i>A. subincarnum</i> , <i>Bleekeria vitiensis</i> , <i>Ochrostia elliptica</i> (Apocynaceae)	DNA (intercalates) (TOPII) [antitrypanosomal, antitumour]
Liriodenine (= Spermatheridine) (benzylisoquinoline)	<i>Fissistigma glaucescens</i> (Annonaceae), <i>Liriodendron tulipifera</i> , <i>Magnolia obovata</i> (Magnoliaceae)	TOPII (catalytic inhibition) [anticancer, antifungal, anti- <i>Leishmania</i> (26), anti- <i>Plasmodium</i> (15) cytotoxic]
Neocryptolepine (indole)	<i>Cryptolepis sanguinolenta</i> (Asclepiadaceae)	TOPII (formation of cleavable TOPII-DNA complex) (DNA)
Mahanimbine (carbazole)	<i>Murraya koenigii</i> (curryleaf) (Rutaceae) [leaf]	TOPII (AO/FRS, TOPI) [antimicrobial, mosquitocidal]
Mahanine (carbazole)	<i>Murraya koenigii</i> (curryleaf) (Rutaceae) [leaf]	TOPII (AO/FRS, TOPI) [antimicrobial, mosquitocidal]
Matadine (pyridoindole)	<i>Strychnos gossweileri</i> (Loganiaceae)	TOPII (DNA)
Murrayanol (carbazole)	<i>Murraya koenigii</i> (curryleaf) (Rutaceae) [leaf]	TOPII (TOPI) [antimicrobial, mosquitocidal]
Serpentine (indole)	<i>Catharanthus roseus</i> , <i>Rauwolfia serpentina</i> , <i>R. tetraphylla</i> (Apocynaceae)	TOPII (formation of cleavable TOPII-DNA complex) (DNA, nAChR antagonist)

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited / macromolecular target (other targets) / in vivo effects
Phenolic		
Aloe-emodin (= 1,8-Dihydroxy-3-(hydroxymethyl)-9,10-anthracenedione; Rhabarberone) (anthraquinone)	<i>Oroxylum indicum</i> (Bignoniaceae), <i>Cassia senna</i> (Fabaceae), <i>Aloe vera</i> , <i>A. spp.</i> , <i>Asphodelus microcarpus</i> , <i>Xanthorrhoea australis</i> (Liliaceae), <i>Rheum</i> spp. (Polygonaceae), <i>Tectona grandis</i> (Verbenaceae)	9.3Gp TOPII (DNA, eEF-2) [anti- <i>Trypanosoma</i> (14)]
Baicalein (flavone)	<i>Scutellaria</i> spp. (Lamiaceae), <i>Oroxylum indicum</i> (Bignoniaceae) [leaf]	TOPII (PKC signalling)
Bakuchicin (coumarin)	<i>Psoralea corylifolia</i> (Fabaceae)	TOPII
Chrysozarin (= Dantron; Danthron; 1,8-Dihydroxy-9,10-anthracenedione) (anthraquinone)	<i>Rheum palmatum</i> (Polygonaceae) [root], <i>Cinchona ledgeriana</i> (Rubiaceae), <i>Xyris semifulcata</i> (Xyridaceae) [leaf, stem]	TOPII (DNA, PK) [cathartic, genotoxic, immunosuppressive, mutagenic, purgative]
Curcumin I (phenol)	<i>Curcuma longa</i> (curcumin) (Zingiberaceae) [rhizome]	TOPII (at 140) (TOPI)
Curcumin II (phenol)	<i>Curcuma longa</i> (curcumin) (Zingiberaceae) [rhizome]	TOPII (at 140) (TOPI)
Curcumin III (phenol)	<i>Curcuma longa</i> (curcumin) (Zingiberaceae) [rhizome]	TOPII (at 70) (TOPI)
Daidzein (= 4',7-Dihydroxyisoflavone) (isoflavone)	<i>Trifolium repens</i> (clover), <i>Ulex europaeus</i> (gorse) (Fabaceae)	TOPII (DNAPOL, GABAA-R)
Daidzin (= Daidzein 7-O-glucoside; 7,4'-Dihydroxyisoflavone 7-O-glucoside) (isoflavone O-glycoside)	<i>Baptisia</i> spp., <i>Glycine max</i> (soybean), <i>Pueraria</i> spp., <i>Trifolium pratense</i> (Fabaceae)	TOPII (formation of cleavable TOPII-DNA complex) (DNAPOL)
Damnacanthal (anthraquinone)	<i>Morinda citrifolia</i> , <i>Neonauclea calycina</i> (Rubiaceae)	TOPII (75) (PK, RTK, TK)
Ellagic acid (= Benzoic acid; Lagistase) (phenolic acid lactone)	Widespread; product of ellagitannin hydrolysis; <i>Psidium guajava</i> (Myrtaceae), <i>Fragaria</i> spp. (strawberry) (Rosaceae)	TOPII (2) (TOPI) [anticarcinogen, haemostatic]
Emodin (= Archin; Frangula emodin; Frangulic acid; Rheum emodin; 1,3,8-Trihydroxy-6-methyl-9,10-anthraquinone) (anthraquinone)	<i>Rumex</i> spp., <i>Rheum palmatum</i> , <i>R. spp.</i> (Polygonaceae) [rhizome], <i>Ventilago calyculata</i> , <i>Rhamnus frangula</i> (Rhamnaceae), <i>Myrsine africana</i> (Myrsinaceae), <i>Psorospermum glaberrimum</i> (Guttiferae), lichen	TOPII (CDC2, CKI, CKII, CDPK, DNA, MLCK, PKA, PKC, p60src TK, RTK p56 ^{ck}) [cathartic, cytotoxic, genotoxic, mutagenic]
(-)-Epicatechin-3-gallate (flavan-3-ol, gallotannin)	<i>Camellia sinensis</i> (tea leaf) (Theaceae)	TOPII (by formation of cleavable TOPII-DNA complex) (RT)
(-)-Epigallocatechin-3-gallate (= EGCG) (flavan-3-ol, gallotannin)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea leaf) (Theaceae)	TOPII (by formation of cleavable TOPII-DNA complex) (β-A R, D1-R, D2-R, O-R, PKC, RT) [AI, blocks COX-2 & iNOS induction]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited / macromolecular target (other targets) / in vivo effects/
[Etoposide (= VP16)] (lignan)	Semi-synthetic from Podophyllotoxin	TOPII (0.2) [antineoplastic, antitumour, apoptotic, cytotoxic]
[Flavellagic acid] (phenolic acid lactone)	Oxidation product of polyhydroxyphenolic Gallic acid	TOPII (TOPI) (12)
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7- Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Trifolium</i> spp. (clover) (Fabaceae); 7- <i>O</i> - glucoside (= Genistin; Genistoside) in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> (Fabaceae); 4'- <i>O</i> - glucoside (= Sophocoroside) in <i>Sophora japonica</i> (Fabaceae) [pod]	TOPII (formation of cleavable TOPII-DNA complex) (AD-R, EGF-RTK, GABAA-R, HISK, lipase, MLCK, peroxidase, PKA, pp60 ^{v-src} TK, pp110 ^{gag-fes} TK) [antiangiogenic, antifungal, oestrogenic]
Genistin (= Genistein 7- <i>O</i> - glucoside; Genistoside; 4',5, 7-Trihydroxyisoflavone 7- <i>O</i> -glucoside) (isoflavone <i>O</i> -glucoside)	<i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> (Fabaceae)	TOPII (formation of cleavable TOPII-DNA complex) (EGF- RTK) [plant growth inhibitor]
β -Lapachone (naphthoquinone)	<i>Tabebuia</i> sp. (trumpet tree) (Bignoniaceae)	TOPII [inhibits LPS-induced macrophage iNOS expression; cytotoxic, pro-apoptotic]
Luteolin (= 5,7,3',4'- Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium</i> <i>graveolens</i> (Apiaceae) widespread as glycosides in Cruciferae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]	TOPII (13) (DNA cleavage) (AR, CDPK, ITDI, MLCK, NADH DH, PKA, PKC, succinate DH,) [antibacterial, AI, anti- <i>Leishmania</i> , nodulation signal]
6'-Methoxy- pseudobaptigenin- 7- <i>O</i> - β -glucoside (isoflavone <i>O</i> -glucoside)	<i>Retama sphaerocarpa</i> (Fabaceae)	TOPII (formation of cleavable TOPII-DNA complex)
Morindone (anthraquinone)	<i>Neonauclea calycina</i> (Rubiaceae)	TOPII (78)
Myricetin (= 3,5,7,3',4',5'- Hexahydroxyflavone) (flavonol)	<i>Haplopappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Azadirachta indica</i> , <i>Soymidia febrifuga</i> (Meliaceae) [wood], <i>Myrica rubra</i> (Moraceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia</i> <i>sinensis</i> (Theaceae) [leaf]	TOPII (CDPK, IKK, 5-LOX, MLCK, NADH DH, PKA, succinate DH) [antibacterial, antigonadotropic]
Peroxisomicine A(1) (dimeric anthraceneone)	<i>Karwinskia humboldtiana</i> (Rhamnaceae)	TOPII (inhibits enzyme catalytic activity) [apoptotic, cytotoxic]
Plumbagin (naphthoquinone)	<i>Plumbago europaea</i> (Plumbaginaceae) [root], <i>Dionaea</i> <i>muscipula</i> , <i>Drosera rotundifolia</i> , <i>D.</i> spp. (Droseraceae), <i>Aristea</i> spp., <i>Sisyrinchium</i> spp., <i>Sparaxis</i> spp. (Iridaceae) [root], <i>Diospyros</i> spp. (Ebenaceae) [bark], <i>Pera ferruginea</i> (Euphorbiaceae) [bark]	TOPII (by formation of cleavable TOPII-DNA complex) (DNA, MLCK, PKA)

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited/macromolecular target (other targets) / in vivo effects/
Podophyllotoxin (= Podophyllinic acid lactone) (lignan)	<i>Callitris drummondii</i> , <i>Juniperus sabina</i> , <i>J. virginiana</i> , <i>Diphylleia grayi</i> , <i>D. sinensis</i> , <i>Podophyllum hexandrum</i> , <i>P. peltatum</i> , <i>P. pleianthum</i> (Podophyllaceae) [rhizome]	TOPII (TUB) [antimitotic, antitumour, antiviral, cathartic]
Podophyllotoxin 1- <i>O</i> -glucoside (= Podophyllinic acid lactone 1- <i>O</i> -glucoside) (lignan)	<i>Podophyllum hexandrum</i> , <i>P. peltatum</i> , <i>P. pleianthum</i> (Podophyllaceae) [rhizome]	Yields Podophyllotoxin – TOPII [cytotoxic]
Podophyllotoxone (lignan)	<i>Diphylleia sinensis</i> , <i>Podophyllum hexandrum</i> , <i>P. peltatum</i> , <i>P. pleianthum</i> (Podophyllaceae) [rhizome]	Yields Podophyllotoxin – TOPII [cytotoxic]
Psorospermin (xanthone)	<i>Psorospermum</i> spp. (Guttiferae) [root]	TOPII-dependent alkylation of DNA trapping TOPII-cleaved DNA complex (DNA) [antileukaemic, antitumour]
Quercetagenin (= 6-Hydroxyquercetin; 3,5,6,7,3',4'-Hexahydroxyflavone) (flavonol)	<i>Eupatorium gracile</i> , <i>Tagetes erecta</i> , <i>T. patula</i> (Asteraceae), other Asteraceae [flower], <i>Acacia catechu</i> (Fabaceae); glycosides in <i>T. erecta</i> (marigold) (Asteraceae) [flower]	TOPII (by formation of cleavable TOPII-DNA complex) (AR, CDPK, MLCK, PKA) [antibacterial, yellow pigment]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	TOPII (46) (DNA cleavage) (AR, cAMP PDE, HIV-1 PR, LOX, PK, TK, PS – EF-1 α) [allergenic, antibacterial, AI, anti- <i>Leishmania</i> , antiviral]
Sanguin H-6 (dimeric ellagitannin)	<i>Sanguisorba officinalis</i> (Rosaceae)	TOPII (direct inhibition) (10nM) (TOPI)
Shikonin (= 1' <i>R</i> -isomer of Alkannin) (naphthoquinone)	<i>Echium lycopsis</i> , <i>Lithospermum erythrorhizon</i> [root], <i>Onosma caucasicum</i> (Boraginaceae)	TOPII (formation of cleavable TOPII-DNA complex) (TOPI) [red colour]
Seco-3,4-friedelin (= Dihydroputranjivic acid) (seco-friedelane triterpenoid)	<i>Alchornea latifolia</i> (Euphorbiaceae) [leaf]	TOPII
Seco-3,4-taraxerone (seco-taraxerane triterpenoid) [Teniposide] (lignan)	<i>Alchornea latifolia</i> (Euphorbiaceae) [leaf] Semi-synthetic from Podophyllotoxin	TOPII
Woodfruticosin (= Woodfordin C) (tannin)	<i>Woodfordia fruticosa</i> (Lythraceae) [leaf]	TOPII
Terpene		9.3Gt
Acetylboswellic acid (triterpene)	<i>Boswellia serrata</i> (frankincense) (Burseraceae) [gum resin]; one of the gifts of the Magi to the infant Jesus	TOPII α (TOPI)
Acetylboswellic acid (immobilized) (triterpene)	<i>Boswellia serrata</i> (frankincense) (Burseraceae) [gum resin]	TOPII α [8nM] (TOPI)

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited / macromolecular target (other targets) / in vivo effects/
Betulin (oleane triterpene)	<i>Betula platyphylla</i> , <i>B.</i> spp. (birch) (Betulaceae), <i>Phyllanthus flexuosus</i> (Euphorbiaceae) [bark]	TOPII (direct inhibition) (at 25) [antitumour]
Betulinic acid (lupene triterpene)	Widespread; <i>Tetracera boiviniana</i> (Dilleniaceae), <i>Rhododendron arboreum</i> (Ericaceae) [bark], <i>Psophocarpus tetragonolobus</i> (Fabaceae), <i>Syzygium claviflorum</i> (Myrtaceae) [leaf]	TOPII α (9) (CDPK, HIV-1 PR, PKA, PKC, TOPI) [antineoplastic]
3- α , 27-Dihydroxylup-20(29)-en-28-oic acid methylester (lupene triterpene)	<i>Peganum nigellastrum</i> (Zygophyllaceae) [root]	TOPII (9)
Lupeol (= Fagasterol; Monogynol B; β -Viscol) (lupane triterpene)	<i>Alstonia boonei</i> (Apocynaceae) [bark, seed], <i>Phyllanthus emblica</i> , <i>P. flexuosus</i> (Euphorbiaceae), <i>Lupinus luteus</i> (Fabaceae) [seed]	TOPII (direct inhibition) (at 25) (CAB Pase, CHY, PKA, PKC, TRY) [anti-arthritic, AI, antitumour]
Olean-12-en-3 β ,15 α -diol (oleane triterpene)	<i>Phyllanthus flexuosus</i> (Euphorbiaceae) [bark]	TOPII (direct inhibition) (at 25)
Oleanolic acid (oleanane triterpene)	<i>Luffa cylindrica</i> (sponge gourd); (Cucurbitaceae), <i>Lavandula latifolia</i> , <i>Rosmarinus officinalis</i> , <i>Thymus vulgaris</i> , <i>Salvia triloba</i> , (Lamiaceae), <i>Syzygium aromaticum</i> (Myrtaceae); 3-O-glucuronide in <i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae), <i>Baeckea gunniana</i> (Myrtaceae)	TOPII α (C3-convertase, CDPK, DNAL, DNAP, ELA, PKA, PKC, TOPI) [AI]
Olean-12-en-3 β ,15 α ,24-triol (oleane triterpene)	<i>Phyllanthus flexuosus</i> (Euphorbiaceae) [bark]	TOPII (direct inhibition) (at 25)
3,4-Seco-8 β H-ferna-4(23),9(11)-diene-3-oic acid (secofernane triterpene)	<i>Euphorbia</i> sp. (Euphorbiaceae)	TOPII (direct inhibition)
3,4-Seco-8 β H-ferna-4(23),9(11)-diene-3-ol (secofernane triterpene)	<i>Euphorbia</i> sp. (Euphorbiaceae)	TOPII (direct inhibition)
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (triterpene)	Widespread; <i>Vaccinium macrocarpon</i> (cranberry), <i>Arctostaphylos uva-ursi</i> (bearberry) (Ericaceae), <i>Lavandula latifolia</i> , <i>Prunella vulgaris</i> , <i>Rosmarinus officinalis</i> , <i>Salvia triloba</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Malus</i> sp. (apple), <i>Pyrus</i> sp. (pear) (Rosaceae) [fruit surface]	TOPII α (CDPK, DNAPOL, PKA, PKC, RT, TOPI) [AI, cytotoxic, antineoplastic]
Non-plant reference		9.3Gn
[Actinomycin D] (cyclic peptide)	<i>Streptomyces chrysomallus</i> (fungus) (Actinomycete)	TOPII (formation of cleavable TOPII–DNA complex) (DNA) [antineoplastic]

(continued)

Table 9.3 (Continued)

Compound (class)	Plant (family) / part	Enzyme inhibited / macromolecular target (other targets) / in vivo effects
[Amsacrine (= <i>m</i> -AMSA; 4'-(9-Acridinylamino)methanesulphon- <i>m</i> -anisidine) (arylsulfonamide aminoacridine)]	Synthetic	TOPII (formation of cleavable TOPII-DNA complex) (DNA) [antineoplastic, antiviral, immunosuppressive]
[Daunomycin (= Daunorubicin; Daunomycinone daunosamine)] (anthracycline)	<i>Streptomyces peucetius</i> (fungus) (Actinomycete) cf. Doxorubicin	TOPII (formation of cleavable TOPII-DNA complex) (DNA) [antineoplastic, cytotoxic]
[Doxorubicin (= Adriamycin; Adriamycinone daunosamine)] (anthracycline)	<i>Streptomyces peucetius</i> (fungus) (Actinomycete) cf. Daunomycin	TOPII (formation of cleavable TOPII-DNA complex) (DNA) [antineoplastic, cytotoxic]
[Fomitelic acid A] (triterpene)	<i>Fomitella fraxinea</i> (fungus) (Basidiomycete)	TOPII (DNAPOL, RT, TOPI) [inhibits NUGC cancer cell growth (38)]
[Fomitelic acid B] (triterpene)	<i>Fomitella fraxinea</i> (fungus) (Basidiomycete)	TOPII (DNAPOL, RT, TOPI)
[Heliquinomycin] (glycosylated rubromycin)	<i>Streptomyces</i> sp. (fungus) (Actinomycete)	TOPII (at 70) (DNAH, DNAS, TOPI, RNAS)

Table 9.4 Dihydrofolate reductase and thymidylate synthetase

Compound (class)	Plant (family) / part	Enzyme / process inhibited (other targets) / in vivo effects
Dihydrofolate reductase (= DHFR)		9.4A
Alkaloid		9.4Aa
Deoxytubulosine (β-carboline benzoquinolizidine alkaloid)	<i>Alangium lamarckii</i> (Alangiaceae)	DHFR – <i>Lactobacillus leichmanii</i> [5] (TS, DNA) [cytotoxic (<i>L. leichmanii</i>) (40)]
Pergularinine (phenanthroindolizidine alkaloid)	<i>Pergularia pallida</i> (Asclepiadaceae)	DHFR – <i>Lactobacillus leichmanii</i> [9] (TS) [cytotoxic (<i>L. leichmanii</i>) (45)]
Tylophorinidine (phenanthroindolizidine alkaloid)	<i>Pergularia pallida</i> (Asclepiadaceae)	DHFR – <i>Lactobacillus leichmanii</i> [7] (TS) [cytotoxic (<i>L. leichmanii</i>) (40)]
Non-plant reference		9.4An
[Aminopterin (= 4-Aminofolic acid; 4-Aminopteroylglutamic acid)] (pteridine alkaloid)	Synthetic	DHFR [rodenticide]
[Methotrexate (= 4-Amino-10-methylfolic acid; 4-Amino- <i>N</i> ¹⁰ -methylpteroylglutamic acid)] (pteridine alkaloid)	Synthetic	DHFR [antineoplastic, antirheumatic]

(continued)

Table 9.4 (Continued)

Compound (class)	Plant (family) part	Enzyme/process inhibited (other targets) in vivo effects
MTA (= LY231514; Multi-targeted antifolate) (polyglutamated <i>in vivo</i>)	Synthetic	DHFR (TS) [polyglutamated <i>in vivo</i> ; anticancer]
[Pyrimethamine (= 2,4-Diamino-5-(<i>p</i> -chlorophenyl)-6-ethylpyrimidine)] (phenylpyrimidine)	Synthetic; Gertrude Elion & George Hitchings (USA, Nobel Prize, Medicine, 1988, drug development)	DHFR (malarial DHFR more sensitive than human) [antimalarial, antiprotozoal, anti- <i>Toxoplasma</i>]
[Trimethoprim] (aryl pyrimidine)	Synthetic; Gertrude Elion & George Hitchings (USA, Nobel Prize, Medicine, 1988, drug development)	DHFR (bacterial DHFR more sensitive than human) [antibacterial]
Thymidylate synthetase (TS)		9.4B
Alkaloid		9.4Ba
Deoxytubulosine (β -carboline benzoquinolizidine alkaloid)	<i>Alangium lamarckii</i> (Alangiaceae)	TS [7] (50) (DHFR, DNA) [cytotoxic]
Pergularinine (phenanthroindolizidine alkaloid)	<i>Pergularia pallida</i> (Asclepiadaceae)	TS [10] (50) (DHFR) [cytotoxic]
Tylophorine (phenanthroindolizidine alkaloid)	<i>Pergularia pallida</i> (Asclepiadaceae)	TS – [9] (50) (DHFR) [cytotoxic]
Non-plant reference		9.4Bn
[5-Fluorouracil (= 2,4-Dioxo-5-fluoropyrimidine)] (fluoropyrimidine alkaloid)	Synthetic	Metabolite 5-Fluorouridine 5'-monophosphate (5'-UMP) inhibits TS [further nucleotide metabolites yield false base insertion into RNA & DNA]
[MTA (= LY231514; Multi-targeted antifolate)] (polyglutamated <i>in vivo</i>)	Synthetic	TS (DHFR) [polyglutamated <i>in vivo</i> ; anticancer]

Table 9.5 HIV-1 integrase and HIV-1 reverse transcriptase

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) /in vivo effects
HIV-1 Integrase (HIV-1 INT)		9.5A
Phenolic		9.5Ap
Acteoside (phenylpropanoid)	<i>Clerodendron trichotum</i> (Verbenaceae)	HIV-1 INT (8)
Acteoside isomer (phenylpropanoid)	<i>Clerodendron trichotum</i> (Verbenaceae)	HIV-1 INT (14)

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part/	Enzyme inhibited (other targets) /in vivo effects/
Alizarin (= 1,2-Dihydroxy-9,10-anthraquinone) (anthraquinone)	<i>Morinda citrifolia</i> , <i>Rheum palmatum</i> (Polygonaceae) [root], <i>Rubia cordifolia</i> , <i>R. tinctorum</i> , <i>Galium</i> spp., <i>Asperula odorata</i> , <i>Morinda citrifolia</i> [wood] (Rubiaceae)	HIV-1 INT (CDPK, MLCK, PKA, PKC) [antineoplastic, red pigment & dye]
(-)-Arctigenin (dibenzylbutyrolactone lignanoid)	<i>Arctium lappa</i> (Asteraceae) [fruit, seed]	HIV-1 INT
Baicalein (= 5,6,7-Trihydroxyflavone) (flavone)	<i>Scutellaria</i> spp. (Lamiaceae) [root, leaf], <i>Oroxylum indicum</i> (Bignoniaceae) [leaf]	HIV-1 INT (0.1; 0.8) (AROM, HIV-1RT, TOPII) [apoptotic]
Caffeic acid phenethyl ester (phenylpropanoid)	<i>Populus</i> sp. (Salicaceae), bee propolis	HIV-1 INT (AO/FRS, 5-LOX) [AI, antioxidant, blocks NFκB activation]
1-Chicoric acid (bisphenylpropanoid)	<i>Cichorium intybus</i> , <i>C. endiva</i> , <i>Echinacea</i> spp. <i>Lactuca sativa</i> , <i>Taraxacum officinale</i> (dandelion) (Asteraceae), <i>Vaccinium arctostaphylos</i> (bilberry) (Ericaceae)	HIV-1 INT (25) [inhibits HIV-1 replication (0.4)]
Curcumin (= Diferuloylmethane; Turmeric yellow) (phenylpropanoid)	<i>Curcuma longa</i> (turmeric), <i>C. aromatica</i> , <i>C. xanthorrhiza</i> (Zingiberaceae) [root]	HIV-1 INT (58) (CDPK, IKK, PhosbK, PKA, PKC, p60 ^{c-src} TK) [AI, antioxidant, hypoglycaemic, cytotoxic]
Deposides (ether phenolic esters)	Lichen	HIV-1 INT (at 10)
Deposidones (ether phenolic esters)	Lichen	HIV-1 INT (at 10)
(-)-Dicafeoylquinic acid (phenylpropanoid)	<i>Aster scaber</i> (Asteraceae) [aerial]	HIV-1 INT (0.4; 8; 13)
(-)-Dicafeoyltartaric acid (phenylpropanoid)	<i>Aster scaber</i> (Asteraceae) [aerial]	HIV-1 INT (0.4)
Ellagic acid (= Benzoic acid; Lagistase) (phenolic acid lactone)	Widespread [leaf], ellagitannin product; <i>Psidium guajava</i> (Myrtaceae), <i>Fragaria</i> spp (strawberry) (Rosaceae)	HIV-1 INT (ITD, PK, RTK) [anti-mutagen, haemostatic]
Fisetin (= 5-Deoxy-quercetin; 3,7,3',4'-Tetrahydroxyflavone) (flavonol)	<i>Rhus cotinus</i> , <i>R. rhodantha</i> (Anacardiaceae), <i>Acacia</i> spp. (Fabaceae) [heartwood]; as glycosides in <i>Rhus succedanea</i> (Anacardiaceae) [wood], <i>Dalbergia odorifera</i> [wood], <i>Trifolium subterraneum</i> (Fabaceae)	HIV-1 INT (9; 28) (ITDI, HIV-1 PR, LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TPO) [allergenic, antibacterial, apoptotic, inhibits SM contraction & histamine release]
Gallic acid flavon-3-yl esters (phenol)	Widespread	HIV-1 INT
Hypericin (bianthraquinone)	<i>Hypericum perforatum</i> , <i>H.</i> spp. (Hypericaceae)	HIV-1 INT (CDPK, EGF-RTK, MLCK, PI3K, PKA, PKC) [photosensitizing, red pigment]

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) /in vivo effects
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium graveolens</i> (Apiaceae); widespread as glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	HIV-1 INT (25; 33) (ACE, AR, AROM, HIV-1 PR, ITDI, NADH DH, Na ⁺ , K ⁺ -ATPase, Nase, NEP, PK, succinate DH, TOPII, TPO) [antibacterial, AI, apoptotic, nodulation signal]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Haplopappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Azadirachta indica</i> , <i>Soymidia febrifuga</i> (Meliaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	HIV-1 INT (3; 8) (AROM, DNAL, DNAP, F ₁ -ATPase, HIV-1 PR, HIV-1 RT, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, Nase, NEP, PGK, PK, 5αR, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic, apoptotic]
Myricetrin (= Myricetin 3-O-rhamnoside; 3,5,7,3',4',5'-Hexahydroxyflavone 3-O-rhamnoside;) (flavonol O-glycoside)	<i>Myrica rubra</i> (Myricaceae) [bark], <i>Myrica multiflora</i> (Myrtaceae) [leaf]	HIV-1 INT (10; 40) (AR) [antibacterial, AI (TPA induced)]
Purpurin (anthraquinone)	<i>Rubia tinctorum</i> , <i>R. cordifolia</i> , <i>Galium</i> spp., <i>Asperula odorata</i> , <i>Relbunium hypocarpum</i> (Rubiaceae); glycoside in <i>Rubia tinctorum</i> (Rubiaceae) [root]	HIV-1 INT (CDPK, MLCK, PKA, PKC) [genotoxic, pigment]
Purpurogallin (bicyclic phenolic)	<i>Dryophanta divisa</i> gall on <i>Quercus pedunculata</i> (Fagaceae)	HIV-1 INT (EGF-RTK, PEP, XO) [antioxidant, red pigment]
Quercetagetin (= 6-Hydroxyquercetin; 3,5,6,7,3',4'-Hexahydroxyflavone) (flavonol)	<i>Eupatorium gracile</i> , <i>Tagetes erecta</i> , <i>T. patula</i> (Asteraceae), other Asteraceae [flower], <i>Acacia catechu</i> (Fabaceae); glycosides in <i>T. erecta</i> (marigold) (Asteraceae) [flower]	HIV-1 INT (0.8) (AR, F ₁ -ATPase, Na ⁺ , K ⁺ -ATPase, PK, TOPII) [antibacterial, yellow pigment]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koelreutetia henryi</i> (Sapindaceae); widespread as glycosides	HIV-1 INT (LOX, PK) [AI, apoptotic feeding stimulant]
Quercetin 3-O-(2'',6''-O-digalloyl)-β-D-galactopyranoside (flavonol glycoside)	<i>Acer okamotoanum</i> (Aceraceae) [leaf]	HIV-1 INT (24; 31)
Quercetin 3-O-(2''-O-galloyl)-α-1-arabinopyranoside (flavonol glycoside)	<i>Acer okamotoanum</i> (Aceraceae) [leaf]	HIV-1 INT (30)

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part/	Enzyme inhibited (other targets) /in vivo effects/
[Quinalizarin (= 1,2,5,8-Tetrahydroxy-9,10-anthraquinone)] (anthraquinone)	Semi-synthetic from Alizarin	HIV-1 INT (CDPK, MLCK, PKA, PKC)
Robinetin (= 3,7,3',4',5'-Pentahydroxyflavone) (flavonol)	<i>Acacia mearnsii</i> , <i>Gleditsia monosperma</i> , <i>Milletia stuhlmannii</i> , <i>Robinia pseudacacia</i> (Fabaceae)	HIV-1 INT (2; 6) (cAMP PDE) [antibacterial]
Rosmarinic acid (phenylpropanoid)	<i>Anethum</i> , <i>Astrantia</i> , <i>Levisticum</i> , <i>Sanicula</i> (Apiaceae), <i>Symphytum</i> (Boraginaceae), <i>Agastach</i> , <i>Melissa</i> , <i>Mentha</i> , <i>Ocimum</i> , <i>Rosmarinus</i> , <i>Teucrium</i> , <i>Salvia</i> (Lamiaceae), spp.	HIV-1 INT (28) (AC, AR, COX-1, COX-2, Gonadotropin release) [AI; antiviral]
Other		9.5Ao
<i>Vigna</i> AFP (protein)	<i>Vigna</i> (cowpea) (Fabaceae) [seed]	HIV-1 INT (HIV-1 RT)
<i>Arachis</i> AFP (protein)	<i>Arachis hypogaea</i> (peanut) (Fabaceae)	HIV-1 INT (HIV-1 RT)
<i>Gelonium</i> GAP 31 (31 kDa)	<i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	HIV-1 INT (< 5) (RIP) [anti-HIV-1 (0.3 nM); not cytotoxic]
<i>Luffa</i> Luffin (~30 kDa)	<i>Luffa cylindrica</i> (Cucurbitaceae)	HIV-1 INT (< 5) (PAG)
<i>Momordica</i> α -Momorcharin (30 kDa; basic; glycoprotein)	<i>Momordica cochinchinensis</i> (Cucurbitaceae) [seed]	HIV-1 INT (> 5) (PAG, PSI)
<i>Momordica</i> β -Momorcharin (30 kDa; basic; glycoprotein)	<i>Momordica cochinchinensis</i> (Cucurbitaceae) [seed]	HIV-1 INT (< 5) (PAG, PSI)
<i>Momordica</i> Momorcochin-S (30 kDa; basic; glycoprotein)	<i>Momordica cochinchinensis</i> (Cucurbitaceae) [seed]	HIV-1 INT (1) (PAG, PSI)
<i>Saponaria</i> Saporin (~30 kDa)	<i>Saponaria officinalis</i> (Caryophyllaceae) [leaf]	HIV-1 INT (< 5) (PAG)
<i>Trichosanthes</i> α -Trichosanthin (~30 kDa)	<i>Trichosanthes kirilowii</i> (Cucurbitaceae) [seed]	HIV-1 INT (< 5) (PAG, PSI)
Non-plant reference		9.5An
[Cyclodidemniserinol] (sulfated serinolipid)	<i>Didemnum guttatum</i> (ascidian)	HIV-1 INT
[dG4-containing oligonucleotide] (dsDNA)	Synthetic	HIV-1 INT (at 10 nM)
[Equisetin] (acyl tetramic acid)	<i>Fusarium</i> fungus toxin	HIV-INT
[HCKFWW] (hexapeptide)	Synthetic	HIV-1 INT
[Integric acid] (eremophilane sesquiterpene)	<i>Fusarium heterosporum</i> (fungus)	HIV-1 INT
[Lamellarin α 20-sulphate] (alkaloid)	Ascidian	HIV-1 INT
[4,5,4',5'-Tetrahydroxylignanolid] (lignanolid, lactone)	Synthetic; homologue of naturally occurring plant lignanolides	HIV-1 INT
[Tyrphostins] (phenolics)	Synthetic	HIV-1 INT (RTK)

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) /in vivo effects
Reverse transcriptase (RT)	Retroviral RNA-dependent DNA polymerase discovery by Howard Temin & David Baltimore (USA, Nobel Prize, Medicine, 1975, reverse transcriptase)	9.5B
Alkaloid		9.5Ba
Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> sp. (Annonaceae), <i>Berberis vulgaris</i> , <i>B.</i> sp., <i>Hydrastis canadensis</i> , <i>Mahonia</i> sp., <i>Nandina</i> sp. (Berberidaceae), <i>Archangelica</i> sp. (Menispermaceae), <i>Argemone</i> sp., <i>Chelidonium</i> sp., <i>Corydalis</i> sp. (Papaveraceae), <i>Coptis</i> sp., <i>Thalictrum</i> sp. (Ranunculaceae), <i>Evodia</i> sp., <i>Toddalia</i> sp., <i>Zanthoxylum</i> sp. (Rutaceae)	HIV-1 RT (179) (α 1A-R, (α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA, 5HT2-R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
Buchapine (quinoline)	<i>Euodia roxburghiana</i> (Rutaceae) [leaf, flower, stem]	HIV-1 RT (12)
<i>Euodia</i> quinolone (quinoline)	<i>Euodia roxburghiana</i> (Rutaceae) [leaf, flower, stem]	HIV-1 RT (8)
Fagaronine (benzophenanthridine)	<i>Zanthoxylum zanthoxyloides</i> (<i>Fagara xanthoxylum</i>) (Rutaceae)	HIV-1 RT (29) (DNAL) [antibacterial, antitumour]
Littoraline (alkaloid)	<i>Hymenocallis littoralis</i> (Amaryllidaceae)	HIV-1 RT
Michellamine B (isoquinoline)	<i>Ancistrocladus korupensis</i> (Ancistrocladaceae)	HIV-1 RT & HIV-2 RT [antiviral, HIV inhibition, inhibits cellular formation & syncytium formation]
O-Methylpsychotrine (emetine isoquinoline)	<i>Cephaelis ipecacuanha</i> (ipecacuanha) (Rubiaceae)	HIV-1 RT (32)
Palmatine (benzophenanthridine)	<i>Berberis</i> , <i>Mahonia</i> spp. (Berberidaceae), <i>Jateorrhiza palmata</i> (Menispermaceae); Papaveraceae	HIV-1RT & AMV, RLV & SSV RTs
Psychotrine (emetine isoquinoline)	<i>Alangium lamarckii</i> (Alangiaceae) [bark, root, seed], <i>Cephaelis ipecacuanha</i> (ipecacuanha), <i>C. acuminata</i> (Rubiaceae) [root]	HIV-1 RT (39)
Sanguinarine (=Pseudochelerythrine) (benzophenanthridine)	<i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> , <i>Sanguinaria canadensis</i> (Papaveraceae), <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	HIV-1 RT (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, DNA, 5HT2-R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, AI]
Phenolic		9.5Bp
Agathisflavone (= 6',8"-Biapigenin)	<i>Agathis dammara</i> , <i>Araucaria bidwillii</i> (Araucariaceae)	HIV-1 RT (100) (cAMP PDE)
Amentoflavone (3',8"-Biapigenin) (biflavone)	<i>Cycas revoluta</i> (cycad) (Cycadaceae), <i>Podocarpus montanus</i> (Podocarpaceae), <i>Rhus succedanea</i> (Anacardiaceae)	HIV-1 RT (119), AMV RT (at 60) (cAMP PDE, BZ-R, cGMP PDE, RT) [antifungal]

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) /in vivo effects/
(-)-Arctigenin (lignan)	<i>Ipomoea cairica</i> (Convolvulaceae)	HIV-1 RT [metabolites inhibit HIV-INT]
Baicalein (= 5,6,7-Trihydroxyflavone) (flavone)	<i>Scutellaria</i> spp. (Lamiaceae) [root, leaf], <i>Oroxylum indicum</i> (Bignoniaceae) [leaf]	HIV-1RT (< 7), RLV RT (< 4) (AROM, PKC signalling, TOPII) [apoptotic]
Baicalin (flavone O-glycoside)	<i>Scutellaria baicalensis</i> (Lamiaceae) [root]	HIV-1 RT [anti-clotting]
(+)-Calanolide A (dipyrancoumarin)	<i>Calophyllum lanigerum</i> (Guttiferae)	HIV-1 RT [70 nM]
(-)-Calanolide B (pyranocoumarin)	<i>Calophyllum lanigerum</i> , <i>C. cerasiferum</i> (Guttiferae)	HIV-1 RT
Cordatolide A (pyranocoumarin)	<i>Calophyllum cordato-oblongum</i> (Guttiferae)	HIV-1 RT (12)
Cordatolide B (pyranocoumarin)	<i>Calophyllum cordato-oblongum</i> (Guttiferae)	HIV-1 RT (19)
Costatolide (coumarin)	<i>Calophyllum inophyllum</i> (Guttiferae) [seed]	HIV-1 RT
Digallic acid (phenolic)	<i>Phyllanthus emblica</i> (Euphorbiaceae) [fruit]	HIV-1 RT (< 2) & MLV RT (DNAP)
1,6-Di-O-galloyl- β -D-glucose (phenolic)	<i>Phyllanthus emblica</i> (Euphorbiaceae) [fruit]	HIV-1 RT
(+)-Dihydrocalanolide A (pyranocoumarin)	<i>Calophyllum lanigerum</i> (Guttiferae)	HIV-1 RT
(-)-Epicatechin-3-gallate (flavan-3-ol, gallotannin)	<i>Camellia sinensis</i> (tea leaf) (Theaceae)	RT (TOPII)
(-)-Epigallocatechin-3-gallate (= EGCG) (flavan-3-ol, gallotannin)	<i>Davidsonia pruriens</i> (Davidsoniaceae), <i>Hamamelis virginiana</i> (Hamamelidaceae), <i>Camellia sinensis</i> (Theaceae)	RT (β -A R, D1-R, D2-R, O-R, PKC, TOPII) [AI, blocks COX-2 & iNOS induction]
GB-1a-7''-O- β -glucoside (biflavone glycoside)	<i>Garcinia multiflora</i> (Guttiferae)	HIV-1 RT (236)
GB-2a (biflavone)	<i>Garcinia multiflora</i> (Guttiferae)	HIV-1 RT (170)
(-)-Gomisin (dibenzocyclooctadiene lignan)	<i>Schisandra chinensis</i> (Schisandraceae) [fruit]	HIV-1 RT (150)
<i>Haplophyllum</i> lignan (tetrahydronaphthalene lignan)	<i>Haplophyllum ptilostylum</i> (Rutaceae)	HIV-1 RT (33)
Hinokiflavone (biflavone)	<i>Rhus succedanea</i> (Anacardiaceae), <i>Cycas revoluta</i> (Cycadaceae), <i>Cupressus funebris</i> (Cupressaceae), <i>Podocarpus macrophyllum</i> (Podocarpaceae), <i>Selaginella tamariscina</i> (Selaginellaceae)	HIV-1 RT (65) (cAMP PDE)
Hypericin (bianthraquinone)	<i>Hypericum perforatum</i> (St John's wort), <i>H. spp.</i> (Hypericaceae)	HIV-1 RT (0.8) (CDPK, EGF-RTK, HIV-1 INT, PI3K, PK) [inhibits HIV-1 budding, photosensitizing, red pigment]
Inophyllum B (coumarin)	<i>Calophyllum inophyllum</i> (Guttiferae) [seed]	HIV-1 RT [42 nM]

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) /in vivo effects
Inophyllum P (coumarin)	<i>Calophyllum inophyllum</i> (Guttiferae) [seed]	HIV-1 RT
β -Lapachone (α -naphthoquinone)	<i>Haplophragma adenophyllum</i> , <i>Phyllanthron comorense</i> [wood], <i>Tabebuia avellanadae</i> [wood] (Bignoniaceae), <i>Tectona grandis</i> (Verbenaceae) [root]	RT (iNOS, TOP) [AI, antimicrobial, antitumour]
Macrocarpal A (phloroglucinol)	<i>Eucalyptus globulus</i> , <i>E. macrocarpa</i> [leaf] (Myrtaceae)	HIV-1 RT [antibacterial (Gram-positive)]
Macrocarpal B (phloroglucinol)	<i>Eucalyptus globulus</i> , <i>E. macrocarpa</i> [leaf] (Myrtaceae)	HIV-1 RT [antibacterial (Gram-positive)]
Macrocarpal C (phloroglucinol)	<i>Eucalyptus globulus</i> (Tasmanian blue gum) [leaf, calyx] (Myrtaceae)	HIV-1 RT
Macrocarpal D (phloroglucinol)	<i>Eucalyptus globulus</i> , <i>E. macrocarpa</i> (Myrtaceae)	HIV-1 RT [antibacterial (Gram-positive)]
Macrocarpal E (phloroglucinol)	<i>Eucalyptus globulus</i> (Tasmanian blue gum) [leaf, calyx] (Myrtaceae)	HIV-1 RT
Mallotochromene (phloroglucinol, chromene)	<i>Mallotus japonicus</i> (Euphorbiaceae)	HIV-1 RT (< 40)
Mallotojaponin (phloroglucinol, chromene)	<i>Mallotus japonicus</i> (Euphorbiaceae)	HIV-1 RT (< 40)
Morelloflavone (flavanonylflavone, biflavonoid)	<i>Garcinia morello</i> , <i>G. multiflora</i> (Guttiferae)	HIV-1 RT (116) (AO/FRS, PLA ₂ [anti-HIV-1 (7)])
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Haplophragma canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Azadirachta indica</i> , <i>Soymidia febrifuga</i> (Meliaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	HIV-1 RT (< 7), RLV RT (< 4) (DNAL, DNAP, F ₁ -ATPase, IKK, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, 5 α R, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic, apoptotic]
Punicacortein C (gallotannin)	<i>Punica</i> sp. (Punicaceae)	HIV-1 RT (5) [inhibits HIV-1 cell adhesion]
Punicalin (gallotannin)	<i>Terminalia catappa</i> (Combretaceae), <i>Punica granatum</i> (Punicaceae)	HIV-1 RT (8) (AO/FRS, CA) [inhibits HIV-1 cell adhesion]
Putranjivain (hydrolysable tannin)	<i>Phyllanthus emblica</i> (Euphorbiaceae) [fruit]	HIV-1 RT (4) (DNAP)
Quercetagetin (= 6-Hydroxyquercetin; 3,5,6,7,3',4'-Hexahydroxyflavone) (flavonol)	<i>Eupatorium gracile</i> , <i>Tagetes erecta</i> , <i>T. patula</i> (Asteraceae), other Asteraceae [flower], <i>Acacia catechu</i> (Fabaceae); glycosides in <i>Tagetes erecta</i> (marigold) (Asteraceae) [flower]	HIV-1 RT (< 7), RLV RT (< 4) (AR, DNAP, F ₁ -ATPase, HIV-1 INT, Na ⁺ , K ⁺ -ATPase, PK, TOPII) [antibacterial, yellow pigment]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	HIV-1 RT (< 7), RLV RT (< 4), AMV RT (at 60) (AR, cAMP PDE, CFTR, DNAP, F ₁ -ATPase, 11 β HSDH, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, NEP, PK, PS-EF-1 α , RTK, TOPII) [allergenic, antibacterial, AI, antiviral]

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) /in vivo effects/
Repandusinic acid (hydrolysable tannin)	<i>Mallotus repandus</i> , <i>Phyllanthus niruri</i> (Euphorbiaceae)	HIV-1 RT (50nM) (DNAPOL) [anti-HIV-1 (at 10)]
Robustaflavone (= 3',6"-Biapigenin) (biflavone)	<i>Araucaria</i> spp. (Araucariaceae), <i>Juniperus</i> spp. (Cupressaceae), <i>Rhus succedanea</i> (Anacardiaceae)	HIV-1 RT (65) (cAMP PDE)
Scutellarein (= 6-Hydroxyapigenin) (flavone)	<i>Pulicaria rivularis</i> (Asteraceae), <i>Scutellaria</i> spp. (Lamiaceae), <i>Asphodeline</i> spp. (Liliaceae), <i>Digitalis orientalis</i> (Scrophulariaceae), <i>Citrus sinensis</i> (Rutaceae); glycosides in Asteraceae, Lamiaceae, Rosaceae	HIV-1 RT (at 60)
Shephagenin A (hydrolysable tannin)	<i>Shepherdia argentea</i> (Elaeagnaceae) [leaf]	HIV-1 RT (49nM)
Shephagenin B (hydrolysable tannin)	<i>Shepherdia argentea</i> (Elaeagnaceae) [leaf]	HIV-1 RT (74nM)
Soulatrolide (coumarin)	<i>Calophyllum teysmannii</i> (Guttiferae) [latex]	HIV-1 RT (0.3) (no inhibition of DNAP α , DNAP β , HIV-2 RT, AMV RT or RNAP)
Swertifrancheside (= 1,5,8-Trihydroxy-3-methoxy-7-(5',7',3",4"-tetrahydroxy-6'-C- β -D-glucopyranosyl-4'-oxy-8'-flavyl)-xanthone) (flavone-xanthone C-glycoside)	<i>Svertia franchetiana</i> (Gentianaceae)	HIV-1 RT (43) (DNA)
β -1,2,3,6-Tetra-O-galloyl-D-glucose (gallotannin)	<i>Juglans mandshurica</i> (walnut) (Juglandaceae) [stem bark]	HIV-1 RT (40nM) & RNase H (39)
Tetragalloylquinic acids (hydrolysable tannins)	Plant	HIV-1 RT (< 100)
(-)-Trachelogenin (lignan)	<i>Ipomoea cairica</i> (Convolvulaceae)	HIV-1 RT (Ca ²⁺ -CH) [metabolites inhibit HIV-INT]
β -1,2,6-Tri-O-galloyl-D-glucose (gallotannin)	<i>Quercus</i> spp. (Fagaceae) [bark], <i>Juglans mandshurica</i> (walnut) (Juglandaceae) [stem bark]	HIV-1 RT (67 nM) (α 2A-R, β A-R, D1-R, 5HT2-R, O-R)
1,4,8-Trihydroxynaphthalene 1-O- β -D-glucopyranoside (naphthalenyl glycoside)	<i>Juglans mandshurica</i> (walnut) (Juglandaceae) [stem bark]	HIV-1 RT (290) & RNase H (156)
4 α ,5,8-Trihydroxy- α -tetralone-5-O- β -D-[6'-O-(3",4",5"-trihydroxybenzoyl)]-glucopyranoside (tetralonyl glycoside)	<i>Juglans mandshurica</i> (walnut) (Juglandaceae) [stem bark]	HIV-1 RT (6)
Terpene [Betulin diacetate] (triterpene ester)	Semi-synthetic from Betulin	9.5Bt HIV-1 RT (1)
Cycloartenol ferulate (triterpene ferulic ester)	Cycloartenol & ferulic acid key plant compound precursors	HIV-1 RT (2)

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part/	Enzyme inhibited (other targets) /in vivo effects/
16 α ,17-Dihydroxy-ent-kaurane-19-oic acid (kaurane diterpene)	<i>Annona glabra</i> (Annonaceae) [fruit]	HIV-1 RT
<i>Euphorbia</i> diterpenoid ester 1 (diterpene)	<i>Euphorbia myrsinites</i> (Euphorbiaceae)	HIV-1 RT (125)
<i>Euphorbia</i> diterpenoid ester 2 (diterpene)	<i>Euphorbia myrsinites</i> (Euphorbiaceae)	HIV-1 RT (103)
β -Hydroxyaleuritic acid 3- <i>p</i> -hydroxybenzoate (triterpene)	<i>Mafrounea africana</i> (Euphorbiaceae) [root]	HIV-1 RT (4)
Karounidiol 29-benzoate (triterpene)	<i>Trichosanthes kirilowii</i> (Cucurbitaceae)	HIV-1 RT (2)
Lupenone (lupane triterpene)	<i>Albizia gummifera</i> (Fabaceae) [stem bark]	HIV-1 RT (2)
24-Methylenecycloartenol ferulate (triterpene ferulic ester)	Cycloartenol & ferulic acid key plant compound precursors	HIV-1 RT (2)
Nigranoic acid (= (3,4-Secocycloarta-4(28),24-(ζ)-diene-3,26-dioic acid) (A ring-secocycloartene triterpene)	<i>Schisandra sphaerandra</i> (Schisandraceae)	HIV-1 RT (40; 158)
Protolichesterinic acid (aliphatic α -methylene- γ -lactone)	<i>Cetraria islandica</i> (lichen)	HIV-1 RT (24)
Salaspermic acid (triterpene)	<i>Tripterygium wilfordii</i> (Celastraceae) [root]	HIV-1 RT (32)
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (triterpene)	Widespread; <i>Vaccinium macrocarpon</i> (cranberry), <i>Arctostaphylos uva-ursi</i> (bearberry) (Ericaceae), <i>Lavandula latifolia</i> <i>Prunella vulgaris</i> , <i>Rosmarinus officinalis</i> , <i>Salvia triloba</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Malus</i> sp. (apple), <i>Pyrus</i> sp. (pear) (Rosaceae) [fruit surface]	HIV-1 RT (CDPK, DNAPOL, PKA, PKC, TOPI, TOPII) [AI, cytotoxic, antineoplastic]
Other		9.5Bo
Cowpea AFP (protein)	<i>Vigna</i> (cowpea) (Fabaceae) [seed]	HIV-1 RT (HIV-1 INT)
Peanut AFP (protein)	<i>Arachis hypogaea</i> (peanut) (Fabaceae)	HIV-1 RT (HIV-1 INT)
Protolichesterinic acid (acetogenin, lactone)	<i>Cetraria islandica</i> (lichen) (Glaciomyceae)	HIV-1 RT (24)
Non-plant reference		9.5Bn
[AZT = 3'-Azido-3'-deoxythymidine; Zidovudine] (3'-deoxynucleoside)	Synthetic nucleoside reverse transcriptase inhibitor (NRTI); see below under NRTIs for other NRTIs in clinical use	[Metabolic conversion to the nucleoside 5'-triphosphate (AZT-TP) and incorporation of AZT-monophosphate (AZT-MP) into DNA gives DNA chain termination because of the absence of a 3'-hydroxyl]

(continued)

Table 9.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) /in vivo effects/
[Aphidicolin] (tetracyclic diterpene)	<i>Cephalosporium aphidicola</i> (fungus)	RT (potato mitochondria) (DNAP)
[Avarol/Avarone] (drimane sesquiterpene quinone/hydroquinone)	<i>Dysidea avara</i> (sponge)	HIV-1 RT [cytostatic, PAI]
[Coralyne] (protoberberine alkaloid)	Synthetic	RT (DNA, TOPI)
[Delavirdine (= Rescriptor; U- 90152)] (bis(heteroaryl)-piperazine)	Synthetic non-nucleoside RT inhibitor (NNRTI) in clinical use	HIV-1 RT [inhibits HIV-1 replication (~0.1)]
[Efavirenz (= DMP-266; Sustiva)] (benzoxazinone)	Synthetic non-nucleoside RT inhibitor (NNRTI) in clinical use	HIV-1 RT [inhibits HIV-1 replication (1 nM)]
[Etidium bromide (= 2,7- Diamino-10-ethyl-9-phenyl- phenanthridinium bromide)] (phenanthridinium)	Synthetic	RT (potato mitochondria) (DNA, DNAH, DNAS, RNAS)
[Fomitelic acid A] (triterpene)	<i>Fomitella fraxinea</i> (fungus) (Basidiomycete)	HIV-1 RT (DNAP, TOPI, TOPII) [inhibits NUGC cancer cell growth (38)]
[Fomitelic acid B] (triterpene)	<i>Fomitella fraxinea</i> (fungus) (Basidiomycete)	HIV-1 RT (DNAP, TOPI, TOPII)
[Illimaquinone] (sesquiterpene)	<i>Dactylosporgia elegans</i> (tropical marine sponge)	HIV-1 RT RNase H [weak anti- trypanosomal & anti-plasmodial]
[Nevirapine = Viramune] (dipyridodiazepinone)	Synthetic non-nucleoside RT inhibitor (NNRTI) in clinical use	HIV-1 RT (84 nM) [inhibits HIV-1 replication (40 nM)]
[NRTIs in clinical use: Abacavir (ABC); Adefovir dipivoxil (9-[2- Phosphonomethoxy]ethyl)- adenine; PMEA); AZT; Didanosine (= 2',3'- Dideoxyinosine); Lamivudine; Stavudine; Zalcitabine (2',3'- Dideoxycytidine)]	Synthetic nucleoside reverse transcriptase inhibitors (NRTIs) in clinical use; metabolic conversion to the nucleoside triphosphate (NTP) (via the nucleoside monophosphate (NMP) and diphosphate (NDP)) gives DNA chain termination because of absence of 3'-hydroxyl (Note: PMEA yields the phosphonate diphosphate; ABC → ABC-MP → Carbovir-MP → Carbovir-TP)	[Metabolic conversion to the nucleoside triphosphate (NTP) (or equivalent) and RT-catalysed incorporation into DNA of the NMP (or equivalent) gives DNA chain termination because of the absence of a 3'-hydroxyl]
[1,2,5,8- Tetrahydroxyanthraquinone] (anthraquinone)	Synthetic	HIV-1 RT (3)

Table 9.6 Actin, histone acetylase, histone deacetylase, cell division and tubulin

Compound (class)	Plant (family) part	Target inhibited (other targets) / in vivo effects
Actin cytoskeleton		
Cucurbitacin E (= α -Elaterine) (cucurbitacin, triterpene)	<i>Ecballium elaterium</i> (Cucurbitaceae), other Cucurbitaceae	9.6A Disrupts actin cytoskeleton (cell adhesion inhibitor) [attractant & feeding deterrent, antineoplastic, cytotoxic]
[Cytochalasin B] (aryl isoindole macrocyclic lactone)	<i>Helminthosporium dematioideum</i> (fungus)	Disrupts actin cytoskeleton; blocks cell division by blocking actin microfilament formation [inhibits Glc transport, toxic]
[Cytochalasins A-M] (aryl isoindole macrocyclics)	Fungi e.g. variously from <i>Aspergillus</i> , <i>Chalara</i> , <i>Helminthosporium</i> , <i>Metarrhizium</i> , <i>Phomopsis</i> , <i>Zygosporium</i> spp.	Disrupts actin cytoskeleton, inhibit mitosis [toxic]
[Goniodomin A] (polyether macrolide)	<i>Goniodoma pseudogoniaulax</i> (dinoflagellate)	Inhibits actin organization [anti-angiogenic, antifungal]
[Phalloidin] (0.8kDa cyclic peptide); Heinrich Otto Wieland (Germany, Nobel Prize, 1927, bile acids)	<i>Amanita phalloides</i> (mushroom)	Binds actin [hepatotoxic]
Histone acetyl transferase (HAT)		
<i>Glycine</i> lunasin (5kDa; 43 aa protein)	<i>Glycine max</i> (soya bean) (Fabaceae)	9.6B HAT [apoptotic, arrests mitosis per histone acetylation blockage, chemopreventive]
Histone deacetylase (HDA)		
[Apicidins B & C] (cyclic tetrapeptides)	<i>Fusarium</i> spp. (soil fungal plant pathogens)	9.6C HDA [antiprotozoal, apoptotic, cytotoxic]
Butyric acid (= Butanoic acid) (aliphatic carboxylic acid)	<i>Vitis vinifera</i> (grape) (Vitaceae); from colonic bacterial catabolism & important chemopreventive agent from digestion of roughage	HDA [anti-cancer, anti-mitotic, chemopreventive]
[HC toxin] (cyclic tetrapeptide epoxide)	<i>Cochliobolus carbonum</i> (maize pathogenic fungus)	HDA (at 2) [anti-mitotic, cytotoxic]
[Chlamydocin] (cyclic tetrapeptide epoxide)	<i>Diheterospora chlamydospora</i> (plant pathogenic fungus)	HDA [anti-mitotic, cytotoxic]
[Trichostatin A] (aminoaryl hydroxamate, X-CO-NH-OH)	<i>Streptomyces hygroscopicus</i> (fungus)	HDA [antibiotic, anti-mitotic]
Protein folding		
L-Canaline (= 2-Amino-4-(aminoxy)butyric acid) (amino acid)	<i>Canavalia ensiformis</i> (jackbean) (Fabaceae) [seed]	9.6D Protein folding – Lysine antimetabolite (OTCase, TRA) [lysine antimetabolite]
L-Canavanine (= 2-Amino-4-(guanidinoxy)butyric acid) (guanidino amino acid)	<i>Canavalia ensiformis</i> (jack bean) (Fabaceae)	Protein folding – impaired by Canavaliine incorporation (as Arginine analogue)

(continued)

Table 9.6 (Continued)

Compound (class)	Plant (family) part	Target inhibited (other targets) / in vivo effects/
Tubulin (TUB)		9.6E
Alkaloid		9.6Ea
Colchicine (benzoheptalene acetamide)	<i>Colchicum autumnale</i> , <i>C. spp.</i> , <i>Gloriosa superba</i> (Liliaceae); poison of Medea of Colchis; 18th century gout immortalized by artists William Hogarth & James Gillray; victims included Benjamin Franklin, Thomas Jefferson, Samuel Johnson & Immanuel Kant	TUB [antimitotic, carcinogen, disrupts MT assembly, irritant, irritant, teratogen]; Colchicine used for treating gout (joint uric acid accumulation)
3-Oxo-rhazinanil (indole)	<i>Rauwolfia serpentina</i> (Apocynaceae)	TUB [anti-mitotic, cytotoxic]
Rhazinanil (indole)	<i>Rauwolfia serpentina</i> (Apocynaceae)	TUB [anti-mitotic, cytotoxic]
Vinblastine (indole)	<i>Vinca rosea</i> (Madagascar periwinkle) (Apocynaceae)	TUB [anti-mitotic, cytotoxic, anticancer, antileukaemic, antitumour]
Vincristine (indole)	<i>Vinca rosea</i> (Madagascar periwinkle) (Apocynaceae)	TUB [anti-mitotic, antileukaemic, antitumour]
Phenolic		9.6Ep
Podophyllotoxin (= Podophyllinic acid lactone) (lignan)	<i>Callitris drummondii</i> , <i>Juniperus sabina</i> [needles], <i>J. virginiana</i> [shoot], <i>Diphylleia grayi</i> , <i>D. sinensis</i> [root], <i>Podophyllum hexandrum</i> , <i>P. peltatum</i> , <i>P. pleianthum</i> (Podophyllaceae) [rhizome]	TUB (TOPII) [anti-mitotic, antitumour, antiviral, cathartic]
Podophyllotoxin 1- <i>O</i> -glucoside (= Podophyllinic acid lactone 1- <i>O</i> -glucoside) (lignan)	<i>Podophyllum hexandrum</i> , <i>P. peltatum</i> , <i>P. pleianthum</i> (Podophyllaceae) [rhizome]	Yields Podophyllotoxin → TUB, TOPII [cytotoxic]
Terpene		9.6Et
Obacunone (= Casimirolide) (limonoid nortriterpene)	<i>Cneorum tricoccon</i> (Cneoraceae), <i>Trichilla trifolia</i> (Meliaceae), <i>Citrus spp.</i> , <i>Dictamnus dasycarpus</i> (Rutaceae), <i>Harrisonia abyssinica</i> (Sinaroubaceae)	Increases 10× effectiveness of TUB-acting Vinblastine, Vincristine & Taxol [bitter]
Other		9.6Eo
Maytansine (macrolide, cyclopeptide)	<i>Maytenus ovatus</i> , <i>M. senata</i> [fruit] <i>Putterlickia verrucosa</i> [wood] (Celastraceae)	TUB [anticancer, antileukaemic, anti-mitotic, cytotoxic]
Taxol (= Paclitaxel; Taxol A) (polycyclic peptide)	<i>Taxus brevifolia</i> , <i>T. cuspidata</i> , <i>T. spp.</i> (yew) (Taxaceae); Briton king Catuvolcus committed suicide by drinking yew sap	TUB [anticancer, antitumour, apoptotic, cytotoxic]
Non-plant reference		9.6En
[Cryptophycin A] (cyclic depsipeptide)	<i>Nostoc</i> (blue-green alga, cyanobacterium)	TUB [anticancer, anti-mitotic, cytotoxic]
[Griseofulvin] (benzofuran)	<i>Penicillium griseofulvin</i> (fungus)	TUB [antifungal, antimitotic, spindle poison]

Table 9.7 Apoptosis-inducing plant compounds

Compound (class)	Plant (family) [part]	Effect (other targets) / in vivo effects/
Apoptosis		9.7
Alkaloid		9.7a
Cepharanthine (biscoclaurine)	<i>Stephania cepharantha</i> (Menispermaceae)	Apoptotic [anti-angiogenic, cytotoxic]
Cryptolepine (indole)	<i>Cryptolepis sanguinolenta</i> , <i>C. triangularis</i> (Asclepiadaceae)	Apoptotic (DNA, TOPII) [hypotensive]
Homoharringtonine (cephalotaxine ester)	<i>Cephalotaxus harringtonia</i> , <i>C. spp.</i> (Cephalotaxaceae)	Apoptotic (PS) [antileukaemic, antitumour, hypotensive, myelosuppressive]
Irniine (pyrrolidine)	<i>Arisarum vulgare</i> (Araceae)	Apoptosis (DNA fragmentation) (at 40–50)
(–)-Lycorine (= Narcissine; Galanthidine) (galanthan Amaryllidaceae)	<i>Lycoris radiata</i> , <i>Narcissus spp.</i> (Amaryllidaceae); also as glycoside FA ester, acetic acid ester	Inhibits apoptosis induced by Calprotectin (PS) [antiviral, cytotoxic, highly toxic]
Neocryptolepine (indole)	<i>Cryptolepis sanguinolenta</i> (Asclepiadaceae)	Apoptotic (DNA, TOPII)
(+)-Tetrandine (bisbenzylisoquinoline)	<i>Cissampelos pareira</i> , <i>Cyclea peltate</i> , <i>Stephania tetrandia</i> , <i>S. discolor</i> (Menispermaceae)	Apoptotic (at 4) (V-Ca ²⁺ CH) [analgesic, AI, antipyretic, antitumour]
Usambarensine (indole)	<i>Strychnos usambarensis</i> (Loganiaceae) [root]	Apoptotic (DNA fragmentation) (mAChR, nAChR, DNA, RNA synthesis) [anti-amoebic, anticancer, antiplasmodial, poison, apoptotic, toxic]
Phenolic		9.7p
Artemetin (flavone)	<i>Vitex rotundifolia</i> (Verbenaceae) [fruit]	Apoptotic (DNA fragmentation) (31)
Baicalein (flavone)	<i>Scutellaria spp.</i> (Lamiaceae), <i>Oroxylum indicum</i> (Bignoniaceae)	Apoptotic (40) (AROM, TOPII)
Bavachinin (flavanone)	<i>Psoralea corylifolia</i> (babchi) (Fabaceae) [fruit]	Apoptotic (~100) [AI]
Butein (= 2',4',3,4-Tetrahydroxy-chalcone) (chalcone)	<i>Dalbergia odorifera</i> (Fabaceae) [wood]; glycosides in <i>Coreopsis</i> , <i>Bidens</i> (Asteraceae), <i>Butea</i> (Fabaceae) spp.	Apoptotic – caspase 3 activation (& DNA fragmentation) (EGF-RTK, F ₁ -ATPase, GST, p60 ^{c-src} TK, 5αR) [antioxidant]
Caffeic acid phenethyl ester (phenylpropanoid)	<i>Populus sp.</i> (Salicaceae), bee propolis	Apoptotic (AO/FRS, HIV-1 INT, 5-LOX) [AI, antioxidant, blocks NFκB activation]
Camelliin B (hydrolysable tannin)	<i>Gordonia axillaris</i> (Theaceae)	Apoptotic (DNA fragmentation) (~100)
Casuarinin (hydrolysable tannin)	<i>Eugenia jambos</i> (Myrtaceae); anti-pyretic & AI herb	Apoptotic (13) (DNA fragmentation)
Cleistanthin A (diphyllin glycoside)	<i>Cleistanthus collinus</i> (Euphorbiaceae)	Apoptotic (membrane blebbing) [cytotoxic]
3,4-Dihydroxyhydrocinnamic acid (phenolic acid)	<i>Citrus limon</i> (lemon) (Rutaceae) [fruit]	Apoptotic (DNA fragmentation)

(continued)

Table 9.7 (Continued)

Compound (class)	Plant (family) [part]	Effect (other targets) / in vivo effects/
(-)-Epicatechin 3- <i>O</i> -gallate (= ECG) (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae)	Apoptotic (AO/FRS, collagenase, EST-R, 5 α R) [apoptotic, asbestos-induced macrophage injury protectant (10)]
(-)-Epigallocatechin (= EGC) (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae)	Apoptotic (DNA fragmentation) (AO/FRS) [antitumour, cytotoxic]
(-)-Epigallocatechin-3-gallate (= EGCG) (flavanone)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea leaf) (Theaceae); green tea cancer chemopreventive	Apoptotic (DNA fragmentation) (AO/FRS) [asbestos-induced macrophage injury protectant (10), AI, blocks COX-2 & iNOS induction, cytotoxic, antitumour]
Eriodictyol (= 3',4',5,7-Tetrahydroxyflavanone) (flavanone)	<i>Eriodictyon californicum</i> (Hydrophyllaceae), <i>Citrus limon</i> (lemon) (Rutaceae) [fruit]	Apoptotic (DNA fragmentation)
Eupatilin (flavone)	<i>Artemisia asiatica</i> (Asteraceae) [herb]	Apoptotic (caspase 9 & 3 activation & DNA fragmentation)
Fisetin (= 5-Deoxyquercetin; 3,7,3',4'-Tetrahydroxyflavone) (flavonol)	<i>Rhus cotinus</i> , <i>R. rhodantha</i> (Anacardiaceae), <i>Acacia</i> spp. (Fabaceae) [heartwood]; as glycosides in <i>Rhus succedanea</i> (Anacardiaceae) [wood], <i>Dalbergia odorifera</i> [wood], <i>Trifolium subterraneum</i> (Fabaceae)	Apoptotic (~100) (ITDI, LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TPO) [allergenic, antibacterial, inhibits SM contraction & histamine release]
[Flavanone] (flavanone)	Synthetic	Apoptotic (~100)
Galic acid (= 3,4,5-Trihydroxybenzoic acid) (phenolic acid)	Widespread; component of gallotannins	Apoptotic [cytotoxic]
1- <i>O</i> -Galloyl castalagin (hydrolysable tannin)	<i>Eugenia jambos</i> (Myrtaceae); anti-pyretic & AI herb	Apoptotic (11) (DNA fragmentation)
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Trifolium</i> spp. (clover) (Fabaceae); glycosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora japonica</i> (Fabaceae)	Apoptotic (40) (AD-R, GABAA-R, lipase, peroxidase, Na ⁺ /K ⁺ /Cl ⁻ TR, PK, TOPII, TPO) [antifungal, apoptotic, oestrogenic]
β -Hydroxyisovalerylshikonin (naphthoquinone)	<i>Lithospermum erythrorhizon</i> (Boraginaceae)	Apoptotic (DNA fragmentation)
Hydroxytyrosol (= 2-(3,4-Dihydroxyphenyl)ethanol) (phenolic)	<i>Olea europaea</i> (olive) (Oleaceae) [seed oil]	Apoptotic (cytochrome <i>c</i> release & caspase 3 activation) (AO/FRS)
Hyperforin (phloroglucinol)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae); major herbal antidepressant	Apoptotic (caspase 3 & 9 activation) (D2-R, Steroid X R) [anti-neoplastic, cytotoxic]
Hypericin (bisanthraquinone)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae)	Apoptotic (caspase 3 & 9 activation) (at 0.2) [antineoplastic, cytotoxic, photosensitizer]

(continued)

Table 9.7 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
β -Lapachone (α -naphthoquinone)	<i>Haplophragma adenophyllum</i> , <i>Phyllanthron comorense</i> [wood], <i>Tabebuia avellaneda</i> [wood] (Bignoniaceae), <i>Tectona grandis</i> (Verbenaceae) [root]	Apoptotic (at < 8) (iNOS, RT, TOPI) [AI, antimicrobial, antitumour, cytotoxic]
Luteolin (= 5,7,3',4'- Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium graveolens</i> (Apiaceae); widespread as glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi- arid zone millet variety) (Poaceae) [seed]	Apoptotic (TOPII activation) (ACE, AR, AROM, ITD, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TOPII, TPO) [antibacterial, AI, nodulation signal]
Myricetin (= 3,5,7,3',4',5'- Hexahydroxyflavone) (flavonol)	<i>Haplophappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	Apoptotic (~100) (DNAL, F1 ATPase, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, 5 α R, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic]
[6] & [10]-Paradol (vanilloid phenolics)	<i>Zingiber officinale</i> (ginger) [rhizome] (Zingiberaceae)	Apoptotic [chemopreventive, pungent]
Peroxisomicine A (dimeric anthraceneone)	<i>Karwinskia humboldtiana</i> (Rhamnaceae)	Apoptotic (TOPOII)
Phloroglucinol (= 1,3,5- Benzenetriol) (phenolic)	<i>Citrus limon</i> (lemon) (Rutaceae) [fruit]	Apoptotic (DNA fragmentation)
Protocatechuic acid (phenolic)	<i>Hibiscus sabdariffa</i> (Malvaceae)	Apoptotic (DNA fragmentation)
Pseudohypericin (polycyclic phenolic)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae)	Apoptotic (caspase 3 & 9 activation) [antineoplastic, cytotoxic, photosensitizer]
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice]	Apoptotic (DNA fragmentation, TOPII activation) (HIV-1 INT, LOX, PK) [AI, feeding stimulant]
<i>trans</i> -Resveratrol (= 3,5,4'- Trihydroxystilbene) (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis</i> (Vitaceae) spp.	Apoptotic (per mitochondrial depolarization & caspase 9 activation) (AO/FRS, COX, LOX)
Shikonin (= 1'-R-isomer of Alkannin) (naphthoquinone)	<i>Echium lycopsis</i> , <i>Lithospermum erythrorhizon</i> [root], <i>Onosma caucasicum</i> (Boraginaceae)	Apoptotic (caspase activation, DNA fragmentation) (TOPI, TOPII) [red colour]
Tangeretin (= 5,6,7,8,4'- Pentamethoxyflavone) (flavone)	<i>Citrus</i> spp. (Rutaceae) [fruit]	Apoptotic (> 3) (DNA fragmentation) [growth suppression (0.2)]
Tea polyphenols (polyphenolics)	<i>Camellia sinensis</i> (tea) (Theaceae)	Apoptotic (DNA fragmentation)
Theaflavin (condensed tannin)	<i>Camellia sinensis</i> (tea) (Theaceae)	Apoptotic (DNA fragmentation)

(continued)

Table 9.7 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
Theaflavin digallate (tannin, polyphenolic)	<i>Camellia sinensis</i> (tea) (Theaceae)	Apoptotic (DNA fragmentation)
Theasinensin D (polyphenolic)	<i>Camellia sinensis</i> (tea) (Theaceae)	Apoptotic (DNA fragmentation)
2',3',5-Trihydroxy-3,6,7-trimethoxyflavone (flavone)	<i>Vitex rotundifolia</i> (Verbenaceae) [fruit]	Apoptotic (DNA fragmentation) (12)
Vitexicarpin (flavone)	<i>Vitex rotundifolia</i> (Verbenaceae) [fruit]	Apoptotic (DNA fragmentation) (0.1)
Terpene		9.7t
Alantolactone (sesquiterpene lactone)		Apoptotic [cytotoxic, phosphatidylserine migration]
Alisol B acetate (glucocorticoid-like triterpene)	<i>Alisma plantago-aquatica</i> (Alismataceae)	Apoptotic (at 10–100) [mitochondrial ψ_m depolarization]
Ambrosin (sesquiterpene lactone)	<i>Ambrosia artemisiifolia</i> , <i>A.</i> spp., <i>Hymenoclea</i> , <i>Iva</i> , <i>Parthenium</i> spp. (Asteraceae)	Apoptotic [cytotoxic, phosphatidylserine migration]
Avicin G (triterpene glycoside, saponin)	<i>Acacia victoriae</i> (Fabaceae)	Apoptotic – caspase 3 activation
Betulinic acid (lupene triterpene)	Widespread; <i>Syzygium claviflorum</i> (Myrtaceae) [leaf], <i>Rhododendron arboreum</i> (Ericaceae) [bark]	Apoptotic (AP, ATP-K ⁺ CH, CDPK, HIV-1 PR, PKA, PKC) [anti-neoplastic]
Borenolide (= 8-O-Acetyl-3,10-dihydroxy-4(15)-guaiaadien-12,6-olide) (guanolid)	<i>Chrysanthemum boreale</i> (Asteraceae)	Inhibits apoptosis induced by Etoposide
Bryonolic acid (triterpene)	<i>Trichosanthes kirilowii</i> (Cucurbitaceae)	Apoptotic (DNA fragmentation ladder)
Dioscin (terpene glycoside, saponin)	<i>Polygonatum zanlanscianense</i> (Liliaceae) [root]	Apoptotic [anti-neoplastic, cytotoxic]
[Diosgenin (= Nitogenin)] (steroid)	From hydrolysis of Gracillin <i>ex Dioscorea</i> spp. (Mexican yam) (Dioscoreaceae) [AI]; from some other steroid saponins	Apoptotic [G1 cell cycle arrest, NF κ B activation & COX-2 induction]; yam-derived diosgenin used \rightarrow progesterone \rightarrow cortisone
Farnesol (sesquiterpene)	Many plant oils	Apoptotic (DNA fragmentation)
Furanoditerpenoids (diterpenes)	<i>Teucrium</i> sp. (germander) (Lamiaceae); hepatotoxic & accordingly no longer used as a weight control herbal medicine	Apoptotic (after P450-mediated conversion to active entities)
Geraniol (= Lemonol) (monoterpene)	<i>Xylopi</i> a (Annonaceae), <i>Asarum</i> (Aristolochiaceae), <i>Andropogon</i> (Poaceae), <i>Rosa</i> (Rosaceae), <i>Citrus</i> (Rutaceae), <i>Litchi</i> (Sapindaceae), <i>Camellia</i> (Theaceae) spp., <i>Vitis vinifera</i> (Vitaceae)	Apoptotic (at 5000) (OD-R – floral, sweet rose) [antiseptic, apoptotic, insect attractant]
Ginkgolic acids (triterpenes)	<i>Ginkgo biloba</i> (Ginkgoaceae)	Quasi-apoptotic (cytotoxic but DNA fragmentation & caspase 3 activation not seen)

(continued)

Table 9.7 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
Ginsenoside Rh-2 (triterpene glycoside, saponin)	<i>Panax ginseng</i> (ginseng) (Araliaceae)	Apoptotic (per ROS, Bcl-xL independent)
Gypenoside (triterpene glycoside)	<i>Gymnostemma pentaphyllum</i> (Cucurbitaceae)	Apoptotic (Na ⁺ , K ⁺ -ATPase) [anti-neoplastic, cytotoxic]
Helenalin (pseudoguaianolide sesquiterpene lactone)	<i>Anaphalis</i> , <i>Balduina</i> , <i>Gaillardia</i> , <i>Helenium</i> spp. (Asteraceae)	Apoptotic (AROM) [cytotoxic, phosphatidylserine migration]
Hymenin (sesquiterpene lactone)	<i>Parthenium confertum</i> (Asteraceae)	Apoptotic [cytotoxic, phosphatidylserine migration]
Methylprotodioscin (terpene glycoside, saponin)	<i>Polygonatum zanlanscianense</i> (Liliaceae) [root]	Apoptotic [anti-neoplastic, cytotoxic]
Remangiolones A & C (noroleane triterpenes)	<i>Physena madagascariensis</i> (Capparidaceae) [leaf]	Apoptotic (at 2) [cytotoxic]
Rotundifuran (labdane diterpene)	<i>Vitex rotundifolia</i> (Verbenaceae) [fruit]	Apoptotic (DNA fragmentation) (23) [chemopreventive]
β-Sitosterol (phytosterol)	In plant plasma membranes	Apoptotic
Tigogenin hexasaccharide- 1 & 2 (steroidal saponins)	<i>Camassia cusickii</i> (Liliaceae) [bulb]	Apoptotic [anti-neoplastic, cytotoxic (60nM)]
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (ursane triterpene)	<i>Calluna vulgaris</i> , <i>Arctostaphylos</i> <i>uva-ursi</i> , <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Plantago major</i> (Plantaginaceae), <i>Prunella vulgaris</i> (Labiatae), <i>Malus</i> sp., <i>Pyrus</i> sp. (Rosaceae) [fruit waxy coat]	Apoptotic (COX-1, COX-2, 5-LOX) [AI, chemopreventive, cytotoxic, anti-leukaemic]
Other		9.7o
<i>Abrus</i> Abrins (toxic lectins) (~60 kDa; S-S-linked ~30 kDa subunits)	<i>Abrus precatorius</i> , <i>A. pulchellus</i> (abrin, jequirity bean) (Fabaceae) [seed]	Apoptotic (Gal-specific lectin) [toxic]
<i>Agrostemma</i> Agrostin (~30 kDa)	<i>Agrostemma githago</i> (Caryophyllaceae) [seed]	Apoptotic (DNA fragmentation) (PAG)
Ajoene (alkene sulfide)	<i>Allium sativum</i> (garlic) (Alliaceae) [bulb]	Apoptotic (caspase 3 activation)
<i>Canavalia</i> lectin (protein)	<i>Canavalia brasiliensis</i> (Fabaceae)	Apoptotic [inflammatory]
Diallyldisulfide (alkyl disulfide)	<i>Allium cepa</i> (onion), <i>A. sativum</i> (garlic) (Alliaceae) [bulb]	Apoptotic – caspase 3 activation [antifungal]
Diethylhexylphthalate (aliphatic diester)	<i>Aloe vera</i> (Liliaceae)	Apoptotic [anti-neoplastic]
<i>Dioclea</i> lectins (proteins)	<i>Dioclea violacea</i> , <i>D. grandiflora</i> (Fabaceae)	Apoptotic [inflammatory]
Ethylene (= CH ₂ =CH ₂) (alkene)	Volatile signal in plants	Apoptotic (DNA fragmentation) (plants)
Goniothalamin (styrylpyrone)	<i>Goniothalamus andersoni</i> (Annonaceae)	Apoptotic – caspase 3 activation, poly(ADPribose) polymerase cleavage
Isothiocyanates (= R-N=C=S) (isothiocyanate)	From glucosinolates	Apoptotic (but protective in some cells)

(continued)

Table 9.7 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
Se-Methylselenocysteine (seleno amino acid)	<i>Oenopsis condensata</i> (Asteraceae), <i>Astragalus bisulcatus</i> (Fabaceae) – selenium (Se) accumulating plants	Apoptotic – caspase 3 activation [animal blind stagers, anti-carcinogenic chemopreventative, selenosis]
1-Monolinolenin, sodium (glycerol ester)	<i>Lolium multiflorum</i> (Italian ryegrass) (Poaceae)	Apoptotic (DNA fragmentation)
Osmotin (PR protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	Apoptotic (yeast <i>Saccharomyces cerevisiae</i>)
<i>Ricinus</i> Ricin (65 kDa; A [32 kDa PAG toxin] S–S-linked to B [34 kDa glycoprotein lectin; binds toxin (A) to PM])	<i>Ricinus communis</i> , <i>R. sanguineus</i> (Euphorbiaceae) [castor bean seed]; Bulgarian dissident Georgi Markov murdered in London by ricin-tipped umbrella (1978)	Apoptotic (PAG RIP) (DNA GAAL (SS DNA); PSI; galactose-specific [toxic; apoptotic, cytotoxic, PSI]
<i>Saraca</i> lectin (protein)	<i>Saraca indica</i> (Fabaceae) [seed]	Apoptotic [mitogenic]
Sulfoquinovosyldiacyl- glycerol (sulfolipid)	Photosynthetic organisms; membrane lipid	Apoptotic (DNA fragmentation)
Taxol (= Paclitaxel; Taxol A) (polycyclic peptide)	<i>Taxus brevifolia</i> , <i>T. cuspidata</i> , <i>T. spp.</i> (yew) (Taxaceae); very toxic	Apoptotic (TUB) [anticancer, antitumour, cytotoxic]
<i>Viscum</i> lectins MLI, MLII & MLIII (~60 kDa; A[~30 kDa PAG] S–S-linked to B [~30 kDa lectins])	<i>Viscum album</i> (mistletoe) (Viscaceae)	Apoptotic (DNA fragmentation) (PS) [PAG (rRNA); cytotoxic]
<i>Viscum</i> polysaccharide (polysaccharide)	<i>Viscum album</i> (mistletoe) (Viscaceae)	Apoptotic (DNA fragmentation; caspase 3 activation (binds carbohydrate) (PS) [cytotoxic]
<i>Viscum</i> viscotoxin (5 kDa)	<i>Viscum album</i> (mistletoe) (Viscaceae)	Apoptotic (DNA fragmentation) (PS) [cytotoxic]
Non-plant reference		9.7n
[Acetyl-Asp-Glu-Val- Asp- α -aldehyde] (peptide)	Synthetic	Anti-apoptotic caspase 3 inhibitor
[Actinomycin D] (cyclic peptide)	<i>Streptomyces chrysomallus</i> (fungus) (Actinomycete)	Variously apoptotic & anti-apoptotic (DNA, DNAS, RNAS (TOPII) [antineoplastic]
[Δ^6 -Benzyladenosine] (purine nucleoside)	Synthetic	Apoptotic [mitogenic cytokinin in plants]
[Brefeldin A] (macrocyclic alicyclic lactone)	<i>Penicillium brefeldianum</i> (fungus)	Apoptotic [inhibits protein trafficking from Golgi]
[Calprotectin] (Ca ²⁺ -binding ectoprotein)	Animals <i>ex</i> leucocytes	Apoptotic
[Cycloheximide] (alicyclic piperidinedione)	<i>Streptomyces griseus</i> (fungus) (Actinomycete)	Variously apoptotic & anti- apoptotic (80S PS) [fungicide]
[Fumonisin B1] (sphingoid-like mycotoxin)	<i>Fusarium moniliforme</i> (fungal pathogen on Poaceae)	Apoptotic (TNF pathway, caspase activation)

(continued)

Table 9.7 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Effect (other targets) / in vivo effects </i>
[Gliotoxin] (pyrazinoindole disulfide)	<i>Trichoderma, Aspergillus, Gladiocladium & Penicillium</i> (fungi) spp.	Apoptotic [antibiotic]; structure by Robert Woodward (1959) (USA, chemist; Nobel Prize, 1965)
[20- <i>O</i> -(β-D-Glucopyranosyl)- 20(<i>S</i>)-protopanaxadiol] (triterpene glucoside, saponin)	Metabolite (human, rat) of Ginsenoside Rb1 & Rb2 from <i>Panax ginseng</i> (ginseng) (Araliaceae)	Apoptotic (24) (cytochrome <i>c</i> release, caspase 3 activation, DNA fragmentation)
[Tunicamycins] (uridine glycosides)	<i>Streptomyces</i> spp. (fungi)	Apoptotic (<i>N</i> -linked protein glycosylation inhibitors)

10 Taste and smell perception, pheromones and semiochemicals

10.1 Introduction

Plants are ultimately consumed by prokaryotes and non-plant eukaryotes and defend themselves through physical barriers and chemical defences. However, as detailed elsewhere in this book, it is more effective to discourage rather than to kill an enemy and hence the preponderance of plant defensive compounds that act on the signal transduction systems of plant-consuming organisms. This bias is most exquisitely reflected in the huge variety of plant substances that we can sense through taste and smell. Of course, we “perceive” the effects of plant defensive substances through their physiological effects, whether these be mediated by, for example, specific hormone receptors or particular enzymes. However, in this chapter, we will be concerned with plant compounds that interact with taste receptors and odour receptors and, further, with plant “semiochemicals” that mimic or antagonize animal pheromones or otherwise alter animal behaviour in a relatively benign fashion. Before dealing with the biochemical mechanisms involved in taste, odour and semiochemical perception it is useful to delineate the rationales for the production of such compounds by plants.

Plants are sessile and accordingly need to disperse seed and pollen. They use animal vectors for such dispersal and accordingly need to attract animals to flowers and fruit. Plants attract animals through provision of readily metabolized sugars and through attractive colour, smell and taste. Conversely, plants need to protect their primary photosynthetic (leaf), nutrient acquiring (root) and scaffold (stem, wood) arrays using defensive chemicals in general but also using the deterrents of unpleasant odour and taste. A further complexity arises because animals, notably insects, regulate their mutual behaviour through volatile sex pheromones (which affect female or male attraction, mating and egg laying or oviposition), trail pheromones (which report successful foraging routes), alarm pheromones (that report danger) and unpleasant toxic substances (which ward off enemies before physical damage can occur). Plants can produce substances that can act as sex, trail and alarm pheromone antagonists or agonists or otherwise interfere with herbivore behaviour. Plants produce other “semiochemicals” or behaviour-modifying signalling molecules that are relatively benign and have little or any adverse physiological effect at the concentrations required for threshold behavioural response.

Several hundred volatile isoprenoid substances that interfere with insect larval moulting have so far been resolved from plants and such “phytoecdysones” will be dealt with in Chapter 11, which is concerned with development-perturbing compounds binding to cytosolic hormone receptors. It must also be noted that plant cells within a plant (and indeed whole plants themselves) can communicate with each other via volatile signalling bioactives

such as nitric oxide, ethylene, jasmonic acid and methyl jasmonate. Such signalling by volatile compounds arises variously from development (e.g. in fruit ripening) or from wounding and pathogen infection with resultant induction of defensive secondary metabolites (e.g. antifungal phytoalexins) and defensive proteins (e.g. antifeedant protease inhibitors) (Chapter 13).

In humans the odour receptors are located on the surface of olfactory sensory neurons at the top of the nasal cavity. The tastant receptors are located on taste bud cells of the tongue. A key difference between odour and taste perception arises because any particular odorant sensory neuron expresses only one particular type of odour receptor, this resulting in a complex, unique signalling combination in the brain and hence ultimately in the ability to discriminate between some thousands of different odorants. In contrast, each gustatory (taste-perceiving) neuron expresses a multiplicity of taste receptors and hence much of the taste complexity is lost on subsequent transmission to the brain. Five basic tastes are perceived, namely sweet (e.g. glucose), salty (e.g. sodium chloride, NaCl), umami (the taste of glutamate or “monosodium glutamate (MSG)), bitter (e.g. quinine) and sour (e.g. acid as with vinegar or unameliorated lemon juice). The sweet, umami and salty tastes are those of potentially nutritive (and hence “attractive”) foods, while the bitter and sour tastes are those of things that are potentially toxic or harmful (and accordingly “unattractive”). The perception of taste is influenced by odour and also by other factors such as colour and remembered associations. Thus, a blocked nose can affect taste and wine tasting can be markedly influenced by learning, prejudice and indeed by deception (e.g. by offering a test “red” that is actually a dye-coloured “white”). The signalling mechanisms involved in taste and odour perception via plasma membrane (PM)-located receptors are outlined below.

10.2 Sweet taste receptors

The sweet receptors belong to the 7 transmembrane α -helix (7TM) receptor superfamily of G protein-coupled receptors (GPCRs). The sweet taste receptors act via the PM-located heterotrimeric G protein gustducin (subunit composition $G\alpha_g$ - $G\beta$ - $G\gamma$) with resultant release of $G\beta$ - $G\gamma$ and formation of the effector activator $G\alpha_g$ -GTP. $G\alpha_g$ -GTP can then activate adenylyl cyclase (AC) with the resultant successive elevation of cyclic AMP (cAMP), opening of cAMP-gated Na^+ channels (as well as activation of cAMP-dependent protein kinase (PKA) with consequent phosphorylation and depolarizing closure of K^+ channels), excitatory depolarization and communication to the brain central nervous system (CNS). The major naturally occurring ligands for sweet receptors are carbohydrates such as glucose, fructose and the disaccharide sucrose. However, the dietary consequences of our primate disposition for sweet-tasting substances can ultimately be quite severe and progressive, for example, obesity, Syndrome X and type 2 diabetes with attendant cardiovascular, vision and kidney problems. The need for “sweetness without calories” has led to the development of non-carbohydrate sweeteners such as the dipeptide methyl ester aspartame and indeed sweet peptides occur in nature (Table 10.1).

10.3 Bitter taste receptors

There are some hundred different 7TM receptors involved in perception of bitter tastants. The bitter taste receptors also couple through the G protein gustducin yielding the activated $G\alpha_g$ -GTP which can thence activate cAMP/cGMP phosphodiesterase, thus lowering cAMP and cGMP concentration. Bitter tastant receptors can also act via pertussis

toxin-insensitive G proteins generating $G_{\alpha i}$ -GTP (which inhibits AC, thus lowering cAMP) or $G_{\alpha o}$ -GTP (which activates PLC, this yielding IP_3 and thence increased cytosolic Ca^{2+}). As indicated above, in contrast to the unique patterns of neuronal stimulation obtaining with odorants, many tastants stimulate the same CNS neurons, thus yielding a “simpler” perception of tastants. The bitterest substances known include the plant-derived alkaloids quinine and strychnine (Table 10.2).

10.4 Salty taste perception

Salty tastants act directly on Na^+ channels in the PM of cells on the tongue surface. Direct passage of Na^+ through these channels causes depolarization and thence signalling to the CNS. Much (but not all) salt taste perception is inhibited by the voltage-sensitive Na^+ channel inhibitor amiloride (see Chapter 4) and evidently some salt perception also occurs via amiloride-insensitive channels.

10.5 Sour taste perception

Sour taste is perceived via the effect of lowered pH on amiloride-sensitive Na^+ channels and on the conductance properties of other PM-located ion channels (such as K^+ channels). A variety of plant carboxylic acids contribute to a sour taste, the most familiar of these being acetic acid (as in vinegar) (Table 10.3).

10.6 Umami (glutamate taste perception)

Umami, or the taste of glutamate, is perceived via glutamate binding to a variant metabotropic glutamate receptor with a lowered affinity for the ligand that is appropriate to the millimolar concentrations encountered in the human diet (as opposed to the micromolar concentrations of glutamate involved in synaptic transmission in the brain). The so-called “Chinese restaurant syndrome” derives from the attractive taste of glutamate (MSG), its use in cooking and the neurological effects of excessive glutamate consumption. Glutamate can readily enter particular brain regions and is excitotoxic, destroying neurons by excessively activating NMDA-type ionotropic glutamate receptors (Chapter 3).

10.7 Odorant perception

Odorant molecules bind to PM 7TM helix GPCRs located on sensory neuron cells in the upper nasal cavity. There are about one million olfactory sensory neurons and about a thousand different odorant receptors (OD-Rs). The OD-Rs couple through olfactory heterotrimeric G proteins yielding $G_{\alpha olf}$ -GTP, which (like $G_{\alpha s}$ -GTP) activates AC, and this successively causes cAMP elevation, the opening of cAMP-gated Na^+ channels, excitatory depolarization and signalling to the brain. As indicated above, each olfactory neuron only expresses one kind of OD-R resulting in a unique pattern of neuronal excitation in the CNS as a result of odorant binding to a multiplicity of different OD-Rs, each OD-R variant being located on a differently “wired up” olfactory neuron. This combinatorial complexity allows us to discriminate between thousands of different odours (Table 10.4). Subtle odorant responses are the basis for aromatherapy.

“Essential oil” preparations from a variety of plants have found industrial applications relating to taste (liqueurs and flavour additives) and odour (perfumes, liqueurs, agents for masking unpleasant odours and pleasant-smelling phenolic antiseptics). Many

pleasant-smelling plant essential oils are reputed aphrodisiacs in particular human cultures. Our lives are awash with a variety of smells including those deriving from: “unconsciously registered” steroid hormone pheromones; urine, faecal matter, breath, sweat and flatus; vehicular, industrial and agricultural waste by-products; applied or consumed industrial products from antiseptics to perfumes; organisms, notably plants; and, of course, food and drink. Further, as indicated above, our taste perceptions are affected by colour, prejudice, experience and concomitant odour. The literature on odours (like the scientific literature in other areas) is heavily influenced by social applications and this is reflected in the huge amount of information on plant-derived odours listed in Table 10.4. Thus, major odour sources in Table 10.4 include many plant products that we commonly consume or apply, including beverages (tea, coffee, orange juice, grapefruit juice, milk, beer and wine), essential oils, fruit and many components used in cooking.

10.8 Animal pheromones and other animal bioactives produced by plants

Animals produce volatile pheromones that variously act as female attractants (i.e. attract females), male attractants, egg laying (oviposition) signals, alarm signals, foraging trail markers and as bioactive, repelling defensive agents. A variety of plants (coincidentally or through insect pheromone-related evolution) produce compounds that are identical to insect pheromones. A notable subset of such compounds are plant bioactives that are consumed by animals and then stored and utilized as defensive agents, for example, the toxic cardenolides that are sequestered by the monarch butterfly (Table 10.5).

10.9 Other plant semiochemicals affecting animal behaviour

In addition to compounds that are identical to animal pheromones, plants produce a variety of compounds that affect animal behaviour by having the same effects as pheromones, antagonizing animal pheromone action or by acting as animal repellants or attractants. Animal herbivores (typically insects) are repelled by particular plant-derived semiochemicals. Animals being attracted by such compounds include insects and other animals involved in pollination or seed dispersal and predators of herbivores. Such benign semiochemicals (and related synthetics) have considerable potential for targeted insect control with minimal environmental damage (Table 10.6). Of course, in addition, a huge variety of toxic plant substances at sublethal doses will affect animal behaviour as will a variety of neuroreceptor ligands and other plant substances interfering with cognitive processes as described in particular in Chapters 3–8.

10.10 Odoriferous animal metabolites of ingested plant compounds

Finally, it should be noted that ingested plant compounds can be metabolized to odorants by herbivores and, in particular, by man. Well-known examples are the pungent urine from ingestion of asparagus, the breath of garlic eaters, malodorous breath from those with bacterial mouth infections and flatulence, notably from eating legume seeds containing indigestible oligosaccharides. The chemical details of these side effects of plant consumption are summarized in Table 10.7.

Table 10.1 Sweet plant compounds

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects
Phenolic		
Anethole (= <i>p</i> -Propenylanisole; <i>p</i> -Propenyl- methoxybenzene)	<i>Foeniculum vulgare</i> (fennel), <i>Pimpinella anisum</i> (aniseed) (Apiaceae), <i>Artemisia porrecta</i> , <i>Aster tartaricus</i> (Asteraceae), <i>Canarium indicum</i> (Burseraceae) <i>Juniperus rigida</i> (Cupressaceae), <i>Illicium anisatum</i> (Illiciaceae), <i>Magnolia salicifolia</i> (Magnoliaceae), <i>Bachhousia anisata</i> (Myrtaceae), <i>Clausenia anisata</i> , <i>Pelea christophersenii</i> (Rutaceae) [oil]	10.1p Sweet (OD-R) [carminative, spasmolytic]
Cinnamaldehyde (aryl aldehyde)	<i>Cinnamomum osmophloem</i> (Lauraceae) [leaf]	Sweet [50× >0.5% (w/v) sucrose]
6-Methoxyaromadendrin 3- <i>O</i> -acetate (dihydroflavonol)	<i>Hymenoxys turneri</i> (Asteraceae) [aerial]	Sweet [20× >sucrose]
6-Methoxytaxifolin (dihydroflavonol)	<i>Hymenoxys turneri</i> (Asteraceae) [aerial]	Sweet [12× >sucrose]
6-Methoxytaxifolin 3- <i>O</i> - acetate (dihydroflavonol)	<i>Hymenoxys turneri</i> (Asteraceae) [aerial]	Sweet [25× >sucrose]
[6]-Paradol (vanilloid phenolic)	<i>Zingiber officinale</i> (ginger) [rhizome] (Zingiberaceae)	Pungent (COX-2) [apoptotic, chemopreventive]
Phyllodulcin (dihydroisocoumarin)	<i>Hydrangea macrophylla</i> (hydrangea) (Saxifragaceae)	Sweet
Selliguaein A (= Epiafzelechin-(4β → 8, 2β → <i>O</i> → 7)-epiafzelechin- (4β → 8)-afzelechin) (proanthocyanidin)	<i>Selliguea feei</i> (fern) (Polypodiaceae) [rhizome]	Sweet
Taxifolin 3- <i>O</i> -acetate (dihydroflavonol)	<i>Baccharis varicans</i> , <i>Hymenoxys turneri</i> , <i>Inula viscosa</i> , <i>Tessaria dodoneifolia</i> (Asteraceae) [aerial]	Sweet [80× >sucrose]
Terpene		
Abrusosides A, B, C, D & E (= Abrusogenin glycosides) (cycloartane triterpene glycosides)	<i>Abrus precatorius</i> (Fabaceae) [leaf]	10.1t Sweet (Abrusoside B 100× >sucrose)
Abrusogenin glycosides (Abrusosides) A, B, C & D (cycloartane triterpene glycosides)	<i>Abrus precatorius</i> (Fabaceae) [leaf]	Sweet (30–100× >sucrose)
Abrusoside E dimethyl ester (cycloartane triterpene glycosides)	<i>Abrus precatorius</i> (Fabaceae) [leaf]	Sweet
Abrusoside E 6"-methyl ester (cycloartane triterpene glycosides)	<i>Abrus precatorius</i> (Fabaceae) [leaf]	Sweet

(continued)

Table 10.1 (Continued)

Compound (details)	Plant source (family) / plant part/	Taste (other targets) / in vivo effects/
Apioglycyrrhizin (triterpene glycoside saponin)	<i>Glycyrrhiza inflata</i> (Fabaceae) [rhizome, root]	Sweet (200× > sucrose) [antiulcerogenic, expectorant]
Araboglycyrrhizin (triterpene glycoside saponin)	<i>Glycyrrhiza inflata</i> (Fabaceae) [rhizome, root]	Sweet (200× > sucrose) [antiulcerogenic, expectorant]
Baiyunoside (diterpene glycoside)	<i>Phlomis medicinalis</i> , <i>P. younghusbandii</i> (Lamiaceae) [root]	Sweet (250× > Sucrose)
Bryodulcoside (= Bryodulcosigenin glycoside) (oxygenated tetracyclic triterpene cucurbitacin glycoside)	<i>Bryonia dioica</i> (Cucurbitaceae) [root]	Sweet
Carnosiflosides IV–VI (oxygenated tetracyclic triterpene cucurbitacin)	<i>Hemsleya carnosiflora</i> (Cucurbitaceae)	Sweet (Carnosifloside I from <i>H. carnosiflora</i> tasteless)
Cyclocarioside A (dammarane triterpene saponin glycoside)	<i>Pterocarya paliuris</i> (Juglandaceae); leaves used as sweeteners in Hubei Province, People's Republic of China	Sweet
Dammarane glycosides (triterpene saponin glycosides)	<i>Hovenia dulcis</i> (Chinese raisin tree) (Rhamnaceae)	Sweetness inhibitors – compete for sweet receptor
Glycyrrhizic acid (= Glycyrrhinic acid; Glycyrrhizin; Glycyrrhizinic acid) (triterpene glycoside saponin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	Sweet (100–150× > sucrose) [antiulcerogenic, expectorant]
Gymnemasaponins III–V (oleanane triterpene glycosides)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	Sweet-taste blockers – compete for sweet taste receptor
Gymnemic acid I (oleanane triterpene glycoside)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	Sweet-taste blockers – compete for sweet taste receptor with Thaumatin, Monellin & Aspartame
Gymnemic acids II–XVIII (oleanane triterpene glycosides)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	Sweet-taste blockers – compete for sweet taste receptor; impair sweet/non-sweet discrimination
Hernandulcin (sesquiterpene)	<i>Lippia dulcis</i> (Aztec sweet herb) (Verbenaceae) [flower, leaf]	Sweet (1000× > Sucrose)
(+)-4β-Hydroxy-hernandulcin (sesquiterpene)	<i>Lippia dulcis</i> (Verbenaceae) [flower, leaf]	Sweet
Jegosaponins (= Barringtogenol 3-O-tetraglycosides) (triterpene glycosides, saponins)	<i>Styrax japonica</i> (Styracaceae) [fresh fruit]	Anti-sweet

(continued)

Table 10.1 (Continued)

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects
Mogroside V (cucurbitane triterpene)	<i>Siratia grosvenorii</i> , <i>Thladiantha grosvenorii</i> (Cucurbitaceae) [fruit]	Sweet (250× >sucrose)
Osladin (steroidal saponin)	<i>Polypodium vulgare</i> (European fern) (Polypodiaceae) [rhizome]	Sweet (500× >sucrose)
Polypodoside A (= Polypodogenin glycoside A) (triterpene steroidal glycoside)	<i>Polypodium glycyrrhiza</i> (licorice fern) (Polypodiaceae) [rhizome]	Sweet (600× >sucrose but with liquorice- like aftertaste)
Polypodosides B & C (= Polypodogenin glycosides B & C) (triterpene steroidal glycosides)	<i>Polypodium glycyrrhiza</i> (licorice fern) (Polypodiaceae) [rhizome]	Sweet
Periandrins I–V (oleane triterpene glycosides)	<i>Periandra dulcis</i> (Fabaceae) [root]	Sweet (90× >sucrose)
Pterocaryosides A & B (secodammarane triterpene saponin glycosides)	<i>Pterocarya paliurus</i> (Juglandaceae); leaves used as sweeteners in Hubei Province, People's Republic of China	Sweet (50× & 100× > sucrose for A & B, respectively, but persistent bitter off-taste)
Rebaudioside (= Steviol tetraglycoside) (kaurane diterpene glycoside)	<i>Stevia rebaudiana</i> (Asteraceae) [leaf]	Sweet
Rubusoside (= Steviol bisglucoside) (kaurane diterpene glycoside)	<i>Rubus suavisissimus</i> (Rosaceae) [leaf]	Sweet
Scandenoside R6 (triterpene cucurbitane glycoside)	<i>Hemsleya</i> spp. (Cucurbitaceae)	Sweet
Selligueain A (trimeric proanthocyanidin)	<i>Selliguea feei</i> (Polypodiaceae) [rhizome]	Sweet (35× >sucrose)
Stevioside (= Steviol triglycoside) (kaurane diterpene glycoside)	<i>Stevia phlebophylla</i> , <i>S. rebaudiana</i> (Asteraceae) [leaf]; sweetener in Thailand	Sweet (300× >sucrose) (Ca ²⁺ CH)
Strogins 1,2 & 4 (oleanane triterpene glycosides)	<i>Staurogyme merguensis</i> (Acanthaceae) [leaf]	Sweet & sweetness-inducing (i.e. H₂O wash abolishes but sweetness then returns)
Telosmosides A8–A18 (polyoxypregnane triterpene glycosides)	<i>Telosma procumbens</i> (Asclepiadaceae) [stem]	Sweet
Ziziphin (dammarane triterpene glycoside)	<i>Ziziphus jujuba</i> (jujube tree) (Rhamnaceae)	Sweet-taste blocker – competes for sweet taste receptor
Other		10.1o
D-Arabitrol (= Arabinitol; 1,2,3,4,5-Pentanepentol) (pentose sugar alcohol)	<i>Persea americana</i> (avocado) (Lauraceae) [seed], <i>Fabiana imbricata</i> (Solanaceae); lichen, fungi	Sweet

(continued)

Table 10.1 (Continued)

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects
D-Asparagine (D- α -amino acid)	From L-Asparagine racemization	Sweet
Brazzein (54 aa, 6kDa protein; α -helix, short α -helix, 2 antiparallel β -strands; 8 Cys, 4 S-S, heat-stable)	<i>Pentadiplandra brazzeana</i> (Pentadiplandraceae) [fruit]	Sweet (2000x sucrose)
Curculin (13kDa, 4Cys, protein)	<i>Curculigo latifolia</i> (Hypoxidaceae) [fruit]	Sweet (modifies taste & induces sweet taste)
Des-pGlu 1-brazzein (= Brazzein missing N-terminal pyroglutamyl) (53 aa, 8Cys, 4 S-S, heat- stable, 6kDa protein)	<i>Pentadiplandra brazzeana</i> (Pentadiplandraceae) [fruit] (minor component)	Sweet – 2 \times >Brazzein, 4000 \times >Sucrose
Dulcitol (= Galactitol; 1,2,3,4,5,6-Hexanehexol) (hexose sugar alcohol)	<i>Euonymus atropurpureus</i> , <i>Gymnosporia deflexa</i> (Celastraceae), <i>Persea americana</i> (Lauraceae), <i>Melampyrum nemorosum</i> (Scrophulariaceae)	Slightly sweet
Erythritol (= 1,2,3,4- Butanetetrol) (tetrose sugar alcohol)	<i>Papaver somniferum</i> (Papaveraceae), <i>Primula</i> sp. (Primulaceae), Poaceae; green algae, fungi, lichens	Sweet (2 \times >sucrose)
Ethyl 2-methylbut-2- enoate (aliphatic ester)	<i>Cydonia oblonga</i> (quince) (Rosaceae) [fruit]	Quince flavour
Fructose (= β -D- Fructopyranose) (hexose monosaccharide)	Universal; <i>Phoenix dactylifera</i> (Arecaceae), <i>Cichorium intybus</i> (Asteraceae), <i>Allium cepa</i> (Liliaceae)	Sweet (2 \times >glucose)
Fucoidin (mainly sulfated fucose polysaccharide)	<i>Fucus vesiculosus</i> , <i>Laminaria digitata</i> (brown algae)	Sweet (\approx Sucrose) [anticoagulant]
Glucose (= α -D- Glucopyranose) (hexose monosaccharide)	Universal; <i>Phoenix dactylifera</i> (Arecaceae), <i>Prosopis juliflora</i> (Fabaceae), <i>Curcuma longa</i> (Zingiberaceae)	Sweet (\approx Sucrose)
D-Glutamine (D- α -amino acid)	From L-Glutamine racemization	Sweet
Glycerol (= 1,2,3- Propanetriol) (triose sugar alcohol)	Universal in glycerol-based fats & phospholipids; <i>Croton tiglium</i> (Euphorbiaceae), <i>Urtica dioica</i> (Urticaceae)	Sweet
Gurmarin (4kDa protein, N-terminal pyroglutamyl, 6 Cys, 3 S-S)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]; synthetic ent-Gurmarin (all D-amino acids) also blocks sweetness of sucrose, D-glucose & L-glucose	Sweet-taste suppressor (at 1)
D-Histidine (D- α -amino acid)	From L-Histidine racemization	Sweet
<i>myo</i> -Inositol (= Inositol; Cyclohexanehexol) (cyclitol)	Widespread e.g. in Phosphoinositol phospholipids, Phytic acid (inositol hexaphosphate); <i>Liriodendron tulipifera</i> (Magnoliaceae), <i>Elytrigia repens</i> (Poaceae), <i>Viscum album</i> (Viscaceae)	Sweet
Lactose (= 4-O- β -D-Gal- D-Glc) (disaccharide)	As Isorhamnetin 3-O-lactoside in <i>Cassia multijuga</i> (Fabaceae); mammalian milk; <i>Phoenix dactylifera</i> (Arecaceae), <i>Vigna mungo</i> (Fabaceae)	Sweet

(continued)

Table 10.1 (Continued)

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects
Mabinlin II (12 kDa, 8 Cys, 4 S-S, heat-stable protein; A chain (33aa)-(S-S) ₂ -B chain (72aa, 2 S-S)	<i>Capparis masaiikai</i> (Capparidaceae) [seed]	Astringent-sweet taste
Maltol (= 3-Hydroxy-2-methyl-4-pyrone) (pyrone)	<i>Cichorium endiva</i> (chicory) (Asteraceae), <i>Abies alba</i> [needle], <i>Larix decidua</i> (larch) [bark], (Pinaceae), <i>Rubus idaeus</i> (Rosaceae); roasted malt <i>ex Hordeum vulgare</i> (barley) (Poaceae)	OD-R (sweet, freshly baked) [sweet, freshly baked taste to bread & cakes; Zn (II) & oxoV(IV) complexes are insulin mimetics]
Maltose (= 4-O- α -D-Glc-D-Glc) (disaccharide)	Widespread as starch hydrolysis product; <i>Artemisia dracunculus</i> (Asteraceae)	Sweet [$<$ sucrose]
D-Mannitol (= 1,2,3,4,5,6-Hexanehexol; Manna sugar) (hexose sugar alcohol)	Widespread; fungi, algae, lichens; <i>Apium graveolens</i> (Apiaceae), <i>Cucurbita pepo</i> (Cucurbitaceae), <i>Fraxinus ornus</i> (Oleaceae), <i>Rehmannia glutinosa</i> (Scrophulariaceae), <i>Tamarix gallica</i> (Tamaricaceae) exudate from insect-damaged desert plant may be manna of biblical Exodus]	Sweet
Mannose (= α -D-Mannopyranose) (hexose monosaccharide)	From hydrolysis of Mannans; <i>Phytelephas macrocarpa</i> (Arecaceae), <i>Senna obtusifolia</i> (Fabaceae)	Sweet (bitter after taste)
Melibiose (6-O- β -D-Gal-D-Glc) (disaccharide)	Widespread in plant exudates; from Raffinose hydrolysis	Sweet [$<$ sucrose]
Miraculin (28 kDa single chain glycoprotein)	<i>Synsepalum dulcificum</i> (miracle fruit) (Sapotaceae) [fruit]	Glycoprotein that modifies sour taste to sweet
Monellin (44 aa β strand element A chain, 50 aa α -helix & β -strand element B chain heterodimeric 10 kDa protein)	<i>Dioscoreophyllum cumminsii</i> (serendipity berry) (Menispermaceae)	Sweet protein (100,000 \times $>$ sucrose) [active residue B chain Asp7; sugars compete for receptor binding]
γ -Nonalactone (aliphatic lactone)	<i>Cocos nucifera</i> (coconut) (Palmae) [fruit]	Coconut flavour
D-Phenylalanine (D- α -amino acid)	From L-Phenylalanine racemization	Sweet
(+)-Quercitol (= Acorn sugar; 2-Deoxy-D-chiro-inositol) (cyclitol)	<i>Quercus robur</i> (oak) (Fagaceae) [acorn], <i>Chamaerops humilis</i> (Palmae) [leaf], <i>Mimusops elengi</i> (Sapotaceae)	Sweet
Rhamnose (= α -L-Rhamnopyranose) (hexose monosaccharide)	Widespread; <i>Acacia nilotica</i> , <i>A. senegal</i> (Fabaceae)	Sweet
Ribulose (= α -D-Ribulose) (pentose monosaccharide)	Universal photosynthetic Calvin Cycle intermediate (phosphorylated); Melvin Calvin (USA, Nobel Prize, 1961, Chemistry, photosynthesis Calvin cycle)	Sweet

(continued)

Table 10.1 (Continued)

Compound (details)	Plant source (family) plant part/	Taste (other targets) / in vivo effects/
D-Sorbitol (= D-Glucitol) (cyclitol)	<i>Cocos nucifera</i> (Palmae) [coconut milk], <i>Plantago major</i> (Plantaginaceae), <i>Sorbus aucuparia</i> (mountain ash) (Rosaceae) [berry]	Sweet
Sucrose (= Cane sugar; 2-O- α -D-Glc- β -D-Fru) (disaccharide)	Universal; major sources <i>Acer saccharum</i> (sugar maple) (Aceraceae), <i>Beta vulgaris</i> (sugar beet) (Chenopodiaceae), <i>Saccharum officinarum</i> (sugar cane), <i>Sorghum bicolor</i> (sweet sorghum) (Poaceae); sugar cane plantation labour – African slave labour to West Indies; Indian indentured labour to S. Africa, Fiji, West Indies & Mauritius; Melanesian (Kanaka) slaves to Australia	Sweet; “pure, white and deadly” attribution reflects its “Western” health impact (Syndrome X, obesity & type 2 diabetes mellitus); semantic distinctions: mellifluous, sweet, sugary, saccharine
Sugars (= Saccharides) (carbohydrates) Sweet taste receptor evolution driven by need to detect good energy sources	Universal; key figures in carbohydrate chemistry & biochemistry include Louis Pasteur (France, optical activity & fermentation); Hermann Emil Fischer (Germany, Nobel Prize, 1902, Chemistry, sugar & purine synthesis); Eduard Buchner (Germany, Nobel Prize, Chemistry, 1907, cell-free fermentation); Sir Walter Haworth (UK, Nobel Prize, Chemistry, 1937, carbohydrates & vitamin C)	Sweet tastants; other key figures in sugar metabolism include: Luis Leloir (Argentina, polysaccharide synthesis); Carl & Gert Cori (Austria/ USA, Nobel Prize, Medicine, 1947, glycogen metabolism)
Thaumatococin I (21 kDa, 16 Cys, 8 S-S, 23 kDa protein; α -helix-rich domain & 2 β -strand-rich domains)	<i>Thaumatococcus danielli</i> (Marantaceae) [fruit]	Sweet protein (100,000 \times > sucrose); among primates only Cercopithecidae (Old World monkeys), Hylobatidae (gibbons), Pongidae (apes) and man respond to this tastant
Thaumatococin II (20 kDa protein)	<i>Thaumatococcus danielli</i> (Marantaceae) [fruit]	Sweet protein
γ -Undecalactone (= 4-Hydroxyundecanoic acid lactone) (aliphatic lactone)	<i>Narcissus tazetta</i> (daffodil) (Liliaceae), <i>Prunus persica</i> (peach) (Rosaceae) [fruit]	Peach flavour
Volemitol (= α -Sedoheptitol) (cyclitol)	<i>Primula elatior</i> (Primulaceae); <i>Pelvetia canaliculata</i> (brown alga); fungi, lichens	Sweet

(continued)

Table 10.1 (Continued)

Compound (details)	Plant source (family) / plant part/	Taste (other targets) / in vivo effects/
Xylose (= α -D-Xylopyranose) (hexose monosaccharide)	Widespread; component of Xylan polysaccharides; <i>Comium maculatum</i> (Apiaceae), <i>Ceratonia siliqua</i> , <i>Senna obtusifolia</i> (Fabaceae)	Sweet [diabetic application]
Xylitol (= xylitol-Pentane-1,2,3,4,5-pentol) (pentose sugar alcohol)	Metabolic product of Xylose; <i>Daucus carota</i> (Apiaceae), <i>Allium cepa</i> (Liliaceae)	Sweet (\approx sucrose) [anticaries use]
Non-plant reference		10.1n
[Acesulphame] (oxathiazine)	Synthetic	Sweet [food sweetener]
[Alitame] (thietanyl dipeptide)	Synthetic	Sweet (2000 \times > sucrose) [non-nutritive sweetener]
[Aspartame (= L-Asp-L-Phe methyl ester; Equal; NutraSweet)] (dipeptide)	Semi-synthetic	Sweet [food sweetener]; L-Asp-D-Phe methylester isomer is bitter
[Coupling sugar (= mixture of monosaccharides & oligosaccharides terminated at reducing end by sucrose) (sugars)]	Semi-synthetic	Sweet (\approx sucrose) [low cariogenicity]
[Cyclamate, sodium (= Hexylsulfamate, sodium)] (alicyclic sulfamate)	Synthetic	Sweet (30 \times > sucrose)
[Dulcin (= (4-Ethoxyphenyl)urea)] (aryl urea)	Synthetic	Sweet (250 \times > Sucrose) [non-nutritive]
[Maltitol (= 4-O- α -D-Glc-D-sorbitol)] (disaccharide alcohol)	Semi-synthetic	Sweet [low cariogenicity]
[(+/-)-2-(4-Methoxyphenoxy)propanoic acid] (aryl acid)	Synthetic	Sweet receptor competitive inhibitor
[Neohesperidin dihydrochalcone] (dihydrochalcone)	Semi-synthetic from flavanone glycoside Naringin ex <i>Citrus paradisi</i> (grapefruit) (Rutaceae)	Sweet (1000–1500 \times > sucrose)
[Perillaldehyde α -syn-oxime (= Perilla sugar) (monoterpene oxime)]	Semi-synthetic from Perillaldehyde, monoterpene from <i>Sium latifolium</i> (Apiaceae), <i>Perilla arguta</i> (Lamiaceae), <i>Citrus reticulata</i> (mandarin peel oil) (Rutaceae)	Sweet (2000 \times > sucrose)
[Saccharin (= 1,2-Dihydro-2-keto-benzisulfonazole)] (benzisulfonazole)	Synthetic	Sweet (500 \times > sucrose) \uparrow cAMP; carcinogenic]
[Single-chain Monellin (= MNEI; Monellin B-Gly-Phe-Monellin A)] (94 aa, 10 kDa protein)	Synthetic	Sweet (\approx Monellin)
[D-Tryptophan] (amino acid, indole)	Synthetic	Sweet [\uparrow Ca ²⁺ per IP ₃]

Table 10.2 Bitter plant compounds

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects
Alkaloid		10.2a
Brucine (= 10,11-Dimethoxystrychnine) (indole)	<i>Strychnos aculeata</i> , <i>S. ignatii</i> , <i>S. nux-vomica</i> (Loganiaceae)	Bitter (G-R antagonist) [toxic]
Caffeine (= 1,3,7-Trimethylxanthine; Coffeine; Guaranine; Thein; Theine) (purine, methylxanthine)	<i>Ilex paraguayensis</i> (maté) (Aquifoliaceae), <i>Coffea arabica</i> , <i>Coffea</i> spp. (coffee) (Rubiaceae) [coffee bean], <i>Paullinia cupana</i> (guarana) (Sapindaceae), <i>Cola acuminata</i> (cola) (Sterculiaceae) [seed], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	Bitter & increases bitterness of Quinine (AD-R, cAMP PDE, cGMP PDE, RYO-R, ATP-, Ca ²⁺ & V-K ⁺ CH) [cardiac, CNS & respiratory stimulant, diuretic, smooth muscle relaxant, vasodilator]
Digitoxin (= Digitoxigenin 3- <i>O</i> -tridigitoxoside) (cardenolide, steroid triterpene glycoside)	<i>Digitalis purpurea</i> (foxglove) (Scrophulariaceae) [digitalis]; high dose yields cloudy “yellow” vision & red-green perception changes (xanthopsia) – anti-epileptic use may have affected late “yellow” period of Vincent Van Gogh]	Bitter (Na ⁺ , K ⁺ -ATPase) [cardiotonic, cytotoxic (<0.1), toxic]
(–)-Nicotine (pyridine pyrrolidine)	<i>Nicotiana tabacum</i> (tobacco), <i>N.</i> spp. (Solanaceae); also in <i>Asclepias syriaca</i> (Asclepiadaceae), <i>Sedum acre</i> (Crassulaceae), <i>Lycopodium</i> spp., <i>Equisetum arvense</i> (Equisetaceae); tobacco smoking introduced to England from America by Sir Walter Raleigh (subsequently beheaded); global annual smoking-related deaths 6 million per year & fire-related cost US\$ 90 billion	Bitter (nACh-R agonist) [addictive, antinociceptive, insecticide, respiratory paralytic, toxic, tranquilizer]; Gamel Abdul Nasser excessive smoker and diabetic (inevitable complications & premature death 1970)
Quinine (quinoline)	<i>Cinchona officinalis</i> [bark], <i>Cinchona</i> spp., <i>Remijia pedunculata</i> (Rubiaceae); Quinine synthesized (1944) by Robert Burns Woodward (USA, Nobel Prize, 1965, Chemistry)	Bitter (at 10) (ECMOX) [abortefacient, analgesic, antimalarial, cardiac depressant, spermicidal]
Steviosalioside A (diterpene alkaloid glycoside)	<i>Stevia salicifolia</i> (Asteraceae) [root]	Bitter
Strychnine (indole); structure (1947) & synthesis (1954) by Robert Burns Woodward (USA, Nobel Prize, 1965, Chemistry)	<i>Strychnos nux-vomica</i> [seed] (nux-vomica), <i>S. ignatii</i> (ignatius bean), <i>S. icaja</i> , <i>S. tieute</i> , <i>S. triplinervia</i> (Loganiaceae); Adolph Hitler took anti-flatulence pills containing Strychnine & Atropine – he also took Methamphetamine & Cocaine as medications	Bitter (G-R, α7nACh-R) [bitter, CNS stimulant, toxic]; South African Mrs Daisy De Melker poisoned 2 husbands with Strychnine & thence her son with arsenic (1923, 1927 & 1932)

(continued)

Table 10.2 (Continued)

Compound (details)	Plant source (family) plant part	Taste (other targets) /in vivo effects
α -Tomatine (= Lycopericin) (steroid glycoside)	<i>Lycopersicon esculentum</i> (tomato), <i>Solanum</i> spp. (Solanaceae)	Bitter [antibacterial, antifungal, antihistamine, anti-insect, insect repellent]
(-)-Vinyloxazolidine-2-thione (= Goitrin) (oxazolidine)	<i>Brassica oleracea</i> (Brussels sprouts), <i>B.</i> spp. (Brassicaceae)	Bitter [affects insect feeding & oviposition, goitrogenic, toxic]
Phenolic		10.2p
Aceoside (= Kusagin); Verbascoside (phenylpropanoid glycoside)	<i>Stachys sieboldii</i> (Lamiaceae), <i>Buddleja globosa</i> , <i>B. officinalis</i> , <i>Forsythia</i> sp. (Oleraceae), <i>Monochasma savatieri</i> , <i>Verbascum sinuatum</i> (Scrophulariaceae), <i>Lippia dulcis</i> (Verbenaceae); Acanthaceae, Bignoniaceae, Gesneriaceae, Oronbranchaceae, Plantaginaceae	Bitter (AR, 5-LOX) [AI]
Aloenin (= 4-Methoxy-6-(2- β - D-glucopyranosyloxy-4- hydroxy-6-methylphenyl)-2- pyrone (phenolic pyrone glycoside)	<i>Aloe arborescens</i> (Liliaceae)	Bitter [inhibits gastric acid secretion]
(+)-Catechin (= Catechinic acid; Catechuic acid; (+)- Cyanidanol; (2 <i>R</i> ,3 <i>S</i>)-5,7,3',4'- Tetrahydroxyflavan-3-ol) (flavan-3-ol)	Widespread; <i>Agrimonia eupatoria</i> (Rosaceae), <i>Salix caprea</i> (willow) (Salicaceae) [flower]	Bitter (AR, COX-1, COX-2, MLCK, PKA) [antioxidant]
Chaparrinone (quassinoid nortriterpene)	<i>Ailanthus altissima</i> , <i>Hannoa klaineana</i> (= <i>Quassia undulata</i>) (Simaroubaceae)	Bitter [antiviral]
Coumarin (= 2H-1- Benzopyran-2-one; 1,2-Benzopyrone; Coumarone) (coumarin)	Widespread; e.g. Pinaceae, Poaceae; <i>Dipteryx odorata</i> (Fabaceae), <i>Myroxylon balsamum</i> (Flacourtiaceae), <i>Hordeum vulgare</i> (Poaceae), <i>Galium odoratum</i> (Rubiaceae)	Bitter [smell of new- mown grass]
Digallic acid (= Gallic acid 3-monogallate) (phenolic)	From Gallotannins	Bitter
(-)-Epicatechin (= (2 <i>R</i> ,3 <i>R</i>)- 5,7,3',4'-Tetrahydroxyflavan- 3-ol) (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), Gymnospermae, <i>Pterocarpus</i> spp. (Fabaceae) [bark], <i>Podocarpus nagi</i> (Podocarpaceae), <i>Crataegus monogyna</i> (Rosaceae), <i>Camellia sinensis</i> (Theaceae)	Bitter (AR, PKA) [antibacterial, AI, anti- oxidant]
Gallic acid (= 3,4,5- Trihydroxybenzoic acid) (phenolic)	Widespread; constituent of gallotannins (hydrolysable tannins); <i>Mangifera indica</i> (Anacardiaceae), <i>Phyllanthus emblica</i> (Euphorbiaceae), <i>Hamamelis virginiana</i> (Hamamelidaceae), <i>Punica granatum</i> (Punicaceae)	Bitter [antibacterial, antifungal, AI, antimutagenic, antitumour, antiviral, astringent, bronchodilatory]
Gentiobiose (= 6- <i>O</i> - β -D- Glc-D-Glc) (disaccharide)	Widespread; component of glycosides;	Bitter
Glycyphyllin (= Rha) Phloretin 2'- <i>O</i> - (dihydrochalcone <i>O</i> -glycoside)	<i>Crocus sativus</i> (saffron) (Iridaceae) <i>Smilax</i> spp. (Smilacaceae)	Bitter

(continued)

Table 10.2 (Continued)

Compound (details)	Plant source (family) [plant part]	Taste (other targets) / in vivo effects]
Humulone (= Humulon; α -Lupulic acid) (phenolic ketone)	<i>Humulus lupulus</i> (hops) (Cannabaceae)	Bitter (in beer)
Hymenosides A, B, C, D, E & F (hemiterpene diphenylacetoxy glucoside)	<i>Hymenophyllum barbatum</i> (fern)	Bitter
Isocoumarin (= 6-Methoxymellein) (coumarin)	<i>Angelica archangelica</i> , <i>Daucus carota</i> (Apiaceae)	Bitter
Isohumulone (phenolic ketone)	<i>Humulus lupulus</i> (hops) (Cannabaceae)	Bitter (in beer)
Kutkin (phenolic glycoside)	<i>Picrorhiza kurroa</i> (Scrophulariaceae) [root]	Bitter
Lupulone (= β -Lupulic acid) (phenolic ketone)	<i>Humulus lupulus</i> (hops) (Cannabaceae)	Bitter (in beer) [antibiotic, toxic]
Naringin (= 2,3-Dihydroapigenin 7-O-Rha-Glc; 2,3-Dihydro-5,7,4'-trihydroxyflavone 7-O-neohesperidoside) (flavanone O-glycoside)	<i>Adiantum</i> spp., <i>Ceterach officinarum</i> (fern) (Adiantaceae), <i>Origanum vulgare</i> (oregano) (Lamiaceae), <i>Citrus paradisi</i> (grapefruit) (Rutaceae)	Bitter (PKA) [oviposition stimulant]
Naringenin (= 5,7,4'-Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> sp., <i>Baccharis</i> sp., <i>Centaurea</i> sp., <i>Dahlia</i> sp. (Asteraceae); <i>Citrus paradisi</i> (grapefruit), <i>Citrus</i> spp. (Rutaceae); glycosides widespread	Bitter (CYP) [mosquito larvicide]
Neeroiocitrin (= Eriodictyol 7-O-neohesperidoside) (flavanone O-glycoside)	<i>Citrus limon</i> (lemon), <i>C.</i> spp. (Rutaceae); bergamot lemon bitter principle	Bitter [rutinoid analogue Eriocitrin tasteless]
Neohesperidin (= Hesperetin 7-O-neohesperidoside) (flavanone O-glycoside)	<i>Citrus paradisi</i> (grapefruit), <i>C.</i> spp. (Rutaceae)	Bitter [Hesperidin = 7-O- rutinoid analogue is tasteless]
Phloridzin (= Phloretin 2'-O-Glc) (dihydrochalcone O-glycoside)	<i>Kalmia</i> , <i>Pieris</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>Malus</i> spp. (Rosaceae) [apple leaf, fruit skin], <i>Symplocos</i> spp. (Symplocaceae)	Bitter (Glc-R (GIP), Glc- TR) [feeding deterrent]
Poncirin (= Citrifolioside; Isosakuranetin 7-O-neohesperidoside) (flavanone O-glycoside)	<i>Acinos</i> spp., <i>Calamintha nepeta</i> (Lamiaceae), <i>Citrus</i> , <i>Eremocitrus</i> , <i>Microcitrus</i> spp. (Rutaceae)	Bitter [rutinoid analogue Didymin tasteless]
Tannins (polyphenolics)	Widespread	Bitter [astringent]
Terpene		10.2t
Absynthine (dimeric guaianolide sesquiterpene lactone)	<i>Artemisia absinthium</i> (wormwood) (Asteraceae)	Bitter
6-Acetylpiropoline (clerodane diterpene)	<i>Teucrium polium</i> (Lamiaceae)	Very bitter
Achillin (= Santolin) (guaianolide sesquiterpene lactone)	<i>Achillea millefolium</i> , <i>A. santolina</i> , <i>A.</i> spp., <i>Artemisia</i> spp. (Asteraceae)	Bitter
Amarogentin (secoiridoid glycoside)	<i>Gentiana lutea</i> , <i>G.</i> spp. (gentian), <i>Sweetia chirata</i> , <i>S.</i> spp. (Gentianaceae) [root]	Very bitter (TOPI)

(continued)

Table 10.2 (Continued)

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects/
Andrographolide (diterpene lactone)	<i>Andrographis paniculata</i> (King of bitters) (Acanthaceae) [leaf]	Bitter [stimulates immune response]
Brucein B (quassinoid nortriterpene)	<i>Brucea amarissima</i> (Simaroubeaceae) [seed]	Bitter [insecticidal]
Brucein C (quassinoid nortriterpene)	<i>Brucea amarissima</i> (Simaroubeaceae) [seed]	Bitter [insecticidal]
Carnosifloside III (oxygenated tetracyclic triterpene, cucurbitacin)	<i>Hemsleya carnosiflora</i> (Cucurbitaceae)	Bitter
Caryoptin (clerodane diterpene)	<i>Caryopteris divaricata</i> (Verbenaceae)	Bitter [antifeedant]
Catalpol (iridoid monoterpene)	<i>Catalpa ovata</i> (Bignoniaceae), <i>Buddleja</i> (Buddlejaceae), <i>Plantago</i> (Plantaginaceae), <i>Rehmannia glutinosa</i> , <i>Veronica</i> (Scrophulariaceae) spp.	Bitter [diuretic, laxative]
Catalposide (= Catalpin) (iridoid monoterpene glucoside)	<i>Catalpa ovata</i> (Bignoniaceae), <i>Veronica</i> (Scrophulariaceae) spp.	Bitter [diuretic, laxative]
Centapicrin (secoiridoid glucoside)	<i>Erythraea centaurium</i> (Gentianaceae)	Bitter
Chaparrulide (quassinoid nortriterpene)	<i>Castela nicholsoni</i> (Simaroubaceae)	Bitter
Chasmanthin (clerodane diterpene)	<i>Jateorhiza columba</i> , <i>J. palmata</i> (columba root) (Menispermaceae); columba root used for bitter tonic	Bitter
Chlorogenin 6- <i>O</i> - β -D-Glc (steroidal glucoside saponin triterpene)	<i>Camassia cusickii</i> (Liliaceae) [bulb]	Bitter
Chlorogenin 6- <i>O</i> - β -D-Glc-(1 \rightarrow 2)- β -D-Glc (steroidal glucoside saponin triterpene)	<i>Camassia cusickii</i> (Liliaceae) [bulb]	Bitter
Chlorogenin 6- <i>O</i> - β -D-Glc-(1 \rightarrow 3)- β -D-Glc (steroidal glucoside saponin triterpene)	<i>Camassia cusickii</i> (Liliaceae) [bulb]	Bitter
Chlorogenin 6- <i>O</i> - β -D-Glc-(1 \rightarrow 2)- <i>O</i> - β -D-Glc-(1 \rightarrow 3)- β -D-Glc (steroidal glucoside saponin triterpene)	<i>Camassia cusickii</i> (Liliaceae) [bulb]	Bitter
Columbin (clerodane diterpene)	<i>Dioscoreophyllum cumminsii</i> [seed], <i>Jateorhiza columba</i> (columba root), <i>J. palmata</i> (Menispermaceae); columba root used for bitter tonic	Bitter
Cucurbitacin A (oxygenated tetracyclic triterpene, cucurbitacin)	<i>Cucumis hookeri</i> , <i>C. leptodermis</i> , <i>C. myriocarpa</i> , <i>C. sativus</i> (Cucurbitaceae)	Bitter [toxic]
Cucurbitacin C (oxygenated tetracyclic triterpene, cucurbitacin)	<i>Cucumis sativus</i> (bitter cucumber) (Cucurbitaceae)	Bitter [toxic]
Cucurbitacin F (oxygenated tetracyclic triterpene, cucurbitacin)	<i>Cucumis angolensis</i> (Cucurbitaceae), <i>Crinodendron hookerianum</i> (Elaeocarpaceae)	Bitter
Cucurbitacin H (oxygenated tetracyclic triterpene, cucurbitacin)	<i>Acanthosicyos horrida</i> , <i>Citrullus naudinianus</i> (Cucurbitaceae), <i>Crinodendron hookerianum</i> (Elaeocarpaceae)	Bitter

(continued)

Table 10.2 (Continued)

Compound (details)	Plant source (family) [plant part]	Taste (other targets) / in vivo effects
Cucurbitacin L (oxygenated tetracyclic triterpene, cucurbitacin)	<i>Citrullus naudinianus</i> (Cucurbitaceae) [as glycoside]	Bitter
Cucurbitacin S (oxygenated tetracyclic triterpene, cucurbitacin)	<i>Bryonia dioica</i> (Cucurbitaceae)	Bitter
8-Deoxylactucin (guaianolide sesquiterpene lactone)	<i>Cichorium intybus</i> (chicory), <i>Lactuca serriola</i> (wild lettuces) (Asteraceae)	Bitter [antitumour, cytotoxic]
(25 <i>R</i>)-3,3-Dimethoxy-5 α -spirostan-6- α -ol 6- <i>O</i> - β -Glc- (1 \rightarrow 3)- β -Glc (steroidal glycoside saponin)	<i>Camassia cusickii</i> (Liliaceae) [bulb]	Bitter
Enmein (seco-kaurane)	<i>Isodon trichocarpus</i> , <i>Plectranthus trichocarpus</i> (Lamiaceae)	Bitter
Erythrocentaurin (iridoid monoterpene)	<i>Swertia japonica</i> (Gentianaceae)	Bitter [aglycone of glucoside Swertiamarin]
Eurycomalactone (quassinoid nortriterpene)	<i>Eurycoma longifolia</i> (Simaroubaceae) [bark]	Bitter
Gentiopicroside (= Gentiopicrin) (seco-iridoid monoterpene lactone)	<i>Centaurium erythraea</i> , <i>Gentiana lutea</i> , <i>G. macrophylla</i> , <i>G. scabra</i> (Gentianaceae) [root]	Bitter [antimalarial]
Germacrenolides (germacrane sesquiterpene lactones)	<i>Cichorium intybus</i> (chicory) (Asteraceae) [dark grown sprouts]	Bitter
Ginkgolide A (ginkgolide diterpene)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	Bitter (PAF-R) [AI, antifeedant, PAI]
Gymnemic acid I (triperpene glycoside saponin)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	[Reversibly abolishes sweet taste due to acesulfam-K, aspartame, monellin, sucrose, thaumatin & xylitol]
Harpagoside (iridoid monoterpene glucoside)	<i>Lamium</i> spp. (Lamiaceae), <i>Harpagophytum procumbens</i> (Pedaliaceae), <i>Scrophularia buergeriana</i> (Scrophulariaceae)	Bitter
(25 <i>R</i>)-6- α -Hydroxy-5 α -spirostan-3-one 6- <i>O</i> - β -glucosyl- (1 \rightarrow 3)- β -glucoside (steroidal glycoside saponin)	<i>Camassia cusickii</i> (Liliaceae) [bulb]	Bitter
Hydroxyveranolide (elemanolide sesquiterpene lactone)	<i>Vernonia amygdalina</i> (Asteraceae) [ingested by parasite-infected chimpanzees]	Bitter [antibacterial, antitumour, antischistosomal]
Ichangin (limonoid nortriterpene)	<i>Citrus ichangensis</i> (Rutaceae)	Bitter
Judaicin (= Tauremisin; Vulgarin) (eudesmanolide sesquiterpene lactone)	<i>Artemisia judaica</i> , <i>A. taurica</i> , <i>A. vulgaris</i> , <i>A.</i> spp. (Asteraceae)	Bitter [antitumour, cytotoxic]
Klaineanone (nortriterpene)	<i>Hannoa klaineana</i> (= <i>Quassia undulata</i>) (Simaroubaceae)	Bitter

(continued)

Table 10.2 (Continued)

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects/
Lactucin (guaianolide sesquiterpene lactone)	<i>Cichorium intybus</i> (chicory), <i>Lactuca canadensis</i> , <i>L. serriola</i> , <i>L. virosa</i> (wild lettuces) (Asteraceae)	Bitter [antitumour, cytotoxic, sedative]
Lactucopicrin (= Intibin) (guaianolide sesquiterpene lactone)	<i>Cichorium intybus</i> (chicory), <i>Lactuca canadensis</i> , <i>L. serriola</i> , <i>L. virosa</i> (wild lettuces) (Asteraceae)	Bitter [hypoglycaemic]
Limonin (= Citrolimonin; Dictamnolactone; Obaculactone; Evodin) (limonoid nortriterpene)	<i>Citrus aurantium</i> , <i>C. limon</i> (lemon), <i>C. paradisi</i> , <i>C. simsensis</i> (orange), <i>C. spp.</i> (Rutaceae) [fruit]	Bitter (delayed bitter taste)
Loganin (= Loganioside) (iridoid monoterpene glucoside)	<i>Catharanthus roseus</i> (Apocynaceae), <i>Strychnos</i> (Loganiaceae), <i>Menyanthes</i> (Menispermaceae), <i>Hydrangea</i> (Saxifragaceae) spp.	Bitter
[Marrubiin] (labdane diterpene)	Post-extraction from Premarrubiin from <i>Marrubium globosum</i> , <i>M. vulgare</i> (Lamiaceae); use as expectorant	Bitter [non-opiate anti-nociceptive]
Mascaroside (kaurane diterpene glycoside)	<i>Coffea vianneyi</i> (Rubiaceae) [bean]	Very bitter
Neoquassin (= Nigakihemi- acetal B; Simalikahemiactal A) (quassinoid nortriterpene)	<i>Picrasma</i> spp., <i>Quassia amara</i> (Simaroubaceae) [wood]	Bitter
Nigakihemiactal A (quassinoid nortriterpene)	<i>Picrasma quassioides</i> (Simaroubaceae) [stem]	Bitter
Nomilin (limonoid nortriterpene)	<i>Citrus</i> spp. (Rutaceae) [fruit]	Bitter
Palmarin (clerodane diterpene)	<i>Jateorhiza columba</i> (columba root) (Menispermaceae); used for bitter tonic	Bitter
Premarrubiin (labdane diterpene)	<i>Marrubium globosum</i> , <i>M. vulgare</i> (Lamiaceae); use as expectorant	Yields Marrubiin – bitter [non-opiate anti-nociceptive]
Obacunone (= Casimirolide) (limonoid nortriterpene)	<i>Cneorum tricoccon</i> (Cneoraceae), <i>Trichilla trifolia</i> (Meliaceae), <i>Casimiroa edulis</i> , <i>Citrus</i> spp., <i>Dictamnus dasycarpus</i> (Rutaceae), <i>Harrisonia abyssinica</i> (Simaroubaceae)	Bitter [greatly increases effectiveness of some TUB inhibitors]
Oleanolic acid glycosides (triterpene glycoside saponins)	<i>Chenopodium quinoa</i> (quinoa) (Chenopodiaceae)	Bitter
Oleuropein (seco-iridoid phenolic glycoside, monoterpene)	<i>Ligustrum lucidum</i> , <i>L. japonicum</i> , <i>Olea europaea</i> (olive) (Oleaceae) [bark, fruit, leaf]	Bitter [antiarrhythmic, coronary dilater, hypotensive, spasmolytic]
Phytol (non-cyclic diterpene)	Universal in chloroplasts (as ester of chlorophyll propionic acid)	Bitter (oats)
Picrasin C (quassinoid nortriterpene)	<i>Picrasma quassioides</i> (Simaroubaceae)	Bitter
Quassin (= Nigakilactone; Quassiin) (quassinoid nortriterpene)	<i>Ailanthus altissima</i> , <i>Picrasma</i> spp., <i>Quassia amara</i> (Simaroubaceae) [wood]	Bitter
Sarsaparillin (= Parillin) (triterpene glycoside saponin)	<i>Smilax aristolochiaefolia</i> (sarsaparilla) (Liliaceae) [root]	Bitter [haemolytic, permeabilizes membranes]

(continued)

Table 10.2 (Continued)

Compound (details)	Plant source (family) [plant part]	Taste (other targets) / in vivo effects
Tenulin (sesquiterpene lactone)	<i>Helenium amarum</i> (bitter sneezeweed) (Asteraceae)	Bitter
Telosmoside A2 (polyoxypregnane triterpene glycosides)	<i>Telosma procumbens</i> (Asclepiadaceae) [stem]	Bitter (related Teosmosides A8–A18 are sweet)
Vernodalin (elemanolide sesquiterpene lactone)	<i>Vernonia amygdalina</i> [ingested by parasite-infected chimpanzees], <i>V. guineensis</i> (Asteraceae)	Bitter [antibacterial, antitumour, antischistosomal]
Vernodalol (elemanolide sesquiterpene lactone)	<i>Vernonia amygdalina</i> , <i>V. anthelmintica</i> (Asteraceae)	Bitter [antibacterial, antitumour, antischistosomal]
Vernolide (germacranolide sesquiterpene lactone)	<i>Vernonia amygdalina</i> , <i>V. colorata</i> (Asteraceae)	Bitter [antibacterial, antitumour, antischistosomal]
Vernoniol A4 (steroid triterpene)	<i>Vernonia amygdalina</i> (Asteraceae) [ingested by parasite-infected chimpanzees – implied taste/ efficacy association]	Bitter
Vernoniosides A1, A2, A3, A4 (steroid glucoside saponin triterpenes)	<i>Vernonia amygdalina</i> (Asteraceae)	Bitter
Other		10.2o
Ala-Ile-Ala (= AIA) (tripeptide)	From pepsin-catalysed hydrolysis of Zein from <i>Zea mays</i> (corn) (Poaceae) [seed]	Bitter (taste threshold at 50–100)
Ala-Ala-Leu (= AAL) (tripeptide)	From pepsin-catalysed hydrolysis of Zein from <i>Zea mays</i> (corn) (Poaceae) [seed]	Bitter (taste threshold at 50–100)
Amygdalin (= Amygdaloside; Mandelonitrile- β - gentiobioside) (aromatic cyanogenic glycoside)	<i>Gerbera jamesonii</i> (Asteraceae) [root], <i>Prunus amygdalus</i> (bitter almond) (Rosaceae) [seed] [actually ineffective and highly toxic “laetrile” “cancer remedy”]	Bitter [toxic]
Asn-Ala-Leu-Lys-Pro-Asp (= NALKPD) (hexapeptide)	From trypsin-catalysed hydrolysis of Proglycinin from <i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Bitter
Asn-Ala-Met-Phe-Val (= NAMFV) (pentapeptide)	From trypsin-catalysed hydrolysis of Proglycinin from <i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Bitter
Asn-Ala-Met-Phe-Val-Pro-His (= NAMFVP) (septapeptide)	From trypsin-catalysed hydrolysis of Proglycinin from <i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Bitter
β -D-(3,4-Disinapoyl)-Fru- α -D-(6-sinapoyl)Glc (fatty acyl disaccharide)	<i>Securidaca longipedunculata</i> (Polygalaceae) [bark]	Bitter
Ethanol (= Ethyl alcohol; Alcohol) (aliphatic alcohol)	From fermentation of plant-derived starch; writers Brendan Behan, Scott Fitzgerald, Henry Lawson, Edgar Allan Poe, Dylan Thomas & Tennessee Williams drank to excess	“Bitter”; Marc Antony (Marcus Antonius) & Modest Mussorgsky (among many others) drank excessively

(continued)

Table 10.2 (Continued)

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects/
Gly-Ala-Leu (= GAL) (tripeptide)	From pepsin-catalysed hydrolysis of Zein from <i>Zea mays</i> (corn) (Poaceae) [seed]	Bitter (taste threshold at 50–100)
His-Asn-Ile-Gly-Gln-Thr (= HNIGQT) (hexapeptide)	From trypsin-catalysed hydrolysis of Proglycinin from <i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Bitter
Ile-Tyr-Pro-Gly-Cys-Pro (= IYPGCP) (hexapeptide)	From trypsin-catalysed hydrolysis of Proglycinin from <i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Bitter
Ile-Tyr-Pro-Gly-Cys-Pro-Ser- Thr (= IYPGCPS) (octapeptide)	From trypsin-catalysed hydrolysis of Proglycinin from <i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Bitter
Leu-Glu-Leu (= LEL) (tripeptide)	From pepsin-catalysed hydrolysis of Zein from <i>Zea mays</i> (corn) (Poaceae) [seed]	Bitter (taste threshold at 3–12)
Leu-Val-Leu (= LVL) (tripeptide)	From pepsin-catalysed hydrolysis of Zein from <i>Zea mays</i> (corn) (Poaceae) [seed]	Bitter (taste threshold at 2–3)
Leu-Pro-Phe-Ser-Gln-Leu-Val- Leu (= LPFSQLVL) (hexapeptide)	From pepsin-catalysed hydrolysis of Zein from <i>Zea mays</i> (corn) (Poaceae) [seed]	Bitter (taste threshold at 0.1–0.2)
Linamarin (= Manihotoxine) (cyanogenic glycoside)	<i>Manihot esculentum</i> (bitter cassava) (Euphorbiaceae) [root]; has to be soaked and washed before cooking	Bitter [toxic per release of cyanide and thiocyanate]
Linoleic acid (= Linolic acid; <i>cis</i> -9, <i>cis</i> -12-Octadecenoic acid) (unsaturated FA)	Widespread; <i>Helianthus annuum</i> (Asteraceae), <i>Arachis hypogaea</i> , <i>Glycine</i> <i>max</i> (Fabaceae), <i>Linum usitatissimum</i> (Linaceae), <i>Gossypium hirsutum</i> (Malvaceae) [oil]	Bitter – “burning bitter” off-taste (at 5)
Ranunculin (aliphatic lactone glycoside)	<i>Actaea rubra</i> , <i>Anemone</i> , <i>Clematis</i> , <i>Ranunculus</i> spp. (buttercup) (Ranunculaceae)	Bitter [wounding plant yields vesicant dermatitic oil Protoanemonin]
Ser-Ile-Ile-Asp-Thr (= SIIDT) (pentapeptide)	From trypsin-catalysed hydrolysis of Proglycinin from <i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Bitter
β -D-(3-Sinapoyl)-Fru- α - D-(6-sinapoyl)Glc (fatty acyl disaccharide)	<i>Securidaca longipedunculata</i> (Polygalaceae) [bark]	Bitter
9,10,13-Trihydroxyoctadec- 11-enoic acid (unsaturated FA)	Linoleic acid-derived oxidation product (catalysis by a <i>Glycine</i> <i>max</i> (soya bean) (Fabaceae) cell-free system)	Bitter (at 1)
9,12,13-Trihydroxyoctadec- 10-enoic acid (unsaturated FA)	Linoleic acid-derived oxidation product (catalysis by a <i>Glycine</i> <i>max</i> (soya bean) (Fabaceae) cell-free system)	Bitter (at 1)
Non-plant reference		10.2n
[L-Asp-D-Phe methyl ester] (dipeptide)	Semi-synthetic; L-Asp-L-Phe methyl ester isomer (Aspartame) is sweet	Bitter
[Bacitracin] (1 kDa peptide)	Animal hormone	Bitter (threshold at 10–20 nM)

(continued)

Table 10.2 (Continued)

Compound (details)	Plant source (family) plant part	Taste (other targets) / in vivo effects
[Denatonium benzoate (=Lignocaine benzyl benzoate)] (aromatic quaternary amine benzoate salt)	Synthetic; added to toxic substances to prevent accidental ingestion	Bitter (one of the bitterest substances known)
[6-Propylthiouracil (= PROP)] (pyrimidine)	Synthetic; used in identification of genetic PROP “tasters” and “non-tasters”	PROP tasters (as compared to genetic “non-tasters”) rate caffeine more bitter
[Sucrose octaacetate] (sugar)	Synthetic	Bitter

Table 10.3 Sour (acid) tasting plant compounds

Compound (class)	Plant (family) part	Taste (other targets) / in vivo effects
Other		10.3o
Acetic acid (aliphatic carboxylic acid)	Universal; <i>Astragalus gummifer</i> (Fabaceae), <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (vinegar); Jesus given vinegar immediately before He said “It is finished”	Sour (acid) taste (OD-R) [metabolic intermediate as acetylcoenzyme A]
Aconitic acid (aliphatic tricarboxylic acid)	Universal; <i>Achillea</i> spp. (Asteraceae), <i>Saccharum officinale</i> (sugar cane juice) (Poaceae), <i>Aconitum napellus</i> , <i>Adonis vernalis</i> (Ranunculaceae) [leaf, tuber]	Sour (acid) taste [TCA cycle intermediate]
Adipic acid (= 1,4- Butanedicarboxylic acid) (aliphatic dicarboxylic acid)	Widespread (traces); <i>Beta vulgaris</i> (beetroot juice) (Chenopodiaceae), <i>Uncaria catechu</i> (Pedaliaceae)	Sour (acid) taste
Citramalic acid (= 2- Methylmalic acid) (aliphatic dicarboxylic acid)	<i>Malus domestica</i> (apple peel) (Rosaceae) <i>Citrus</i> spp. (Rutaceae) [fruit]	Sour (acid) taste
Citric acid (aliphatic tricarboxylic acid)	Universal; <i>Hibiscus sabdariffa</i> (Malvaceae), <i>Citrus limon</i> (lemon), <i>C. mitis</i> (Rutaceae) [fruit juice]	Sour (acid) taste (OD-R) [TCA cycle intermediate]
Formic acid (carboxylic acid)	Widespread (low); <i>Croton tiglium</i> (Euphorbiaceae), <i>Urtica dioica</i> (stinging nettle) (Urticaceae)	Acid taste [toxic]
Fumaric acid (aliphatic dicarboxylic acid)	Universal; <i>Helianthus annuus</i> (Asteraceae), <i>Capsella bursa-pastoris</i> (Brassicaceae), <i>Pisum sativum</i> (Fabaceae), <i>Averrhoa carambola</i> (Oxalidaceae) <i>Glaucium flavum</i> (Papaveraceae) [leaf], <i>Malus domestica</i> (apple) (Rosaceae) [green fruit]	Sour (acid) taste [TCA cycle intermediate]
Glutaric acid (= 1,3- Propanedicarboxylic acid) (aliphatic dicarboxylic acid)	<i>Beta vulgaris</i> (beetroot juice) (Chenopodiaceae), <i>Avena sativa</i> (Poaceae)	Sour (acid) taste [toxic]

(continued)

Table 10.3 (Continued)

Compound (class)	Plant (Family) part	Taste (other targets) / in vivo effects
Glycolic acid (= Hydroxyacetic acid) (carboxylic acid)	Universal; <i>Allium cepa</i> (Liliaceae), <i>Malus domestica</i> (apple), <i>Pyrus communis</i> (pear) (Rosaceae), <i>Vitis vinifera</i> (Vitaceae) [green fruit]; <i>Saccharum officinale</i> (sugar cane juice) (Poaceae)	Sour (acid) taste [irritant]
Glyoxylic acid (= Oxoacetic acid) (carboxylic acid)	Universal; unripe fruit, young leaf; <i>Beta vulgaris</i> (young sugar beet) (Chenopodiaceae), <i>Ribes uva-crispa</i> (Grossulariaceae) [fruit]	Sour (acid) taste [irritant]
Isocitric acid (aliphatic tricarboxylic acid)	Universal; <i>Daucus carota</i> (Apiaceae), <i>Bryophyllum calycinum</i> (Crassulaceae) [leaf], <i>Rubus</i> spp. (blackberry) (Rosaceae)	Sour (acid) taste [TCA cycle intermediate]
α -Ketoglutaric acid (aliphatic dicarboxylic acid)	Universal; <i>Averrhoa carambola</i> (Oxalidaceae), <i>Hordeum vulgare</i> (barley seed) (Poaceae)	Sour (acid) taste [TCA cycle intermediate]
l.-Lactic acid (= 2-Hydroxypropionic acid) (carboxylic acid); accumulation in anaerobic muscle shown by Sir Frederick Gowland Hopkins (UK, Nobel Prize, Medicine, 1929, growth stimulating vitamins)	<i>Musa</i> spp. (banana) (Musaceae), <i>Papaver somniferum</i> (Papaveraceae), <i>Malus domestica</i> (apple), <i>Pyrus communis</i> (pear) (Rosaceae), <i>Vitis vinifera</i> (Vitaceae) [fruit]; <i>Digitalis purpurea</i> (Scrophulariaceae)	Sour (acid) taste
l.-Malic acid (= Hydroxysuccinic acid) (aliphatic dicarboxylic acid)	Universal; <i>Mangifera indica</i> (Anacardiaceae), <i>Hibiscus sabdariffa</i> (Malvaceae), <i>Musa</i> spp. (Musaceae), <i>Malus domestica</i> , <i>Prunus armeniaca</i> , <i>P. persica</i> (peach) (Rosaceae), <i>Vitis vinifera</i> (grape) (Vitaceae) [fruit]; night-time accumulation in CAM plants	Sour (acid) taste [TCA cycle intermediate; key Crassulacean Acid Metabolism (CAM) intermediate]
Mevalonic acid (aliphatic dicarboxylic acid)	Universal; <i>Zea mays</i> (Poaceae), <i>Malus domestica</i> (Rosaceae), <i>Citrus sinensis</i> (Rutaceae)	Acid [isoprenoid metabolism]
Oxaloacetic acid (= Oxosuccinic acid) (aliphatic dicarboxylic acid)	Universal; <i>Hordeum vulgare</i> (barley seed) (Poaceae), <i>Malus domestica</i> (Rosaceae)	Sour (acid) taste [TCA cycle intermediate]
Malonic acid (= Methanedicarboxylic acid) (aliphatic dicarboxylic acid)	Universal as malonylcoenzyme A intermediate in fatty acid synthesis; <i>Apium graveolens</i> (Apiaceae), <i>Beta vulgaris</i> (beetroot) (Chenopodiaceae), <i>Avena sativa</i> (oats), <i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	Sour (acid) taste (Succinate DH) [Fatty acid synthesis intermediate]
Nonanedioic acid (= Azelaic acid) (aliphatic dicarboxylic acid)	<i>Olea europaeae</i> (Oleaceae) [rancid olive oil], <i>Solanum tuberosum</i> (Solanaceae) [leaf]	Sour taste [anti-acne]

(continued)

Table 10.3 (Continued)

Compound (class)	Plant (Family) part	Taste (other targets) / in vivo effects
Oxalic acid (= Ethanedioic acid) (dicarboxylic acid)	<i>Chenopodium album</i> , <i>Spinacia oleracea</i> (spinach leaf) (Chenopodiaceae), <i>Averrhoa carambola</i> , <i>Oxalis</i> spp. (Oxalidaceae), <i>Fagopyrum</i> <i>esculentum</i> , <i>Rheum rhabonticum</i> (Polygonaceae)	Sour (acid) taste [toxic; sequesters Ca ²⁺ , haemostatic]
Pimelic acid (= Heptanedioic acid) (dicarboxylic acid)	<i>Ricinus communis</i> (castor oil) (Euphorbiaceae)	Sour (acid) taste
Pyruvic acid (= 2-Oxopropionic acid) (carboxylic acid)	Universal; <i>Panax quinquefolius</i> (Araliaceae), <i>Allium cepa</i> (Liliaceae)	Sour (acid) taste
Quinic acid (alicyclic carboxylic acid)	<i>Pistacia lentiscus</i> (Anacardiaceae), <i>Vaccinium myrtillus</i> (Ericaceae), <i>Musa</i> spp. (banana) (Musaceae), <i>Malus domestica</i> (apple), <i>Prunus</i> <i>armeniaca</i> (apricot), <i>P. persica</i> (peach), <i>Pyrus communis</i> (pear) (Rosaceae) [fruit]	Sour (acid) taste [green apple sourness]
Sebacic acid (= Decanedioic acid) (dicarboxylic acid)	<i>Ricinus communis</i> (castor oil) (Euphorbiaceae)	Sour (acid) taste
Shikimic acid (alicyclic carboxylic acid)	Universal; <i>Actinidia deliciosa</i> (gooseberry) (Actinidiaceae), <i>Pistacia lentiscus</i> (Anacardiaceae), <i>Mammea americana</i> (Clusiaceae), <i>Terminalia chebula</i> (Combretaceae), <i>Illicium religiosum</i> (Magnoliaceae), <i>Fragaria virginiana</i> (strawberry), <i>Prunus</i> <i>cerasus</i> (cherry) (Rosaceae)	Sour (acid) taste [Shikimate pathway for aromatic compound biosynthesis]
Subaric acid (= Octanedioic acid) (dicarboxylic acid)	<i>Ricinus communis</i> (castor oil) (Euphorbiaceae)	Sour (acid) taste
Succinic acid (= Butanedioic acid) (aliphatic dicarboxylic acid)	Universal; <i>Panax quinquefolius</i> (Araliaceae), <i>Averrhoa carambola</i> (Oxalidaceae), <i>Fragaria virginiana</i> (strawberry), <i>Pyrus communis</i> (pear), (Rosaceae), <i>Vitis vinifera</i> (grape) (Vitaceae) [fruit]; <i>Medicago sativa</i> (alfalfa) (Fabaceae) [leaf]	Sour (acid) taste [TCA cycle intermediate]
l(+)-Tartaric acid (= (2 <i>R</i> ,3 <i>R</i>)- 2,3- Dihydroxybutanedioic acid) (aliphatic dicarboxylic acid)	<i>Tamarindus indica</i> (tamarind) (Fabaceae), <i>Morus indica</i> (mulberry) (Moraceae), <i>Averrhoa carambola</i> (Oxalidaceae), <i>Vitis</i> <i>vinifera</i> (grape) (Vitaceae) [fruit]; <i>Pelargonium</i> spp. (geranium) (Geraniaceae) [leaf]	Sour (acid) taste; separation & optical activity of dextro- tatory (2<i>R</i>,3<i>R</i>)- & laevorotatory (2<i>S</i>,3<i>S</i>)-tartaric acid by Louis Pasteur

Table 10.4 Odorant plant compounds

Compound (details)	Plant source (family) / plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Alkaloid		
2-Acetyl-1-pyrroline (pyrroline)	<i>Oryza sativa</i> (aromatic rice, cooked rice) (Poaceae); non-fat dry milk aroma-active	10.4a OD-R (pop-corn); main aroma of cooked rice
Damascenine (= Methyl damasceninate; Nigelline) (alkaloid)	<i>Nigella damascena</i> , <i>N. arvensis</i> (Nigella seed) (Ranunculaceae)	OD-R (nigella seed) [antioedema, antipyretic]
2-Ethylpyrazine (pyrazine)	<i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]	OD-R (nutty)
Indole (= 2,3- Benzopyrrole) (indole)	<i>Amorphophallus</i> spp., <i>Arum maculatum</i> , <i>Dracunculus vulgaris</i> , <i>Sauromatum guttatum</i> (Araceae), <i>Jasminum officinale</i> (Oleaceae), <i>Citrus</i> spp. (Rutaceae) [flower], <i>Cynodon</i> <i>dactylon</i> , <i>Zea mays</i> (Poaceae)	OD-R (animal, faecal) [insect attractant]
2-Methoxy-3,5- dimethylpyrazine (pyrazine)	<i>Coffea</i> spp. (coffee seed) (Rubiaceae)	OD-R (earthy)
2-Methoxy-3- isobutylpyrazine (pyrazine)	<i>Coffea</i> spp. (coffee seed) (Rubiaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (peasy)
2-Methoxy-3-isopropyl- pyrazine (pyrazine)	<i>Coffea</i> spp. (coffee seed) (Rubiaceae), <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (beany, earthy, peasy)
Skatole (= 3-Methyl- 1 <i>H</i> -indole (indole)	<i>Arum</i> spp. (Araceae), <i>Tecoma stans</i> (Bignoniaceae), <i>Beta vulgaris</i> (Chenopodiaceae), <i>Nectandra</i> sp. (Lauraceae), <i>Cynodon dactylon</i> (Bermuda grass) (Poaceae)	OD-R (faecal)
Phenolic		
1'-Acetoxyeugenol acetate (phenylpropanoid)	<i>Alpinia galanga</i> (Thai ginger) (Zingiberaceae)	10.4p OD-R (pungent)
Anethole (= <i>p</i> -Propenylanisole) (phenylpropanoid)	<i>Foeniculum vulgare</i> , <i>Pimpinella anisum</i> Apiaceae), <i>Artemisia porrecta</i> , <i>Aster</i> <i>tartaricus</i> (Asteraceae), <i>Canarium</i> <i>indicum</i> (Burseraceae), <i>Juniperus</i> <i>rigida</i> (Cupressaceae), <i>Illicium anisatum</i> (Illiciaceae), <i>Magnolia salicifolia</i> (Magnoliaceae), <i>Backhousia anisata</i> (Myrtaceae), <i>Clausenia anisata</i> , <i>Pelea</i> <i>christophersenii</i> (Rutaceae) [oil]	OD-R [carminative, spasmolytic]
<i>p</i> -Anisaldehyde (= 4- Methoxybenzaldehyde) (aryl aldehyde)	<i>Cuminum cyminum</i> , <i>Foeniculum vulgare</i> , <i>Pimpinella anisum</i> (Apiaceae), <i>Acacia</i> spp., <i>Cassia</i> spp. (Fabaceae), <i>Illicium anisatum</i> (Illiciaceae), <i>Agastache rugosa</i> (Lamiaceae), <i>Magnolia salicifolia</i> (Magnoliaceae), <i>Vanilla</i> spp. (Orchidaceae), <i>Pinus</i> spp. (Pinaceae), <i>Pelea madagascariensis</i> (Rutaceae) [oil]	OD-R (coumarin-like odour)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects
β -Asarone (phenylpropanoid)	<i>Daucus carota</i> (Apiaceae), <i>Acorus calamus</i> (Araceae), <i>Asarum europaeum</i> (Aristolochiaceae), <i>Piper angustifolium</i> (Piperaceae)	OD-R [carcinogen, insect attractant, spasmolytic]
Bergaptene (= Bergapten) (coumarin)	<i>Ficus carica</i> (Moraceae), <i>Citrus aurantium</i> , <i>Fagara</i> spp., <i>Ruta graveolens</i> (Rutaceae); Apiaceae, Pittosporaceae [oil]	OD-R (DNA) [anti-vitilego, anti-psoriasis , toxic]
Cinnamaldehyde (= Cinnamic aldehyde; Phenylacrolein) (phenylpropanoid) Cinnamic acid (phenylpropanoid)	<i>Commiphora</i> spp. (Bursaceae), <i>Lavandula</i> spp., <i>Pogostemon cablin</i> (Lamiaceae), <i>Cinnamomum aromaticum</i> , <i>C. verum</i> , <i>C. zeylanicum</i> (Lauraceae), <i>Hyacinthus</i> spp., <i>Narcissus</i> spp. (Liliaceae)	OD-R (cinnamon) [germination inhibition]
Cinnamyl acetate (phenylpropanoid ester)	<i>Commiphora</i> spp. (Bursaceae), <i>Cinnamomum verum</i> , <i>C. zeylanicum</i> (Lauraceae) [oil]	OD-R
Coumarin (coumarin)	Widespread; most Angiosperms e.g. <i>Dipteryx odorata</i> (Fabaceae), <i>Camellia sinensis</i> (tea) (Theaceae), Poaceae; Gymnosperms e.g. Pinaceae; ferns	OD-R (newly cut grass) [antifungal, antitumour, haemorrhagic, rodenticide]
<i>m</i> -Cresol (= 3-Methylphenol) (phenol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (shoe polish, machine)
2,6-Dimethoxyphenol (phenol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (phenolic, chemical)
Estragole (= Methylchavicol) (phenylpropanoid)	<i>Foeniculum vulgare</i> , <i>Pimpinella anisum</i> (Apiaceae), <i>Artemisia</i> , <i>Solidago</i> , <i>Tagetes</i> sp. (Asteraceae), <i>Croton</i> sp. (Euphorbiaceae), <i>Illicium anisatum</i> (Illiciaceae), <i>Agastache</i> spp., <i>Ocimum basilicum</i> (Lamiaceae), <i>Magnolia kobus</i> (Magnoliaceae), <i>Myrcia acris</i> (Myrtaceae), <i>Pinus</i> sp. (Pinaceae), <i>Piper betel</i> (Piperaceae), <i>Citrus</i> spp., <i>Dictamnus alba</i> (Rutaceae) [oil]	OD-R (DNA)
Ethyl dihydrocinnamate (phenolic)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (flowery)
4-Ethylguaiaicol (= 4-Ethyl-2-methoxyphenol; 4-Ethyl- <i>O</i> -methylcatechol) (catechol)	<i>Coffea</i> spp. (coffee seed) (Rubiaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (flowery, phenolic, sweet)
3-Ethylphenol (phenol)	<i>Xylopia aethiopica</i> (Annonaceae) [fruit]	OD-R (phenol)
4-Ethylphenol (phenol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (phenolic, shoe polish)
Ethyl vanillate (phenolic ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (pollen, flowery)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Eugenol (= Allylguaiacol, Caryophylllic acid, Eugenic acid; 2- Methoxy-4-(2- propenyl)phenol) (phenylpropanoid)	<i>Pimenta dioica</i> , <i>Syzygium aromaticum</i> (Myrtaceae); <i>Achillea</i> , <i>Artemisia</i> (Asteraceae), <i>Cinnamomum</i> , <i>Ocimum</i> (basil), <i>Origanum</i> (Lamiaceae), <i>Sassafras</i> (Lauraceae), <i>Illicium</i> (Magnoliaceae), <i>Musa</i> (Musaceae), <i>Myristica</i> (Myristicaceae), <i>Eugenia</i> (Myrtaceae), <i>Piper</i> (Piperaceae), <i>Vitis</i> (Vitaceae) <i>Rosa</i> (Rosaceae), <i>Camellia</i> (Theaceae) spp.	OD-R (cinnamon, clove, balsamic, floral, spicy) (COX-1, COX-2, GST) [anticonvulsant, antioxidant, anaesthetic, antiseptic, AI, PAI]
[6]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	OD-R (pungent) (COX, 5-LOX)
Guaiacol (2-Methoxyphenol; O-Methylcatechol) (catechol)	<i>Apium graveolens</i> (celery seed) (Apiaceae), <i>Betula</i> sp. (Betulaceae), <i>Camellia sinensis</i> (tea) (Theaceae), <i>Vitis vinifera</i> (Vitaceae) (wine), <i>Guaiacum</i> sp. (guaiac resin) (Zygophyllaceae)	OD-R (burnt, chemical, phenolic) [anti-eczema]
<i>p</i> -Hydroxy- benzaldehyde (phenolic aldehyde)	Widespread	OD-R
2-Hydroxy- cinnamaldehyde (phenolic)	<i>Cinnamomum cassia</i> (cinnamon-like) (Lauraceae) [stem oil]	OD-R (cinnamon aroma) (FPTase) [sweet taste]
Isoeugenol (= 4-Propenylguaiacol) (phenylpropanoid)	<i>Cananga odorata</i> (Annonaceae), <i>Juniperus</i> <i>scopulorum</i> (Cupressaceae), <i>Myristica</i> <i>fragrans</i> (Myristicaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (flowery, clove) [PAI]
Methyl salicylate (= 2- Hydroxybenzoic acid methyl ester) (phenolic ester)	<i>Betula lenta</i> (sweet birch oil) (Betulaceae), <i>Gaultheria fragrantissima</i> , <i>G. procumbens</i> (Ericaceae), <i>Malus domestica</i> (apple) (Rosaceae); wintergreen oil, betula, teaberry	OD-R
[6]-Paradol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	OD-R (pungent) – ginger flavour
Piperonal (benzaldehyde)	<i>Eryngium potericum</i> (Apiaceae), <i>Baccharis</i> <i>rosemarinifolia</i> (Asteraceae), <i>Heliotropium</i> spp. (Boraginaceae), <i>Robinia pseudoacacia</i> (Fabaceae), <i>Doryphora sassafras</i> (Monimiaceae), <i>Vanilla</i> spp. (Orchidaceae), <i>Viola</i> spp. (Violaceae)	OD-R
4-Propylguaiacol (= 4-Propyl-2-methoxy- phenol; 4-Propyl- O-methylcatechol) (catechol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (phenolic, sweet)
Safrole (= 5-(2- Propenyl)-1,3- benzodioxole; Shikimol) (benzodioxole)	<i>Cinnamomum mollissimum</i> , <i>C. petrophilum</i> , <i>Ocotea pretios</i> , <i>Sassafras albidum</i> , <i>S. officinale</i> , <i>S. varifolium</i> (root, Sassafras oil) (Lauraceae), <i>Illicium anisatum</i> (anise oil) (Magnoliaceae), <i>Myristica fragrans</i> (Myristicaceae), <i>Piper hispidinervum</i> (Piperaceae) [Sassafras oil]	OD-R (fragrant) (DNA) [anticonvulsant, antiseptic, carcinogen, carminative, toxic]

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects
[6]-Shogaol (phenylpropane ketone)	<i>Anomum melegueta</i> [seed], <i>Zingiber officinale</i> (ginger) [rhizome] (Zingiberaceae)	OD-R (pungent) [molluscicide]
Sinapine (Phenylpropanoid)	<i>Brassica napus</i> (rapeseed), <i>B. spp.</i> , <i>Crambe asiatica</i> , <i>Draba nemorosa</i> , <i>Lepidium sativum</i> , <i>Sinapis alba</i> , <i>Sisymbrium columnae</i> (Brassicaceae)	OD-R; taint of eggs from hens fed on rapeseed meal
Vanillin (= 3-Methoxy-4-hydroxy-benzaldehyde; Methylprotocatechuic aldehyde) (phenolic acid)	Widespread as aglycone & glucoside (Vanilloside); <i>Xylopiia aethiopica</i> (Annonaceae), <i>Dahlia spp.</i> (Asteraceae), <i>Beta vulgaris</i> (Chenopodiaceae), <i>Asparagus spp.</i> (Liliaceae), <i>Syzygium aromaticum</i> (Myrtaceae), <i>Gymnolenia spp.</i> , <i>Vanilla planifolia</i> (Orchidaceae), <i>Hordeum vulgare</i> (Poaceae), <i>Coffea spp.</i> (Rubiaceae), <i>Citrus paradisi</i> , <i>Ruta spp.</i> (Rutaceae), <i>Litchi chinensis</i> , <i>Nephelium lappaceum</i> (Sapindaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (vanilla-like, candy) [antifungal]; non-fat dry milk aroma-active (elevated by higher heat-treatment)
4-Vinylguaiacol (= 4-Vinyl-2-methoxyphenol; 4-Vinyl-O-methylcatechol) (catechol)	<i>Coffea spp.</i> (coffee seed) (Rubiaceae), <i>Citrus sinensis</i> (orange) (Rutaceae)	OD-R (clove-like) [orange juice “off” odour]
4-Vinylphenol (phenol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (cypress, vanilla)
Terpene		10.4t
Anethofuran (monoterpene)	<i>Anethum graveolens</i> (dill oil), <i>Carum carvi</i> (Caraway oil) (Apiaceae)	OD-R
Ascaridole (= Ascaridol) (monoterpene)	<i>Chenopodium ambrosioides</i> (aerial, chenopodium oil) (Chenopodiaceae)	OD-R [anthelmintic, toxic]
(+)-Borneol (monoterpene)	<i>Tanacetum vulgare</i> (Asteraceae), <i>Asarum canadense</i> Aristolochiaceae), <i>Dryobalanops aromatica</i> (Dipterocarpaceae), <i>Lavandula spica</i> , <i>Rosmarinus officinalis</i> , <i>Salvia officinalis</i> (Lamiaceae), <i>Myristica fragrans</i> (nutmeg) (Myristicaceae), <i>Elettaria cardamomum</i> (Zingiberaceae)	OD-R
(-)-Borneol (monoterpene)	<i>Blumea balsamifera</i> (ngai camphor oil) (Asteraceae)	OD-R
D-Bornyl acetate (= Borneol acetate) (monoterpene)	<i>Lavandula angustifolia</i> , <i>Rosmarinus officinalis</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Abies alba</i> , <i>A. siberica</i> , <i>Pinus montana</i> , <i>P. sylvestris</i> (Pinaceae), <i>Valeriana spp.</i> (root oil) (Valerianaceae)	OD-R (pine needle)
β -Cadinene (sesquiterpene)	<i>Juniperus communis</i> (fruit, needle, juniper oil) (Cupressaceae), <i>Piper betel</i> (Piperaceae)	OD-R

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Camphene (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Artemisia salsoloides</i> (Asteraceae), <i>Salvia officinalis</i> (Lamiaceae), <i>Myristica fragrans</i> (Myristicaceae), <i>Abies siberica</i> , <i>Cupressus sempervirens</i> , <i>Pinus roxburghii</i> , <i>P</i> spp. (Pinaceae), <i>Andropogon</i> (<i>Cymbopogon</i>) <i>nardus</i> (Poaceae)	OD-R (fruity, spicy)
(+)- Camphor (= Borman-2-one; Camphan-2-one) (monoterpene)	<i>Achillea</i> spp., <i>Artemisia salsoloides</i> , <i>Tanacetum vulgare</i> (leaf & tops, Tansy oil) (Asteraceae), <i>Cinnamomum camphora</i> (camphor oil) (Lauraceae), <i>Myrtus communis</i> (leaf, myrtle oil) (Myrtaceae)	OD-R (camphor) [irritant, insect repellent]
3-Carene (= (-)-Car-3-ene) (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Abies</i> , <i>Picea</i> , <i>Pinus sylvestris</i> , <i>P. longifolia</i> , <i>P</i> spp. (turpentine oil) (Pinaceae), <i>Kaempferia galanga</i> (Zingiberaceae)	OD-R (terpeny) [irritant]
Carotol (sesquiterpene)	<i>Daucus carota</i> (seed, carrot oil) (Apiaceae)	OD-R
Carvacrol (monoterpene)	<i>Monarda fistulosa</i> , <i>Origanum vulgare</i> (flower, organum oil), <i>Satureja montana</i> , <i>Thymus vulgaris</i> (leaf, thyme oil) (Lamiaceae)	OD-R [antifungal, anthelmintic, antiseptic]
(<i>R</i>)-Carvone (= (-)- Carvone) (monoterpene)	<i>Mentha spicata</i> (flower, spearmint oil), <i>Mosla dianthera</i> (miniature beefsteakplant) (Lamiaceae)	OD-R (spearmint; <i>Mosla</i> odour) [antiseptic, carminative]
(<i>S</i>)-Carvone (= (+)- Carvone) (monoterpene)	<i>Anethum graveolens</i> (dill seed oil), <i>Carum carvi</i> (fruit, Caraway oil) (Apiaceae), <i>Mosla dianthera</i> (miniature beefsteakplant) (Lamiaceae)	OD-R (caraway) [antiseptic, carminative]
α -Caryophyllene (= Humulene) (humulane sesquiterpene)	<i>Humulus lupulus</i> (Cannabaceae), <i>Didymocarpus pedicellata</i> (leaf oil) (Gesneriaceae), <i>Mosla dianthera</i> (miniature beefsteakplant) (Lamiaceae), <i>Lindera strychnifolia</i> (Lauraceae)	OD-R (hops)
β -Caryophyllene (sesquiterpene)	<i>Copaifera</i> sp. (Fabaceae), <i>Mosla dianthera</i> (Lamiaceae), <i>Eugenia caryophyllata</i> (flower, Clove oil) (Myrtaceae), <i>Piper</i> sp. (Piperaceae)	OD-R
γ -Caryophyllene (= Isocaryophyllene) (sesquiterpene)	<i>Eugenia caryophyllata</i> (flower, clove oil) (Myrtaceae)	OD-R
α -Cedrene (sesquiterpene)	<i>Juniperus virginiana</i> (red cedar, cedar wood oil), <i>J.</i> spp. (Cupressaceae)	OD-R (cypress)
α -Cedrol (= Cedar camphor) (sesquiterpene)	<i>Cupressus sempervirens</i> (cypress oil), <i>Juniperus virginiana</i> (red cedar, Cedar wood oil), <i>J.</i> spp. (Cupressaceae)	OD-R (cypress)
Chrysanthenone (= 2-Pinen-7-one) (monoterpene)	<i>Chrysanthemum indicum</i> (chrysanthemum) (Asteraceae) [oil]	OD-R

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects
1,8-Cineole (= Eucalyptol) (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Artemisia maritima</i> (Asteraceae), <i>Lavandula spica</i> , <i>Ocimum basilicum</i> , <i>Eucalyptus globulus</i> , <i>E. spp.</i> , <i>Melaleuca leucadendron</i> , <i>Melaleuca viridiflora</i> , <i>M. spp.</i> , <i>Myrtus communis</i> (Myrtaceae), <i>Elettaria cardamomum</i> (Zingiberaceae); Dame Mary Gilmore reported antiseptic leaf use in puerperal fever-free Australian aboriginal birthing	OD-R (eucalyptus , peppermint-like) [anthelmintic, antiseptic, expectorant, insect repellent]; Ignaz Semmelweis discovered the importance of aseptic conditions for avoiding puerperal fever
Citral (= mixture of Citral A (Geranial) & Citral B (Neral) = <i>trans</i> - & <i>cis</i> -3,7-Dimethyl-2,6-octadienal) (monoterpene)	<i>Melissa officinalis</i> (balm oil) (Lamiaceae), <i>Myrcia acris</i> (bay oil) (Myrtaceae), <i>Citrus Andropogon citratus</i> (lemon grass oil) (Poaceae), <i>Rosa spp.</i> (rose oil) (Rosaceae), <i>Citrus limon</i> (lemon peel), <i>C. sinensis</i> (orange) (Rutaceae) [flower], <i>Verbena triphylla</i> (verbena) (Verbenaceae)	OD-R (lemon-like) [antiseptic]
Citronellal (= 3,7-Dimethyloct-6-enal) (monoterpene)	<i>Melissa officinalis</i> (Lamiaceae), <i>Eucalyptus citriodora</i> , <i>E. spp.</i> (Myrtaceae), <i>Andropogon nardus</i> (Poaceae), <i>Citrus limon</i> (Rutaceae)	OD-R [antiseptic, insect defence, sedative]
(+)- α -Citronellol (= 3,7-Dimethyl-6-octen-1-ol) (monoterpene)	<i>Andropogon nardus</i> (leaf, citronella oil) (Poaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (green, clove)
(-)- β -Citronellol (= 3,7-Dimethyl-6-octen-1-ol) (monoterpene)	<i>Pelargonium odoratissimum</i> (Geraniaceae), <i>Rosa damascena</i> , <i>R. gallica</i> (Rosaceae), <i>Boronia citriodora</i> (boronia leaf oil) (Rutaceae)	OD-R
α - & β -Cubebene (sesquiterpene)	<i>Piper cubeba</i> (fruit, cubeb oil) (Piperaceae)	OD-R (spicy)
Cumic alcohol (= <i>p</i> -Isopropyl benzyl alcohol) (monoterpene)	<i>Carum carvi</i> (seed, caraway oil) (Apiaceae), <i>Commiphora myrrha</i> (myrrh) (Bursaceae) [magi gift to infant Jesus], <i>Glycyrrhiza glabra</i> (Fabaceae)	OD-R (caraway-like odour, burning taste)
Cuminaldehyde (= 4-Isopropyl-benzaldehyde) (monoterpene)	<i>Carum carvi</i> , <i>Cuminum cyminum</i> (fruit, seed, cumin oil) (Apiaceae), <i>Commiphora abyssinica</i> (Bursaceae), <i>Cassia fistula</i> (cassia) (Fabaceae), <i>Eucalyptus globulus</i> (Myrtaceae)	OD-R (curry) (TYR) [Cumin major curry powder component]
α - & β -Curcumene (sesquiterpene)	<i>Curcuma aromatica</i> , <i>C. xanthorrhiza</i> (rhizome, turmeric oil), <i>Zingiber officinale</i> (rhizome, Ginger oil) (Zingiberaceae)	OD-R
<i>p</i> -Cymene (= <i>p</i> -Isopropyl toluene) (monoterpene)	<i>Carum copticum</i> , <i>Cuminum cuminum</i> (Apiaceae), <i>Chenopodium ambrosioides</i> (Chenopodiaceae), <i>Thymus spp.</i> (Lamiaceae)	OD-R
β -Damascone (norisoprenoid)	<i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae)	OD-R (honey-like)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
β -Damascenone (norisoprenoid, carotene)	<i>Sambucus canadensis</i> , <i>S. nigra</i> (Caprifoliaceae), <i>Ipomoea pes-caprae</i> (Convolvulaceae), <i>Citrus sinensis</i> (Rutaceae), <i>Litchi chinensis</i> , <i>Nephelium lappaceum</i> (Sapindaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (elderberry, fruity, honey-like, canned peach)
Daucol (sesquiterpene)	<i>Daucus carota</i> (seed, carrot oil) (Apiaceae)	OD-R (earthy)
(ζ)-Dihydrocarvone (monoterpene)	<i>Mosla dianthera</i> (miniature beefsteakplant) (Lamiaceae)	OD-R (spearminty, pepperminty)
Dipentene (= <i>d,l</i> -Limonene) (monoterpene)	<i>Boswellia sacra</i> (frankincense) (Burseraceae) [magi gift to infant Jesus], <i>Myristica fragrans</i> (Myristicaceae), <i>Myrtus communis</i> (Myrtaceae), <i>Pinus</i> spp. (Pinaceae), <i>Piper cubeba</i> (Piperaceae), <i>Andropogon citratius</i> , <i>A. nardus</i> , <i>A. schoenanthus</i> (Poaceae), <i>Citrus aurantium</i> (orange peel, bergamot oil) (Rutaceae)	OD-R [irritant]
γ -Elemene (sesquiterpene)	<i>Piper bisasperatum</i> (Piperaceae) [leaf, spike oil]	OD-R
α -Farnesene (sesquiterpene)	<i>Xylopiya aethiopica</i> (Annonaceae), <i>Malus</i> sp. (apple), <i>Pyrus</i> sp. (pear) (Rosaceae) [fruit]	OD-R (sweet, flowery) [alarm pheromone]
β -Farnesene (sesquiterpene)	<i>Solanum berthaultii</i> (Solanaceae) [leaf oil]	OD-R (sweet, flowery) [alarm pheromone]
<i>trans-trans</i> -Farnesol (sesquiterpene); synthesis by Leopold Ruzicka (Croatia/ Switzerland) (Nobel Prize, Chemistry, 1939, sex hormones, with Adolph Butenandt)	Widespread in many oils & flowers e.g. <i>Abelmoschus moschatus</i> (seed oil) (Malvaceae), <i>Andropogon citratius</i> (lemon grass), <i>A. nardus</i> (leaf, citronella oil) (Poaceae), <i>Rosa</i> spp. (rose oil) (Rosaceae),	OD-R (floral)
Fenchol (= 1,3,3- Trimethyl-2- norcamphanol) (monoterpene)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit], <i>Citrus aurantiifolia</i> (lime) (Rutaceae)	OD-R (coffee, woody)
(+)-Fenchone (= 1,3,3- Trimethyl-2- norcamphanone) (monoterpene)	<i>Xylopiya aethiopica</i> (Annonaceae) [fruit], <i>Foeniculum vulgare</i> (fruit, fennel oil) (Apiaceae), <i>Lavandula stoechas</i> (Lavender oil) (Lamiaceae)	OD-R (sweet, camphoracious)
(-)-Fenchone (= 1,3,3- Trimethyl-2- norcamphanone) (monoterpene)	<i>Thuja occidentalis</i> (white cedar oil) (Pinaceae)	OD-R
(<i>E</i>)-Furan linalool oxide (monoterpene)	<i>Litchi chinensis</i> (lychee fruit) (Sapindaceae)	OD-R

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects
Geraniol (= Lemonol) (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Monarda fistulosa</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Asarum canadense</i> (Aristolochiaceae), <i>Andropogon nardus</i> , <i>A. schoenanthu</i> , <i>A. citratus</i> (Poaceae), <i>Rosa damascena</i> , <i>R. gallica</i> (Rosaceae), <i>Citrus vulgaris</i> (Rutaceae), <i>Litchi chinensis</i> (Sapindaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (Vitaceae)	OD-R (floral, sweet rose) [antiseptic, apoptotic, insect attractant]
Geranyl acetate (monoterpene)	<i>Bursera delpechiana</i> (Burseraceae), <i>Pelargonium odoratissimum</i> (Geraniaceae), <i>Thymus vulgaris</i> (Lamiaceae), <i>Eucalyptus</i> spp. (Myrtaceae), <i>Rosa</i> spp. (Rosaceae), <i>Citrus limonum</i> (lemon), <i>Citrus vulgaris</i> (leaf, pettigrain oil) (Rutaceae)	OD-R (rose)
Geranyl acetone (monoterpene)	<i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae)	OD-R (hay-like)
Geranyl tiglate (monoterpene ester)	<i>Pelargonium graveolens</i> , <i>P. odoratissimum</i> (Geraniaceae), <i>Eucalyptus</i> spp. (eucalyptus leaf) (Myrtaceae), <i>Rosa</i> spp. (Rosaceae), <i>Citrus limon</i> (Rutaceae)	OD-R (rose)
Germacrene D (sesquiterpene)	<i>Piper biasperatum</i> (Piperaceae) [leaf, spike oil]	OD-R
Guaiol (= Champacol) (sesquiterpene)	<i>Michelia champaca</i> (Magnoliaceae), <i>Eucalyptus citriodora</i> (Myrtaceae), <i>Cymbopogon parkeri</i> (Poaceae), <i>Guaiacum officinale</i> (Zygophyllaceae)	OD-R
Hotrienol (terpene)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [flower], <i>Cinnamomum camphora</i> (Lauraceae)	OD-R
Ionone (= α - & β -Ionone mixture) (carotenoid)	<i>Trifolium pratense</i> (Fabaceae), <i>Iris germanica</i> (Iridaceae), <i>Boronia megastigma</i> (boronia oil) (Rutaceae), <i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]	OD-R (cedar-like; very dilute, violet-like) [dermatitic; Vitamin A precursor]
α -, β - & γ -Irones (norsesquiterpenes)	<i>Iris florentina</i> (iris) (Iridaceae), <i>Viola</i> spp. (violets) (Violaceae)	OD-R (violet); synthesis by Leopold Ruzicka (Nobel Prize, Chemistry, 1939)
Ledol (= Ledum camphor) (sesquiterpene)	<i>Hyssopus officinalis</i> (Lamiaceae), <i>Ledum columbianum</i> , <i>L. groenlandicum</i> , <i>L. palustre</i> (leaf, Ledum oil), <i>Renealmia chrysotrycha</i> (Zingiberaceae)	OD-R (fragrant) [toxic]
(+)-Limonene (monoterpene)	<i>Anethum graveolens</i> , <i>Apium graveolens</i> (Apiaceae), <i>Mosla dianthera</i> (Lamiaceae), <i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae), <i>Citrus aurantium</i> , <i>C. limonum</i> , <i>C. vulgaris</i> , <i>C. spp.</i> (Rutaceae) [fruit peel oil]	OD-R (citrus, orange) [expectorant, irritant, sedative]

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects
(-)-Limonene (monoterpene)	<i>Anethum graveolens</i> , <i>Carum carvi</i> (Apiaceae), <i>Mentha</i> spp., <i>Mosla dianthera</i> (Lamiaceae), <i>Abies alba</i> (Pinaceae), <i>Citrus aurantium</i> , <i>C. limonum</i> (peel, Lemon oil) (Rutaceae) [flower]	OD-R (less citrus, more terpentine) [expectorant, irritant, sedative]
(Z)-Limonene oxide (monoterpene)	<i>Mosla dianthera</i> (miniature beefsteakplant) (Lamiaceae)	OD-R (lemon, floral)
Linalol (= Linalool) (monoterpene); synthesis by Leopold Ruzicka (Croatia/ Switzerland) (Nobel Prize, Chemistry, 1939, sex hormones, with Adolph Butenandt)	<i>Xylopiya aethiopica</i> (Annonaceae), <i>Coriandrum sativum</i> (Apiaceae), <i>Asarum canadense</i> (Aristolochiaceae), <i>Bursera delpechiana</i> , <i>B.</i> spp. (Bursaceae), <i>Sambucus canadensis</i> , <i>S. nigra</i> (Caprifoliaceae), <i>Lavandula</i> spp., <i>Mosla dianthera</i> , <i>Ocimum basilicum</i> (Lamiaceae), (Lamiaceae), <i>Coffea</i> spp. (Rubiaceae), <i>Citrus aurantium</i> , <i>C. limon</i> , <i>C. paradisi</i> (Rutaceae), <i>Prunus domestica</i> (Rosaceae), <i>Litchi chinensis</i> (Sapindaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (floral, flowery, fruity, green, lemon , sweet) [antiseptic, antifungal]; pleasant perfume e.g. lavender oil (mainly linalol & linalyl acetate); promotes higher singer's pitch
Linalyl acetate (= Bergamol) (monoterpene)	<i>Coriandrum sativum</i> (Apiaceae), <i>Bursera delpechiana</i> (Bursaceae), <i>Lavandula</i> spp. (flower, lavender oil) (Lamiaceae), <i>Citrus aurantium</i> (orange peel, bergamot oil; orange flower oil), <i>C. vulgaris</i> (leaf, pettigrain oil) (Rutaceae)	OD-R
<i>p</i> -1-Menthene-8-thiol (monoterpene thiol)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (fruity, grapefruit- like, red-fruit-like)
Menthofuran (monoterpene)	<i>Mentha piperita</i> (peppermint oil), <i>M. aquatica</i> (watermint) (Lamiaceae)	OD-R
Menthol (monoterpene)	<i>Mentha piperita</i> (peppermint oil), <i>M.</i> spp. (mint) (Lamiaceae)	OD-R (peppermint) [analgesic, antiseptic, carminative, decongestant, gastric sedative]
Menthone (monoterpene)	<i>Mentha piperita</i> (peppermint oil), <i>M.</i> spp. (mint) (Lamiaceae)	OD-R (peppermint) [antiseptic]
Menthyl acetate (monoterpene)	<i>Mentha piperita</i> (peppermint oil), <i>M.</i> spp. (mint) (Lamiaceae)	OD-R (floral)
β -Myrcene (monoterpene)	<i>Xylopiya aethiopica</i> (Annonaceae), <i>Humulus lupulus</i> (Cannabaceae), <i>Myrcia acris</i> (Myrtaceae), <i>Citrus paradisi</i> (Rutaceae)	OD-R (moss-like, metallic)
Myrtenol (monoterpene)	<i>Xylopiya aethiopica</i> (Annonaceae) [fruit], <i>Hyssopus officinalis</i> (Lamiaceae)	OD-R (flowery)
Nerol (monoterpene)	<i>Rosa</i> spp. (Rosaceae), <i>Citrus aurantium</i> , <i>C. limon</i> , <i>C. vulgaris</i> (fruit, leaf) (Rutaceae)	OD-R (sweet rose)
Nerol oxide (monoterpene)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [flower]	OD-R
Nerolidol (= Peruviol) (farnesane sesquiterpene)	<i>Myroxylon pereirae</i> (wood oil) (Fabaceae), <i>Zea mays</i> (Poaceae), <i>Citrus sinensis</i> (orange flower, neroli oil) (Rutaceae)	OD-R (floral); synthesis by Leopold Ruzicka

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects
Noonkatone (sesquiterpene ketone)	<i>Andropogon muricatus</i> (<i>Vetiveria zizanioides</i>) (Poaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Alpinia oxyphylla</i> (bitter cardamon fruit) (Zingiberaceae)	OD-R (grapefruit-like) [insect repellent]
<i>trans</i> - β -Ocimene (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Sambucus nigra</i> (Caprifoliaceae), <i>Ocimum basilicum</i> (Lamiaceae), <i>Evodia rutaecarpa</i> (Rutaceae)	OD-R (floral)
Patchouli alcohol (= Patchouli camphor) (sesquiterpene)	<i>Pogostemon cablin</i> (patchouli oil) (Lamiaceae)	OD-R (fragrant)
(-)- α -Phellandrene (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae) [fruit], <i>Eucalyptus</i> spp. (eucalyptus oil) (Myrtaceae)	OD-R (minty) [irritant]
(+)- α -Phellandrene (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Foeniculum vulgare</i> (Apiaceae), <i>Piper nigrum</i> (Piperaceae)	OD-R (minty) [irritant]
(-)- β -Phellandrene (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae) [fruit], <i>Abies</i> , <i>Picea</i> & <i>Pinus</i> spp. (pine oil) (Pinaceae)	OD-R (terpeny) [expectorant]
(+)- β -Phellandrene (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Phellandrium</i> (<i>Oenanthe aquatica</i>) (Apiaceae)	OD-R (terpeny) [expectorant]
α -Pinene (= 2-Pinene) (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae) [fruit], <i>Kunzea ericoides</i> (Kanuka oil), <i>Myrtus communis</i> (leaf, myrtle oil) (Myrtaceae), <i>Pinus palestris</i> , <i>P.</i> spp. (turpentine, pine oil) (Pinaceae), <i>Piper</i> sp. (Piperaceae), <i>Citrus</i> spp. (peel) (Rutaceae); Cupressaceae, Lamiaceae	OD-R (pine, terpeny) [irritant]
β -Pinene (= Nopinene) (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Cuminum cyminum</i> (Apiaceae), <i>Pinus palestris</i> , <i>P.</i> spp. (Pinaceae), <i>Piper</i> sp. (Piperaceae), <i>Citrus paradisi</i> (Rutaceae)	OD-R (pine, terpeny) [irritant]
Pinocarvone (monoterpene)	<i>Artemisia salsoloides</i> (Asteraceae), <i>Eucalyptus globulus</i> (Tasmanian blue gum) (eucalyptus oil) (Myrtaceae)	OD-R
Piperitone (monoterpene)	<i>Mentha</i> spp. (Lamiaceae), <i>Eucalyptus dives</i> (Myrtaceae), <i>Andropogon iwarancusa</i> (Poaceae), <i>Lippia alba</i> (Verbenaceae)	OD-R (camphor- & peppermint-like)
Pulegone (= 1-Methyl- 4-isopropylidene-3- cyclohexanone) (monoterpene)	<i>Hedeoma pulegioides</i> (American pennyroyal oil), <i>Mentha pulegium</i> (European pennyroyal oil) (Lamiaceae)	OD-R
<i>cis</i> -Rose oxide (monoterpene)	<i>Sambucus nigra</i> (Caprifoliaceae), <i>Melissa officinalis</i> (Lamiaceae), <i>Litchi chinensis</i> (Sapindaceae)	OD-R
Rotundifolone (= Piperitenone oxide) (monoterpene)	<i>Mentha longifolia</i> , <i>M. rotundifolia</i> , <i>M. spicata</i> (Lamiaceae)	OD-R
Sabinene (monoterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Origanum majorana</i> (leaf, marjoram oil) (Lamiaceae), <i>Myristica fragrans</i> (Myristicaceae)	OD-R (terpeny)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Sabinol (monoterpene)	<i>Juniperus sabina</i> (tops, savin oil) (Cupressaceae)	OD-R (anthelmintic, emmenagogue, toxic)
Sabinyl acetate (monoterpene ester)	<i>Juniperus sabina</i> (tops, savin oil) (Cupressaceae)	OD-R
Safranal (monoterpene aldehyde)	<i>Crocus sativus</i> (saffron) (Iridaceae) [dried stigma], <i>Camellia sinensis</i> (Theaceae)	OD-R
β -Santalene (sesquiterpene)	<i>Santalum album</i> (wood, sandalwood oil) (Santalaceae)	OD-R (cedar-like)
α - & β -Santalol (sesquiterpene)	<i>Santalum album</i> (wood, sandalwood oil) (Santalaceae)	OD-R (cedar-like)
β -Selinene (sesquiterpene)	<i>Apium graveolens</i> (seed, celery oil), <i>Seseli</i> sp. (Apiaceae)	OD-R
α - & β -Sinensal (sesquiterpene aldehydes)	<i>Citrus sinensis</i> (orange peel) (Rutaceae)	OD-R (mandarin peel)
α -Terpinene (monoterpene)	<i>Xylopiya aethiopica</i> (Annonaceae), <i>Ocimum</i> spp., <i>Origanum majorana</i> , (Lamiaceae), <i>Citrus limonum</i> (Rutaceae), <i>Elettaria cardamomum</i> (seed, Cardamom oil) (Zingiberaceae)	OD-R (lemon-like, terpeny)
γ -Terpinene (monoterpene)	<i>Carum copticum</i> (seed, Ajowan oil) (Apiaceae)	OD-R
Terpinen-4-ol (monoterpene)	<i>Xylopiya aethiopica</i> (Annonaceae) [fruit], <i>Musa acuminata</i> , <i>M. paridasiaca</i> (banana) (Musaceae)	OD-R (dusty, light mint, terpeny)
α -Terpineol (= <i>p</i> -Menth-1-en-8-ol; Terpineol) (monoterpene)	<i>Xylopiya aethiopica</i> (Annonaceae), <i>Sambucus canadensis</i> , <i>S. nigra</i> (Caprifoliaceae), <i>Origanum majorana</i> , (Lamiaceae), <i>Melaleuca viridiflora</i> (Myrtaceae), <i>Citrus vulgaris</i> (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine), <i>Elettaria cardamomum</i> (Zingiberaceae)	OD-R (anise) [antiseptic]
Terpinolene (monoterpene)	<i>Pastinaca sativa</i> (Apiaceae), <i>Ocimum kilimandscharicum</i> (Lamiaceae), Pinaceae [oil]	OD-R (pine)
α -Thujene (monoterpene)	<i>Xylopiya aethiopica</i> (Annonaceae) [fruit], <i>Mosla dianthera</i> , <i>Origanum onites</i> (Lamiaceae)	OD-R (grassy, soy sauce, sweet, terpeny)
α - & β -Thujone (monoterpenes)	<i>Artemisia absinthia</i> , <i>Tanacetum vulgare</i> (Asteraceae), <i>Thuja occidentalis</i> (Cupressaceae); neurotoxic component of absinthe – affected Gaugin, Toulouse-Lautrec, Picasso, Van Gogh et al.	OD-R (sweet, terpeny) (GABAA-R) [convulsant, hallucinogen, irritant]
Thujopsene (= Widdrene) (thujopsane sesquiterpene)	<i>Thujopsis dolabrata</i> (wood, hiba oil) (Cupressaceae)	OD-R

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects
Thujyl acetate (monoterpene acetate)	<i>Artemisia absinthia</i> (leaf & tops, wormwood oil) (Asteraceae)	OD-R
Thujyl alcohol (monoterpene alcohol)	<i>Artemisia absinthia</i> (leaf & tops, wormwood oil) (Asteraceae)	OD-R
Thymol (= 6-Isopropyl- <i>m</i> -cresol) (monoterpene)	<i>Monarda punctata</i> , <i>Thymus vulgaris</i> (Thyme oil) (Lamiaceae), <i>Citrus limon</i> (Rutaceae)	OD-R (thyme) [antiseptic, irritant]
Thymyl acetate (monoterpene)	<i>Thymus vulgaris</i> (thyme oil) (Lamiaceae)	OD-R [antiseptic, carminative, irritant]
Umbellulone (monoterpene)	<i>Mentha longifolia</i> (Lamiaceae), <i>Umbellularia californicum</i> (Lauraceae)	OD-R
Verbenone (= Pin-2-en-4-one) (monoterpene)	<i>Artemisia salsoloides</i> (Asteraceae), <i>Juglans</i> spp. (walnut) (Juglandaceae), <i>Verbena triphylla</i> (leaf, Verbena oil) (Verbenaceae)	OD-R [toxic]
α-Vetivone (sesquiterpene ketone)	<i>Vetiveria zizanioides</i> (root, vetiver oil) (Poaceae)	OD-R
β-Vetivone (sesquiterpene ketone)	<i>Vetiveria zizanioides</i> (root, vetiver oil) (Poaceae)	OD-R
α-Ylangene (= 8-Isocopaene) (sesquiterpene)	<i>Cananga odorata</i> (Annonaceae), <i>Betula</i> sp., <i>Juniperus oxycedrus</i> (Cupressaceae), <i>Piper bisperatum</i> (Piperaceae) [oil]	OD-R
l-Zingiberene (sesquiterpene)	<i>Curcuma</i> spp., <i>Zingiber officinale</i> (rhizome, Ginger oil) (Zingiberaceae)	OD-R [carminative]
Other		10.4o
Acetal (= 1,1-Diethoxyethane) (alkyl ether)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (fruity, green)
Acetic acid (aliphatic carboxylic acid)	Universal; <i>Citrus paradisi</i> (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (vinegar); Jesus given vinegar immediately before He said "It is finished"	OD-R (sour, pungent, vinegar)
Acetophenone (= Acetylbenzene) (aryl ketone)	<i>Cistus ladaniferus</i> (Cistaceae), <i>Orthodon</i> (Lamiaceae), <i>Stirlingia</i> (Proteaceae), <i>Populus</i> (Salicaceae), <i>Urtica</i> (Urticaceae) species	OD-R (V-K ⁺ CH) [hypnotic, odorant]
Acetoin (= 3-Hydroxy-2-butanone) (aliphatic ketone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (fatty, pleasant, wet)
Allicin (= S-Oxodiallyl disulfide) (alkene disulfide)	<i>Allium sativum</i> (bulb, garlic oil) (Liliaceae)	OD-R (garlic); main garlic odour [antibiotic, antidiabetic, antihypertensive, PAI]
O-Aminoacetophenone (aryl ketone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (sweet, grape-like)
Apiole (dill) (= 4,5-Dimethoxy-6-(2-propenyl)-1,3-benzodioxole) (benzodioxole)	<i>Anethum graveolus</i> (seed, dill oil) (Apiaceae)	OD-R (dill)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Apiole (parsley) (= 4,7-Dimethoxy-5-(2-propenyl)-1,3-benzodioxole) (benzodioxole)	<i>Petroselinum hortense</i> (seed, parsley oil) (Apiaceae)	OD-R (parsley)
Benzaldehyde (aryl aldehyde)	Widespread <i>ex</i> cyanogenic glycosides e.g. Amygdalin <i>ex Prunus dulcis</i> , <i>P. armeniaca</i> , <i>P. persica</i> , <i>P. cerasus</i> , <i>P. spp.</i> (Rosaceae); <i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Michelia champaca</i> (Magnoliaceae), <i>Piper bisperatum</i> (Piperaceae)	OD-R [mutagen, sex pheromone]
Benzyl alcohol (aryl alcohol)	<i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Michelia champaca</i> (Magnoliaceae)	OD-R
Benzyl benzoate (aryl ester)	<i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Piper bisperatum</i> (Piperaceae)	OD-R
2,3-Butanedione (aliphatic ketone)	<i>Citrus paradisi</i> (Rutaceae), <i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (buttery, caramel, cream)
Butanoic acid (= Butyric acid) (aliphatic carboxylic acid)	<i>Coffea spp.</i> (Rubiaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine); non-fat dry milk aroma-active	OD-R (cheese, sweaty, rancid, unpleasant)
Butanol (alkyl alcohol)	<i>Aloe arborescens</i> (Liliaceae), <i>Citrus aurantium</i> (Rutaceae)	OD-R (pleasant, fragrant)
Butyl acetate (alkyl ester)	<i>Plectranthus coleoides</i> (Lamiaceae), <i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (candy, sweet)
Butyl butyrate (aliphatic ester)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit], <i>Malus domestica</i> (Rosaceae)	OD-R (grassy, spicy)
Citric acid (aliphatic tricarboxylic acid)	Universal; <i>Citrus limon</i> (lemon) (Rutaceae) [fruit juice]	OD-R (curry)
(<i>E,E</i>)-2,4-Decadienal (alkyl aldehyde)	<i>Olea europaea</i> (olive) (Oleaceae), <i>Camellia sinensis</i> (Theaceae) [leaf]	OD-R (fatty, waxy)
δ -Decalactone (lactone)	<i>Nephelium lappaceum</i> (Sapindaceae), <i>Vitis vinifera</i> (Vitaceae); non-fat dry milk aroma	OD-R (coconut , sweet)
γ -Decalactone (lactone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (lactone-like)
Decanal (aliphatic aldehyde)	<i>Xylophia aethiopica</i> (Annonaceae), <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (flowery, fatty, sweaty, rancid)
Decanoic acid (aliphatic carboxylic acid)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (synthetic, fatty)
(<i>E</i>)-2-Decenal (alkene aldehyde)	<i>Olea europaea</i> (olive) (Oleaceae)	OD-R
Diallyl sulfide (alkyl disulfide)	<i>Allium sativum</i> (bulb, garlic oil) (Liliaceae)	OD-R (garlic)
Diallyl disulfide (alkyl disulfide)	<i>Allium sativum</i> (bulb, garlic oil) (Liliaceae)	OD-R (garlic)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Diallyl trisulfide (alkyl trisulfide)	<i>Allium sativum</i> (bulb, garlic oil) (Liliaceae)	OD-R (garlic)
Dimethylsulfide (dialkyl sulfide)	<i>Hordeum vulgare</i> (barley) (Poaceae) [malt]	OD-R (cooked vegetable-like)
3,5-Dimethyl-1,2,4-trithiolane (trithiolane)	<i>Durio zibethinus</i> (durian) (Bombacaceae) [fruit]; “hell on the outside, heaven on the inside”	OR-R (foul); worst smell, best taste
4,5-Epoxy-(E)-2-decenal (epoxy alkene aldehyde)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae); non-fat dry milk aroma-active	OD-R (metallic)
Ethyl acetate (aliphatic ester)	<i>Telosma cordata</i> (Asclepiadaceae), <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (fruity)
Ethyl butanoate (= Ethyl butyrate) (aliphatic ester)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (Musaceae), <i>Malus</i> sp. (Rosaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (fruity, floral, green, strawberry); apple aroma
(E)-Ethyl cinnamate (aryl ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (flowery)
Ethyl(E,E)-Deca-2,4-dienoate (alkene ester)	<i>Durio zibethinus</i> (durian) (Bombacaceae) [fruit]	OD-R (fruity)
Ethyl(E,Z)-Deca-2,4-dienoate (alkene ester)	<i>Durio zibethinus</i> (durian) (Bombacaceae) [fruit]	OD-R (fruity)
Ethyl(Z,Z)-Deca-2,4-dienoate (alkene ester)	<i>Durio zibethinus</i> (durian) (Bombacaceae) [fruit]	OD-R (fruity)
Ethyl(3Z,6Z)-Decadienoate (alkene ester)	<i>Durio zibethinus</i> (durian) (Bombacaceae) [fruit]	OD-R (fruity)
Ethyl(E,E,Z)-Decatrienoate (alkene ester)	<i>Durio zibethinus</i> (durian) (Bombacaceae) [fruit]	OD-R (fruity)
Ethyl(E,Z,Z)-Decatrienoate (alkene ester)	<i>Durio zibethinus</i> (durian) (Bombacaceae) [fruit]	OD-R (fruity)
Ethyl dihydrocinnamate (aryl ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (flowery)
Ethyl hexanoate (aliphatic ester)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (fruity, strawberry)
Ethyl 3-hydroxybutanoate (aliphatic ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (hay-like, sweaty)
Ethyl 3-hydroxyhexanoate (aliphatic ester)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (fruity, sweet)
Ethyl isobutyrate (aliphatic ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (fruity, strawberry)
Ethyl isohexanoate (aliphatic ester)	<i>Litchi chinensis</i> (lychee fruit) (Sapindaceae)	OD-R

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Ethyl isovalerate (aliphatic ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (sweet fruit)
4-Ethyl-methoxyphenol (phenol)	<i>Xylopia aethiopica</i> (Annonaceae) [fruit]	OD-R (smokey)
Ethyl 2-methylbutyrate (aliphatic ester)	<i>Xylopia aethiopica</i> (Annonaceae) [fruit], <i>Durio zibethinus</i> (Bombacaceae), <i>Coffea</i> spp. (Rubiaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Nephelium lappaceum</i> (Sapindaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (blackberry, berry, fruity, strawberry)
Ethyl 3-methylbutyrate (aliphatic ester)	<i>Coffea</i> spp. (coffee seed) (Rubiaceae)	OD-R (fruity)
Ethyl 2- methylpropanoate (aliphatic ester)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (fruity)
Ethyl octanoate (aliphatic ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (sweet, fruity)
Ethyl pentanoate (aliphatic ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (green, mint)
Ethyl propanoate (aliphatic ester)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (fruity)
Ethyl 2- methylpropanoate (aliphatic ester)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (fruity)
Ethyl valerate (aliphatic ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OR-R (fruity orange)
Furaneol (= 2,5- Dimethyl-4-hydroxy- 3(2H)-furanone (furanone)	<i>Fragaria virginiana</i> (strawberry) (Rosaceae), <i>Litchi chinensis</i> (lychee fruit) (Sapindaceae), <i>Lycopersicon esculentum</i> (Solanaceae) [fruit], <i>Vitis vinifera</i> (Vitaceae) (wine); non-fat dry milk aroma-active	OR-R (candy cotton, burnt sugar-like); major flavour in strawberry; home- grown tomato has 4–30 times more than “commercial”
Furfural (= 2-Furane- carboxaldehyde) (furan)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OR-R (fruity, flowery)
Furfuryl mercaptan (= Furanmethanethiol) (furan thiol)	<i>Coffea</i> spp. (coffee seed) (Rubiaceae) [from roasted coffee]; identified by Hermann Staudinger (Germany, Nobel Prize, Chemistry, 1953, polyisoprenoids; coined term “macromolecule”)	OD-R (coffee odour)
Heptanal (aliphatic aldehyde)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [flower], <i>Monarda punctata</i> (Lamiaceae)	OD-R
(<i>Z</i>)-4-Heptanal (aliphatic aldehyde)	<i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]	OD-R (hay-like)
2-Heptanol (aliphatic alcohol)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (acid, fruity, humid, pungent)
1-Hepten-3-one (aliphatic ketone)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (geranium-like)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Hexanal (aliphatic aldehyde)	<i>Sambucus nigra</i> (Caprifoliaceae) [flower], <i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Lavandula intermedia</i> (Lamiaceae), <i>Aloe arborescens</i> (Liliaceae), <i>Olea europaea</i> (Oleaceae), <i>Coffea</i> spp. (Rubiaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Lycopersicon esculentum</i> (Solanaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (grassy, green, herbal)
Hexanoic acid (alkyl carboxylic acid)	<i>Xylophia aethiopica</i> (Annonaceae), <i>Glycyrrhiza glabra</i> (Fabaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (Vitaceae) (wine); non-fat dry milk aroma-active	OD-R (green, acid, cheese, vinegar-like)
1-Hexanol (aliphatic alcohol)	<i>Sambucus nigra</i> (Caprifoliaceae), <i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (dry, green, toasted)
2-Hexanol (aliphatic alcohol)	<i>Dianthus caryophyllus</i> (carnation) (Caryophyllaceae) [flower]	OD-R
(E)-2-Hexen-1-al (= trans-2-Hexen-1-al; Leaf aldehyde) (aliphatic aldehyde)	Damaged leaf tissue; e.g. <i>Brassica oleracea</i> (Brassicaceae), <i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Quercus rubra</i> (Fagaceae), <i>Aloe arborescens</i> (Liliaceae), <i>Musa acuminata</i> , <i>M. paradisiaca</i> (Musaceae), <i>Olea europaea</i> (Oleaceae), <i>Solanum tuberosum</i> (Solanaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (floral, herbal) [major damaged leaf “ green odour ” & insect herbivore attractant]
(Z)-3-Hexenal (aliphatic aldehyde)	<i>Aloe arborescens</i> (Liliaceae), <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae), <i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	OD-R (grass, grape, green, leaf-like)
(E)-3-Hexen-1-ol (aliphatic alcohol)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [flower], <i>Dianthus caryophyllus</i> (carnation) (Caryophyllaceae) [flower], <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (green, fresh cut grass)
(Z)-Hex-3-en-1-ol (= cis-Hex-3-en-1-ol; Leaf alcohol) (aliphatic alcohol)	<i>Brassica oleracea</i> (Brassicaceae); <i>Robinia pseudacacia</i> (Fabaceae), <i>Mosla dianthera</i> (Lamiaceae), <i>Morus</i> spp. (Moraceae), <i>Aloe arborescens</i> (Liliaceae), <i>Solanum tuberosum</i> (Solanaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (fresh cut grass, grassy, leafy, metallic) [major damaged leaf “ green odour ” & insect attractant]
(Z)-3-Hexenyl acetate (aliphatic ester)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (floral, fruity)
(Z)-3-Hexenyl (Z)-3- hexanoate (aliphatic ester)	<i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]	OD-R (green)
Homofuraneol (furanone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (candy cotton)
3-Hydroxy-2-butanone (alkyl ketone)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (butyric acid, pungent)
3-Hydroxy-4,5- dimethyl-2(5H)- furanone (= Sotolon) (furanone)	<i>Hordeum vulgare</i> (barley) (Poaceae) [malt], <i>Coffea</i> spp. (coffee seed) (Rubiaceae), <i>Camellia sinensis</i> (Chinese green tea) (Theaceae) [leaf], <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (curry, spicy; burnt, spicy flavour of stored citrus soft drinks; non-fat dry milk aroma)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects/
4-Hydroxy-2,5-dimethyl-3(2H)-furanone (furanone)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (caramel-like)
Isoamyl acetate (aliphatic ester)	<i>Nepeta racemosa</i> (Lamiaceae), <i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OR-R (fresh & over-ripe banana , sweet)
Isoamyl alcohol (aliphatic alcohol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OR-R (bitter, harsh)
Isoamyl butyrate (aliphatic ester)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (acid, floral, fruity)
Isobutyl acetate (aliphatic ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (fruity, plastic, pungent, rancid, strawberry)
Isobutyl isobutyrate (aliphatic ester)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (pungent, rancid)
Isobutyric acid (aliphatic carboxylic acid)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OR-R (fatty, phenolic)
Isovaleric acid (= Isopropylacetic acid) (aliphatic carboxylic acid)	<i>Humulus lupulus</i> (hops) (Cannabaceae), <i>Litchi chinensis</i> (lychee fruit) (Sapindaceae), <i>Nicotiana tabacum</i> (tobacco) (Solanaceae), <i>Valeriana</i> spp. (Valerianaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OR-R (rancid, cheese)
(Z)-Jasmone (= 3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one) (alicyclic ketone)	<i>Jasminum officinale</i> (jasmine flower) (Oleaceae); Jasmone structure by Leopold Ruzicka (Croatia/Switzerland) (Nobel Prize, Chemistry, 1939, sex hormones, with Adolph Butenandt)	OD-R (jasmine odour) [insect attractant]
Maltol (= 3-Hydroxy-2-methyl-4-pyrone) (pyrone)	<i>Cichorium endiva</i> (chicory) (Asteraceae), <i>Abies alba</i> [needle], <i>Larix decidua</i> (larch) [bark], (Pinaceae), <i>Hordeum vulgare</i> (barley) (Poaceae) [roasted malt], <i>Rubus idaeus</i> (Rosaceae), <i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]	OD-R (sweet, freshly baked) [sweet, freshly baked taste to bread & cakes; Zn (II) & oxoV(IV) complexes are insulin mimetics]
3-Mercaptohexanol (thioalkyl alcohol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (vegetable, dry)
3-Mercaptohexyl acetate (thioalkyl ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (anise, box tree)
3-Mercapto-2-methylpentanal (alkane thiol)	<i>Allium cepa</i> (onion) (Liliaceae) [bulb]	OD-R
3-Mercapto-2-methylpentan-1-ol (alkane thiol)	<i>Allium cepa</i> (onion) (Liliaceae) [bulb]	OD-R (meat broth, sweaty, onion, leek-like)
4-Mercapto-4-methylpentan-2-one (alkyl ketone thiol)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (catty, black-currant-like, box tree)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Methional (= 3-(Methylthio)propanal; 3-(Methylthio)propionaldehyde) (thioether aldehyde)	<i>Hordeum vulgare</i> (Poaceae), <i>Coffea</i> spp. (Rubiaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Lycopersicon esculentum</i> (Solanaceae), <i>Camellia sinensis</i> (Theaceae); <i>Vitis vinifera</i> (Vitaceae) (wine); non-fat dry milk aroma	OD-R (garlic, raw potato, baked potato, cooked-potato-like)
Methionol (= 3-(Methylthio)propanol) (thioether alcohol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (raw potato); “off-flavour” in beer & wine
4-Methoxy-2-methyl-2-butanethiol (alkyl thiol)	<i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]	OD-R (meaty)
Methyl allyl disulfide (alkyl disulfide)	<i>Allium sativum</i> (bulb, garlic oil) (Liliaceae)	OD-R (garlic)
Methyl allyl trisulfide (alkyl disulfide)	<i>Allium sativum</i> (bulb, garlic oil) (Liliaceae)	OD-R (garlic)
Methyl anthranilate (= Methyl 2-aminobenzoate) (aryl ester)	<i>Cananga odorata</i> (Annonaceae), <i>Jasminum officinale</i> (Oleaceae), <i>Citrus aurantium</i> , <i>Citrus paradisi</i> , <i>Ruta graveolens</i> (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (coconut flowery)
Methyl benzoate (aryl ester)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (flowery, honey)
3-Methylbutanal (alkane aldehyde)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (Musaceae), <i>Hordeum vulgare</i> (Poaceae) [malt], <i>Lycopersicon esculentum</i> (Solanaceae)	OD-R (malty, pungent)
2-Methylbutanoic acid (aliphatic carboxylic acid)	<i>Hordeum vulgare</i> (barley) (Poaceae) [malt], <i>Coffea</i> spp. (coffee seed) (Rubiaceae), <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (sweaty)
3-Methylbutanoic acid (aliphatic carboxylic acid)	<i>Hordeum vulgare</i> (barley) (Poaceae) [malt], <i>Coffea</i> spp. (coffee seed) (Rubiaceae), <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (sweaty)
2-Methyl-1-butanol (alkane alcohol)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (malty)
3-Methyl-1-butanol (aliphatic alcohol)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit], <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (malty, pungent, rancid)
2-Methyl-3-buten-2-one (aliphatic ketone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (buttery, caramel)
2-Methyl-3-furanthiol (furan)	<i>Citrus sinensis</i> (orange) (Rutaceae) [fruit juice]	OD-R (“off-flavour” in ageing orange juice)
6-Methyl-1-heptenone (aliphatic ketone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (grass, green)
Methyljasmonate (alicyclic ketone ester)	Universal plant signalling component e.g. <i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]; <i>Jasminum officinale</i> (jasmine oil) (Oleaceae)	OD-R (floral) [plant wounding & pathogen attack response mediator]
Methyl mercaptan (= Methane thiol) (alkyl thiol)	<i>Raphanus sativus</i> (radish) (Brassicaceae) [root]; widespread from bacterial action on Cysteine & Methionine & as trace plant volatile; flatulence & periodontal disease malodorous volatile	OD-R (rotting cabbage) [attractant for blowflies causing sheep blowfly strike]

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
2-Methyl-3-mercaptofuran (furan thiol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (barbecue, fatty, onion)
3-Methylnonane-2,4-dione (alkyl ketone)	<i>Camellia sinensis</i> (Chinese & Japanese green tea) (Theaceae) [leaf]	OD-R (green)
Methyl nonyl acetate (alkyl ketone)	<i>Ruta graveolens</i> (rue oil) (Rutaceae)	OD-R
4-Methyl-3-pentenol (alkene alcohol)	<i>Aloe arborescens</i> (Liliaceae)	OD-R
4-Methyl-3-penten-2-one (aliphatic ketone)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [flower]	OD-R
2-Methylpropanal (alkyl aldehyde)	<i>Hordeum vulgare</i> (barley) (Poaceae) [malt]	OD-R (malty)
2-Methylpropanol (aliphatic alcohol)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit], <i>Vitis vinifera</i> (Vitaceae) (wine)	OR-R (acid, bitter, fruity, floral)
2-Methyltetrahydrothiophen-3-one (thiophene)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OR-R (chlorine, wet, ozone)
Myristicin (= 4-Methoxy-6-(2-propenyl)-1,3-benzodioxole) (benzodioxole)	<i>Pastinaca sativa</i> (parsnip) (Apiaceae), <i>Myristica fragrans</i> (expressed nutmeg oil) (Myristicaceae)	OD-R (nutmeg)
Nona-2,4-dienal (alkyl dialdehyde)	<i>Capsicum annuum</i> (sweet pepper) (Solanaceae)	OD-R
(E, Z)-Nona-2,6-dienal (alkene aldehyde)	<i>Cucumis sativus</i> (Cucurbitaceae), <i>Nephelium lappaceum</i> (Sapindaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (green, cucumber, melon) [threshold 0.0001 ppm]
Nonanal (alkane alcohol)	<i>Sambucus nigra</i> (Caprifoliaceae), <i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Monarda didyma</i> (Lamiaceae), <i>Olea europaea</i> (Oleaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Nephelium lappaceum</i> (Sapindaceae)	OD-R (fatty, soapy, citrus-like, waxy; non-fat dry milk aroma)
γ-Nonalactone (lactone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (coconut , wood)
4-Nonanolide (= Pentylloxolan-2-one) (lactone)	<i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]	OD-R (sweet)
(Z)-2-Nonenal (aliphatic aldehyde)	<i>Coffea</i> spp. (Rubiaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Nephelium lappaceum</i> (Sapindaceae)	OD-R (cardboard-like, fatty, green)
(E)-2-Nonenal (aliphatic aldehyde)	<i>Olea europaea</i> (Oleaceae), <i>Coffea</i> spp. (Rubiaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Litchi chinensis</i> (Sapindaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (cardboard-like, fatty, tallowy, wet, earthy)
(Z)-1,5-Octadienedione (aliphatic ketone)	<i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf]	OD-R (metallic)
(Z)-1,5-Octadiene-3-one (aliphatic ketone)	<i>Citrus paradisi</i> (Rutaceae), <i>Camellia sinensis</i> (Chinese green tea) (Theaceae) [leaf]	OD-R (geranium-like)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Odour receptor (OD-R) binding (other targets) / in vivo effects/
Octanal (aliphatic aldehyde)	<i>Citrus paradisi</i> , <i>C. sinensis</i> , <i>C. spp.</i> (grapefruit juice) (Rutaceae)	OD-R (green, citrus-like)
Octanoic acid (carboxylic acid)	<i>Vitis vinifera</i> (Vitaceae) (wine); non-fat dry milk aroma-active	OD-R (cheese, waxy)
(<i>E</i>)-2-Octenal (aliphatic aldehyde)	<i>Olea europaea</i> (olive) (Oleaceae)	OD-R
(<i>Z</i>)-3-Octen-1-ol (aliphatic alcohol)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (pungent, rancid)
1-Octen-3-one (aliphatic ketone)	<i>Mosla dianthera</i> (Lamiaceae), <i>Hordeum vulgare</i> (Poaceae), <i>Coffea spp.</i> (Rubiaceae), <i>Lycopersicon esculentum</i> (Solanaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (Vitaceae) (wine); non-fat dry milk aroma	OD-R (earthy, mushroom-like , woody)
Pentanal (aliphatic alcohol)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [flower], <i>Micromeria fruticosa</i> (Lamiaceae)	OD-R
Pentanoic acid (aliphatic carboxylic acid)	<i>Coffea spp.</i> (coffee seed) (Rubiaceae)	OD-R (sweaty)
2-Pentanol acetate (aliphatic ester)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (floral, herbal, sweet)
1-Penten-3-one (aliphatic ketone)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae), <i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	OD-R (ethereal, pungent)
Phenylacetaldehyde (= Hyacinthin) (aryl aldehyde)	<i>Zea mays</i> (Poaceae), <i>Rosa sp.</i> (Rosaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Camellia sinensis</i> (Theaceae) [leaf], <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (caramel, honey-, lilac- & hyacinth-like , sweaty, syrup)
Phenylacetic acid (aryl carboxylic acid)	<i>Nephelium lappaceum</i> (rambutan fruit) (Sapindaceae), <i>Vitis vinifera</i> (Vitaceae) (wine); non-fat dry milk aroma-active	OD-R (honey, pollen, rose-like)
Phenethyl alcohol (= β -Phenylethanol) (aryl alcohol)	<i>Petroselinum crispum</i> (Apiaceae), <i>Tagetes minuta</i> (Asteraceae), <i>Glycyrrhiza glabra</i> (Fabaceae), <i>Pinus spp.</i> (Pinaceae), <i>Piper longum</i> (Piperaceae), <i>Rosa rugosa</i> (Rosaceae), <i>Citrus spp.</i> (Rutaceae), <i>Populus tremuloides</i> (Salicaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (flowery, pollen, roses)
<i>n</i> -Propyl acetate (alkyl ester)	<i>Musa acuminata</i> , <i>M. paradisiaca</i> (banana) (Musaceae) [fruit]	OD-R (acid, propionic acid)
3a,4,5,7a-Tetrahydro-3,6-dimethyl-2[3H]-benzofuranone (= wine lactone) (furanone)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (sweet, spicy)
<i>trans</i> -Tridec-2-en-1-al (alkene aldehyde)	<i>Coriandrum sativum</i> (coriander) (Apiaceae) [leaf]	OD-R (coriander leaf)
Trimethylamine (aliphatic tertiary amine)	<i>Chenopodium vulvaria</i> (stinking goosefoot) (Chenopodiaceae); human menstrual blood; fox (<i>Vulpes vulpes</i>) anal gland	OD-R (fish)

(continued)

Table 10.4 (Continued)

Compound (details)	Plant source (family) plant part	Odour receptor (OD-R) binding (other targets) / in vivo effects
2,2,6-Trimethyl-1-butenylidene-cyclohexenes (= Megastigmatrienes) (alicyclic hydrocarbons)	<i>Passiflora</i> spp. (passion fruit) (Passifloraceae) [fruit]	OD-R (pleasant, floral, fruity, passion fruit tropical fruit odour)
Valeric acid (= Pentanoic acid) (aliphatic carboxylic acid)	<i>Angelica archangelica</i> , <i>Apium graveolens</i> (Apiaceae), <i>Prunus domestica</i> (Rosaceae), <i>Valeriana officinalis</i> (Valerianaceae); non-fat dry milk aroma	OD-R (sweaty, unpleasant)
(E)-Whiskey lactone (lactone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (flowery, lactone-like)
(Z)-Whiskey lactone (lactone)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (coconut, lactone-like)
Winelactone (lactone)	<i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	OD-R (sweet fruity)

Table 10.5 Animal pheromones and defensive agents occurring in plants

Compound (details)	Plant source (family) plant part	Animal source (other targets) / in vitro effects
Alkaloid		10.5a
Anabasine (= 3-(2-Piperidinyl)pyridine; Neonicotine) (pyridine piperidine)	<i>Alangium</i> spp. (Alangiaceae), <i>Zinnia elegans</i> , <i>Zollikoferia eliquiensis</i> (Asteraceae), <i>Anabasis aphylla</i> (Chenopodiaceae), <i>Sophora pachycarpa</i> (Fabaceae), <i>Nicotiana</i> spp. (Solanaceae)	Ant (<i>Aphaenogaster</i>) venom (nACh-R agonist) [insecticidal, toxic]
5-Hydroxytryptamine (= 5HT; Serotonin) (indole)	<i>Ananas comosus</i> (Bromeliaceae), <i>Hippophae rhamnoides</i> (Elaeagnaceae), <i>Juglans regia</i> (Juglandaceae), <i>Mucuna pruriens</i> (Fabaceae), <i>Musa sapientum</i> (Musaceae), <i>Lycopersicon esculentum</i> , <i>Solanum tuberosum</i> (Solanaceae), <i>Theobroma cacao</i> (Sterculiaceae), <i>Urtica dioica</i> (Urticaceae)	Tiger moth (<i>Arctia caja</i>) defensive barbs (5HT-R) CNS stimulatory NT]
Senecionine (pyrrolizidine)	<i>Senecio vulgaris</i> , <i>S. jacobaea</i> , <i>S.</i> spp. (Asteraceae), <i>Crotalaria juncea</i> (Fabaceae)	Cinnabar moth (<i>Tyria</i>) & tiger moth (<i>Arctia caja</i>) defence (derived from plant) [genotoxic, toxic]
Phenolic		10.5p
<i>p</i> -Cresol (phenol)	<i>Cynodon dactylon</i> (Bermuda grass) (Poaceae) [fermented]	Ground-beetle (<i>Calosoma</i>) defence (semiochemical)
Guaiacol (2-Methoxyphenol; <i>O</i> -Methylcatechol) (catechol)	<i>Apium graveolens</i> (celery seed) (Apiaceae), <i>Betula</i> sp. (Betulaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (Vitaceae) (wine), <i>Guaiacum</i> sp. (Zygophyllaceae)	Bee (<i>Xylocopa sulcatipes</i>) aggressiveness in other males, female attractant (OD-R) [anti-eczema]

(continued)

Table 10.5 (Continued)

Compound (details)	Plant source (family) plant part/	Animal source (other targets) / in vitro effects/
Hydroquinone (= 1,4-Benzenediol) (phenol)	<i>Pimpinella anisum</i> , <i>Petroselinum</i> spp. (Apiaceae) [oil], <i>Xanthium canadense</i> (Asteraceae) [seed], <i>Arbutus unedo</i> , <i>Vaccinium vitis-idaea</i> (Ericaceae) [leaf], <i>Pinus resinosa</i> (Pinaceae) [wood], <i>Protea</i> <i>mellifera</i> (Proteaceae) [leaf]	Water beetle (<i>Dytiscus</i>) defence; bombardier beetle (<i>Brachynus</i>) peroxidase substrate for ultimate benzoquinone discharge
[(<i>R</i>)-Mellein] (phenolic lactone)	<i>Aspergillus alutaceum</i> (fungus)	Wax moth (<i>Aphomia</i> <i>sociella</i>) male pheromone
Salicylaldehyde (= 2- Hydroxybenzaldehyde) (phenol aldehyde)	Oxidation product Salicylic acid <i>ex</i> <i>Sauromatum guttatum</i> (Araceae), <i>Betula</i> <i>lenta</i> (birch) (Betulaceae) [bark]	Water boatman (<i>Notonecta</i>) defence
Vanillin (= Methyl- protocatechuic aldehyde) (phenolic acid)	Widespread as aglycone & glucoside (Vanilloside); <i>Beta vulgaris</i> (Chenopodiaceae), <i>Dahlia</i> spp. (Asteraceae), <i>Asparagus</i> spp. (Liliaceae), <i>Syzygium aromaticum</i> (Myrtaceae), <i>Gymnadenia</i> spp., <i>Vanilla planifolia</i> (Orchidaceae), <i>Citrus paradisi</i> , <i>Ruta</i> spp. (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	Bee (<i>Xylocopa sulcatipes</i>) aggressiveness in other males, female attractant (OD-R) [antifungal]
4-Vinylphenol (phenol)	<i>Vitis vinifera</i> (Vitaceae) (wine)	OD-R (cypress, vanilla)
Terpene		10.5t
5 α -Androst-16-en-3-ol (= Priapol) (steroid triterpene)	Reduction product of 5 α -Androst-16- en-3-one; <i>Tuber melanospermum</i> (fungus; truffles); sows attracted & accordingly used to find truffles	Priapol R [1 nM] [boar (<i>Sus scrofa domestica</i>) pheromone; female attractant, musky odour]
5 α -Androst-16-en-3-one (= boar pheromone) (steroid triterpene)	<i>Apium graveolens</i> , <i>Pastinaca sativa</i> (parsnip) (Apiaceae); <i>Tuber melanospermum</i> (fungus; truffles); sows used to find truffles; supposed human female attraction by handkerchief rubbed in aroused male armpit	Priapol R [1 nM] [boar (<i>Sus scrofa domestica</i>) pheromone; female attractant, urine-like odour]
D-Bornyl acetate (= Borneol acetate) (monoterpene)	<i>Rosmarinus officinalis</i> , <i>Thymus vulgaris</i> (Lamiaceae) [oil], <i>Abies alba</i> , <i>A. siberica</i> , <i>Pinus montana</i> , <i>P. sylvestris</i> (Pinaceae) [oil]	American cockroach (<i>Periplaneta americana</i>) male attractant (OD-R)
Cardenolides (triterpene glycosides & aglycones); see Table 4.1 for cardenolide Na ⁺ , K ⁺ -ATPase inhibitors	e.g. Digitoxin (aglycone Digitoxigenin) <i>ex</i> <i>Digitalis purpurea</i> (foxglove) (Scrophulariaceae) [digitalis]	Monarch butterfly (<i>Danaus</i> <i>plexippus</i>), defence; grasshopper (<i>Poekilocerus</i> <i>bufonius</i>) defence (squirts) (derived from plant)
Citral (= mixture of α -Citral (Geranial) & β -Citral (Neral) = <i>trans</i> - & <i>cis</i> -3,7-Dimethyl-2,6- octadienal) (monoterpene)	<i>Rosa</i> spp. (rose oil) (Rosaceae), <i>Andropogon</i> <i>citratus</i> (lemon grass) (Poaceae), <i>Citrus</i> <i>limon</i> (lemon peel), <i>C. sinensis</i> (orange) (Rutaceae) [flower], <i>Verbena triphylla</i> (verbena) (Verbenaceae)	Ant (<i>Acanthomyops claviger</i>) defence; bee (<i>Oxaea</i>) male territory marker (OD-R) [antiseptic]
Citronellal (= 3,7- Dimethyloct-6-enal) (monoterpene)	<i>Melissa officinalis</i> (Lamiaceae), <i>Eucalyptus</i> spp. (Myrtaceae), <i>Andropogon nardus</i> (Poaceae), <i>Citrus limon</i> (Rutaceae)	Ant (<i>Acanthomyops claviger</i>) defence (OD-R) [antiseptic, sedative]
α -Farnesene (sesquiterpene)	<i>Xylopia aethiopica</i> (Annonaceae), <i>Malus</i> sp., <i>Pyrus</i> sp. (pear) (Rosaceae) [fruit peel]	Aphid alarm pheromone

(continued)

Table 10.5 (Continued)

Compound (details)	Plant source (family) / plant part/	Animal source (other targets) / in vitro effects/
(<i>Z,E</i>)- α -Farnesene (sesquiterpene)	<i>Gossypium hirsutum</i> (Malvaceae) [induction by wound-induced Methyljasmonate]; <i>Malus domestica</i> (apple) (Rosaceae)	Beetle (<i>Maladera matrida</i>) male and female attractant
β -Farnesene (sesquiterpene)	<i>Solanum berthaultii</i> (Solanaceae) [leaf oil]	Aphid alarm pheromone
<i>trans-trans</i> -Farnesol (sesquiterpene)	Widespread in many oils & flowers e.g. <i>Rosa</i> spp. (rose oil) (Rosaceae), <i>Andropogon citratus</i> (lemon grass), <i>A. nardus</i> (leaf, citronella oil) (Poaceae); <i>Ophrys sphegodes</i> (spider orchid) (Orchidaceae) [flower]	Bee (<i>Andrena</i> spp., <i>Psithyrus</i> sp., <i>Xylocopa varipuncta</i>) male territory marker, male & female attractant (OD-R); spider orchid pheromone mimicry
Geranial (= α -Citral) (monoterpene)	<i>Ocimum citriodorum</i> (Lamiaceae), <i>Andropogon citratus</i> (Poaceae), <i>Rosa</i> spp. (Rosaceae), <i>Citrus limon</i> (lemon peel), <i>C. sinensis</i> (orange) (Rutaceae) [flower], <i>Verbena triphylla</i> (verbena) (Verbenaceae)	Bee (<i>Panurgus banksianus</i>) male attractant (OD-R) [antiseptic, insect attractant]
Geraniol (= Lemonol) (monoterpene)	<i>Ocimum basilicum</i> (basil) (Lamiaceae), <i>Rosa</i> spp. (rose oil) (Rosaceae), <i>Andropogon nardus</i> (citronella oil), <i>A. schoenanthus</i> (palmarosa oil), <i>A. citratus</i> (lemon grass) (Poaceae), <i>Camellia sinensis</i> (Japanese green tea, Sen-cha) (Theaceae) [leaf], <i>Vitis vinifera</i> (Vitaceae)	Bee (<i>Centris adani</i> , female attractant; <i>Panurgus banksianus</i> , male attractant); honey bee <i>Apis mellifera</i> , trail pheromone (OD-R) [antiseptic, insect attractant]
Geranyl acetate (monoterpene ester)	<i>Coriandrum sativum</i> , <i>Thapsia villosa</i> (Apiaceae), <i>Bursera delpechiana</i> (Burseraceae), <i>Eusteralis deccanensis</i> , <i>Thymus</i> spp. (Lamiaceae), <i>Cymbopogon martini</i> (Poaceae) [flower]	Bee (<i>Centris adani</i>) male territory marker, female attractant
<i>all trans</i> -Geranylgeraniol (diterpene alcohol)	<i>Spinacia oleracea</i> (spinach) (Chenopodiaceae), <i>Oryza sativa</i> (Poaceae) [leaf]	Bee (<i>Xylocopa varipuncta</i>) female attractant
Ginkgolide A (ginkgolide diterpene)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	Antifeedant, (PAF-R) [AI, bitter, PAI]
Nagilactone C (totarane-like diterpene)	<i>Podocarpus nagi</i> , <i>P.</i> spp. (Podocarpaceae); glucoside and aglycone notably found in larvae but only the aglycone in plant leaves	Moth (<i>Milonia basalis</i>) larvae protection against predator stink bug (<i>Eocanthecona furellata</i>)
Inflexin (kaurane diterpene)	<i>Isodon excisus</i> , <i>I. lungshengensis</i> (Lamiaceae)	antifeedant (AROM) [cytotoxic]
Isodomedin (kaurane diterpene)	<i>Isodon shikokianus</i> (Lamiaceae)	Antifeedant [antibacterial, cytotoxic]
Linalool (= Linalol) (monoterpene)	<i>Bursera delpechiana</i> , <i>B.</i> spp. (Burseraceae), <i>Lavandula</i> spp., <i>Origanum siphyleum</i> (Lamiaceae), <i>Citrus aurantium</i> , <i>C. limon</i> , <i>C. paradisi</i> (Rutaceae), <i>Prunus domestica</i> (Rosaceae), <i>Camellia sinensis</i> (Theaceae), <i>Coriandrum sativum</i> (Apiaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	Bee (<i>Colletes cunicularius</i>) male attractant (OD-R)
Neocembrene (macrocyclic diterpene)	<i>Picea obovata</i> (Pinaceae)	Insect trail pheromone

(continued)

Table 10.5 (Continued)

Compound (details)	Plant source (family) plant part	Animal source (other targets) / in vitro effects
Neral (= β -Citral) (monoterpene aldehyde)	<i>Ocimum citriodorum</i> , <i>Thymus pulegioides</i> (Lamiaceae), <i>Andropogon citratus</i> (Poaceae), <i>Citrus limon</i> , <i>C. sinensis</i> (Rutaceae), <i>Rosa</i> spp. (Rosaceae), <i>Verbena triphylla</i> (Verbenaceae)	Bee (<i>Centris adani</i> , female attractant; <i>Panurgas banksianus</i> , male attractant)
Nerol (monoterpene)	<i>Rosa</i> spp. (Rosaceae), <i>Citrus aurantium</i> , <i>C. limon</i> , <i>C. vulgaris</i> (fruit, leaf) (Rutaceae)	Bee (<i>Centris adani</i>) female attractant (OD-R)
α -Pinene (monoterpene)	<i>Pinus palestris</i> , <i>P.</i> spp. (turpentine, pine oil) (Pinaceae), <i>Citrus</i> spp. (peel) (Rutaceae); Cupressaceae, Lamiaceae, Myrtaceae	Sawfly (<i>Neodoiprion setifer</i>) defence (derived from plant) (<i>Pinus</i> sp.) (OD-R) [irritant]
β -Pinene (monoterpene)	<i>Cuminum cyminum</i> (cumin oil) (Apiaceae), <i>Pinus palestris</i> , <i>P.</i> spp. (turpentine, pine oil) (Pinaceae), <i>Citrus paradisi</i> (grapefruit juice) (Rutaceae)	Sawfly (<i>Neodoiprion setifer</i>) defence (derived from plant) (<i>Pinus</i> sp.) (OD-R) [irritant]
β -Selinene (sesquiterpene)	<i>Apium graveolens</i> (celery) <i>Seseli</i> sp. [seed oil] (Apiaceae)	Moth (<i>Battus polydamus</i>) larval defence
Terpinolene (monoterpene)	<i>Ocimum kilimandscharicum</i> (Lamiaceae), Pinaceae [oil]	Termite (<i>Amitermes</i>) alarm pheromone (OD-R)
(+)- & (-)-Verbenone (= Pin-2-en-4-one) (monoterpene)	<i>Verbena triphylla</i> (Verbena oil) (Verbenaceae)	<i>Ips typographica</i> (bark beetle) anti-aggregation (dispersal) pheromones
Other		10.5o
Aristolochic acid (nitro phenanthrene)	<i>Aristolochia clematis</i> , <i>A. indica</i> , <i>A. longa</i> , <i>A. rotundo</i> , <i>Asarum canadense</i> (Aristolochiaceae)	Butterfly (<i>Battus archidamus</i> , <i>Pachlioptera aristolochiae</i>) (derived from plant) [AI, cytotoxic]
Benzaldehyde (aryl aldehyde)	Widespread <i>ex</i> cyanogenic glycoside e.g. Amygdalin <i>ex Prunus</i> spp. (Rosaceae), <i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Michelia champaca</i> (Magnoliaceae)	Moth (<i>Leucania impuris</i>) sex pheromone; insect defence (OD-R)
Cyanide (= C \equiv N ⁻) (deprotonated hydrogen cyanide)	Widespread <i>ex</i> cyanogenic glycosides e.g. Amygdalin <i>ex Prunus</i> spp. (Rosaceae) [fruit]	Moth (<i>Zygaena</i> spp.) & butterfly (<i>Heliconius</i> spp.) defence
Formic acid (carboxylic acid)	Widespread (at low levels); <i>Urtica dioica</i> (stinging nettle) (Urticaceae)	Ant (<i>Formica</i>) alarm pheromone & defensive agent [toxic]
Hexadecanal (alkane aldehyde)	<i>Cucumis sativus</i> (cucumber) (Cucurbitaceae) [fruit], <i>Citrus limon</i> (Rutaceae)	Sphecid wasp (<i>Philanthus</i> spp.) male territory marker, female attractant
1-Hexanal (alkane aldehyde)	Oxidized precursor Hexanoic acid <i>ex Cocos nucifera</i> (palm oil) (Palmae), <i>Annona cherimolia</i> (cherimoya) (Annonaceae) [fruit]	Weaver ant (<i>Oecophylla longinoda</i>) alarm pheromone
1-Hexanol (alkane alcohol)	Oxidized precursor Hexanoic acid <i>ex Cocos nucifera</i> (palm oil) (Palmae)	Weaver ant (<i>Oecophylla longinoda</i>) alarm pheromone
(<i>E</i>)-2-Hexenal (alkene aldehyde)	<i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Brassica oleracea</i> (Brassicaceae) [leaf]	Insect defence
Methyl anthranilate (= Methyl 2-aminobenzoate) (aryl ester)	<i>Cananga odorata</i> (Annonaceae), <i>Jasminum sambac</i> (Oleaceae), <i>Citrus aurantium</i> , <i>Citrus paradisi</i> (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	Ant (<i>Camponotus</i> spp.) male pheromone (OR-R)

(continued)

Table 10.5 (Continued)

Compound (details)	Plant source (family) plant part/	Animal source (other targets) / in vitro effects/
<i>cis-trans</i> -Nepetalactone (iridoid monoterpene lactone)	<i>Nepeta cataria</i> (catnip) (Lamiaceae) [leaf]	Vetch aphid (<i>Megoura viciae</i>) male attractant [insect repellent; excites cats]
Pentadecanal (alkane aldehyde)	<i>Cucumis sativus</i> (cucumber) (Cucurbitaceae) [fruit], <i>Mitracarpus scaber</i> (Rubiaceae)	Sphecid wasp (<i>Philanthus</i> spp.) male territory marker, female attractant
2-Phenylethanol (aryl alcohol)	<i>Asclepias syriaca</i> (Asteraceae), <i>Beta vulgaris</i> (Chenopodiaceae), <i>Jasminum sambac</i> (Oleaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	Bee (<i>Panurgus banksianus</i>) male attractant
Trimethylamine (alkyl tertiary amine)	<i>Chenopodium vulvaria</i> (stinking goosefoot) (Chenopodiaceae)	Human menstrual blood; fox (<i>Vulpes vulpes</i>) anal gland (OD-R)
Undecane (alkane)	Tobacco smoke <i>ex Nicotiana tabacum</i> (Solanaceae)	Ant (<i>Formica lugubris</i>) male pheromone
Valeric acid (= Pentanoic acid) (aliphatic carboxylic acid)	<i>Valeriana officinalis</i> (valerian) (Valerianaceae) [oil]; other essential oils	Insect pheromone (<i>Limonius californicus</i> , sugar beet wireworm)

Table 10.6 Some further plant-derived semiochemicals

Compound (details)	Plant source (family) plant part/	Organism affected
Alkaloid		
Indole (indole)	<i>Cynodon dactylon</i> (Bermuda grass) [fermented], <i>Zea mays</i> (Poaceae)	10.6a Mosquito (<i>Culex quinquefasciatus</i> , <i>C. tarsalis</i>) responses
Gramine (indole)	<i>Arundo donax</i> , <i>Hordeum vulgare</i> , <i>Phalaris</i> spp., <i>Triticum aestivum</i> (Poaceae)	Insect antifeedant (5HT-R) [causes sheep "Phalaris staggers"]
3-Methylindole (indole)	<i>Cynodon dactylon</i> (Bermuda grass) (Poaceae) [fermented], bacterial fermentation; oviposition synergist for <i>Culex quinquefasciatus</i>, vector of <i>Wuchereria bancrofti</i> (filariasis agent, >15 million infected/450 million susceptible, 1 million new infections per year)	Mosquito (<i>Culex quinquefasciatus</i> , <i>C. tarsalis</i>) responses; synergises with <i>Culex</i> oviposition pheromone 6-Acetoxy-5-hexadecanolide
Phenolic		
Agatharesinol (norlignan)	<i>Cryptomeria japonica</i> (Japanese cedar)	10.6p Snail (<i>Acusta despecta</i>) antifeedant
β -Asarone (phenylpropanoid)	<i>Acorus calamus</i> (calamus oil) (Aracaceae), <i>Asarum europaeum</i> (Aristolochiaceae), <i>Piper angustifolium</i> (Piperaceae)	Insect attractant (OD-R) [carcinogen, spasmolytic]
<i>p</i> -Cresol (phenol)	<i>Cynodon dactylon</i> (Bermuda grass) (Poaceae) [fermented]	Mosquito (<i>Culex quinquefasciatus</i> , <i>C. tarsalis</i>) responses

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) plant part	Organism affected
4-Ethylphenol (phenol)	<i>Cynodon dactylon</i> (Bermuda grass) (Poaceae) [fermented]	Mosquito (<i>Culex quinquefasciatus</i> , <i>C. tarsalis</i>) responses
Hordenine (phenolic arylamine)	<i>Ariocarpus</i> spp. (Cactaceae), <i>Hordeum vulgare</i> (barley), <i>Phalaris</i> spp. (Poaceae)	Sheep & insect antifeedant
Methyl salicylate (= 2-Hydroxybenzoic acid methyl ester) (phenolic ester)	<i>Malus domestica</i> (apple) (Rosaceae)	Antennal response by female codling moth (<i>Cydia pomonella</i>) (apple) (OD-R)
Phenol (phenol)	<i>Origanum majorana</i> (Lamiaceae), <i>Cynodon dactylon</i> (Bermuda grass) (Poaceae) [fermented]	Mosquito (<i>Culex quinquefasciatus</i> <i>C. tarsalis</i>) responses
Sequirin-C (norlignan)	<i>Cryptomeria japonica</i> (Japanese cedar)	Snail (<i>Acusta despecta</i>) antifeedant
Terpene		10.6t
Ajugarin I (clerodane diterpene)	<i>Ajuga remota</i> (Lamiaceae)	Insect antifeedant
Alantolactone (eudesmanolide sesquiterpene lactone)	<i>Inula helenium</i> I. spp. (Asteraceae)	Insect antifeedant
Alatolide (germacranolide sesquiterpene lactone)	<i>Jurinea alata</i> (Asteraceae)	Insect antifeedant
Archangelolide (germacranolide sesquiterpene lactone)	<i>Laserpitium archangelica</i> (Apiaceae) [fruit, root]	Insect antifeedant
Artecenin (= Chrysartemin B) (germacranolide sesquiterpene lactone)	<i>Artemisia cana</i> , <i>Chrysanthemum macrophyllum</i> (Asteraceae)	Insect antifeedant
Bakkenolide A (bakkenolide sesquiterpene lactone)	<i>Cacalia</i> , <i>Homogyne alpina</i> , <i>Ligularia</i> , <i>Petasites</i> , <i>Senecio</i> spp. (Asteraceae)	Insect antifeedant [antitumour, cytotoxic]
Bergamotene (sesquiterpene)	Induced in <i>Zea mays</i> (corn) (Poaceae) [leaf] by wounding-inducible Jasmonic acid & by beet armyworm <i>Spodoptera exigua</i>	Likely attractant for predators on insect herbivores
(+)-Camphor (= Bornan-2-one; Camphan-2-one) (monoterpene)	<i>Artemisia salsoloides</i> , <i>Tanacetum vulgare</i> (leaf & tops, tansy oil) (Asteraceae), <i>Cinnamomum camphora</i> (camphor oil) (Lauraceae), <i>Myrtus communis</i> (leaf, Myrtle oil) (Myrtaceae)	Moth repellent (OD-R) [irritant]
Canin (guaianolide sesquiterpene lactone)	<i>Artemisia cana</i> A. spp., <i>Tanacetum parthenium</i> (feverfew), <i>Handelia trichophylla</i> (Asteraceae)	Insect antifeedant

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) plant part	Organism affected
3-Carene (monoterpene)	<i>Picea abies</i> (spruce), <i>Pinus sylvestris</i> (Scots pine) (Pinaceae) [bark, needle]	Reduced attraction of bark beetle (<i>Pityogenes bidentatus</i>) by pheromones
α -Caryophyllene (= α -Humulene) (sesquiterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [stored odorant released by damage from beet armyworm & other insect herbivores]	Attractant for cotton pest predators
β -Caryophyllene (sesquiterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [stored odorant released by damage from beet armyworm & other insect herbivores]; <i>Malus domestica</i> (apple) (Rosaceae)	Attractant for cotton pest predators; antennal response by female codling moth (<i>Cydia pomonella</i>) (apple) (OD-R)
Caryoptin (clerodane diterpene)	<i>Caryopteris divaricata</i> (Verbenaceae)	Antifeedant (bitter)
Catalpol (iridoid monoterpene)	<i>Catalpa</i> (Bignoniaceae), <i>Buddleja</i> (Buddlejaceae), <i>Plantago</i> (Plantaginaceae), <i>Veronica</i> (Scrophulariaceae) spp.	Phagostimulant (bitter) [diuretic, laxative]
Catalposide (= Catalpin) (iridoid monoterpene glucoside)	<i>Catalpa</i> (Bignoniaceae), <i>Veronica</i> (Scrophulariaceae) spp.	Phagostimulant & antifeedant (bitter) [diuretic, laxative]
1,8-Cineole (= Eucalyptol) (monoterpene)	<i>Artemisia maritima</i> (Asteraceae), <i>Ocimum basilicum</i> (Lamiaceae), <i>Eucalyptus globulus</i> , <i>E.</i> spp., <i>Melaleuca leucadendron</i> , <i>M.</i> spp. (Myrtaceae), <i>Curcuma longa</i> , <i>Elettaria cardamomum</i> (Zingiberaceae)	Insect repellent (OD-R) [anthelmintic, antiseptic, expectorant]
Citral (= mixture of Citral A (Geranial) & Citral B (Neral) = <i>trans</i> - & <i>cis</i> -3,7-Dimethyl-2,6-octadienal) (monoterpene)	<i>Melissa officinalis</i> (Lamiaceae), <i>Myrcia acris</i> (Myrtaceae), <i>Andropogon citratus</i> (Poaceae), <i>Rosa</i> spp. (Rosaceae), <i>Citrus limon</i> , <i>C. sinensis</i> (Rutaceae), <i>Verbena triphylla</i> (Verbenaceae) [oil], <i>Zingiber officinale</i> (Zingiberaceae)	Rat antidepressant (adjudged from decreased immobility time in forced swimming test) (OD-R – lemon odour) [antiseptic]
Clerodendrin A (clerodane diterpene)	<i>Caryopteris trichotomum</i> (Verbenaceae)	Insect antifeedant
Coronopilin (pseudoguaianolide sesquiterpene lactone)	<i>Ambrosia</i> , <i>Hymenoclea</i> , <i>Iva</i> , <i>Parthenium</i> spp. (Asteraceae)	Insect antifeedant
Cucurbitacin E (= α -Elaterine) (cucurbitacin, triterpene)	<i>Eballium elaterium</i> (Cucurbitaceae), other Cucurbitaceae	Attractant & feeding deterrent [antineoplastic, cytotoxic, disrupts actin cytoskeleton]
4,8-Dimethyl-1,3E,7-dimethylnonatriene (= Homoterpene I) (sesquiterpene)	<i>Phaseolus lunatus</i> (Fabaceae) [leaf; induced by Jasmonic acid, β -galactosidase application & by red spotted spider mite (<i>Tetranychus urticae</i>); induced in <i>Zea mays</i> (corn) (Poaceae) [leaf] by Jasmonic acid & by beet armyworm <i>Spodoptora exigua</i>	Likely attractant for predators on insect herbivores

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) / plant part/	Organism affected
Dolichodial (iridoid monoterpene)	<i>Teucrium marum</i> (Lamiaceae)	Insect repellent; beetle (<i>Plagioderia</i>) larval secretes defensive dolichodial isomer
(<i>E,E</i>)- & (<i>Z,E</i>)- α -Farnesene (sesquiterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [induction by wound-induced Methyljasmonate]; <i>Malus domestica</i> (apple) (Rosaceae)	Likely attractant for predators on insect herbivores; antennal response by female codling moth (<i>Cydia pomonella</i>) (apple) (OD-R)
(<i>E,E</i>)- α -Farnesene (sesquiterpene)	<i>Brassica napus</i> (oilseed rape) (Brassicaceae), <i>Gossypium hirsutum</i> (cotton) (Malvaceae) [induction by wound-induced Methyljasmonate], <i>Malus domestica</i> (apple) (Rosaceae)	Likely attractant for predators on insect herbivores; antennal response by female codling moth (<i>Cydia pomonella</i>) (apple) & bee (OD-R)
(<i>E</i>)- β -Farnesene (sesquiterpene)	<i>Gossypium hirsutum</i> (Malvaceae) [systemic induction by wound-induced Methyljasmonate]; induced in <i>Zea mays</i> (corn) (Poaceae) [leaf] by wounding-inducible Jasmonic acid & by beet armyworm <i>Spodoptera exigua</i> ; <i>Malus domestica</i> (apple tree) (Rosaceae)	Likely attractant for predators on insect herbivores; antennal response by female codling moth (<i>Cydia pomonella</i>) (apple) (OD-R)
Geraniol (= Lemonol) (monoterpene)	<i>Xylopiia aethiopica</i> (Annonaceae), <i>Asarum canadense</i> (Aristolochiaceae), <i>Andropogon</i> spp. (Poaceae), <i>Rosa</i> spp. (Rosaceae), <i>Citrus</i> spp. (Rutaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (Vitaceae)	Moth proboscis extension stimulant (OD-R), insect attractant [antiseptic]
Germacrene D (sesquiterpene)	<i>Mentha longifolia</i> (Lamiaceae), <i>Malus domestica</i> (apple) (Rosaceae)	Antennal response by female codling moth (<i>Cydia pomonella</i>) (apple) (OD-R)
Ginkgolide A (diterpene)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae)	Antifeedant, (PAF-R) [AI, antiasthmatic, bitter, bronchodilatory]
Hesperetin (= Eriodictyol 4'-methyl ether) (flavanone)	<i>Mentha aquatica</i> M. spp. (Lamiaceae), <i>Citrus</i> spp. (Rutaceae); glycosides in <i>Cordia obliqua</i> (Boraginaceae), <i>Prunus persica</i> (Rosaceae)	Antifeedant (AROM) [modulation gene expression induction]
Inflexin (kaurane triterpene)	<i>Isodon excisus</i> , <i>I. lungshengensis</i> (Lamiaceae)	Antifeedant (AROM) [cytotoxic]
[(+)-Ipsdienol] (monoterpene)	Product from Myrcene <i>ex</i> Pinaceae bark	Bark beetle (<i>Ips paraconfusus</i>) aggregation pheromone; <i>Ips pini</i> aggregation inhibitor
[(-)-Ipsdienol] (monoterpene)	Product from Myrcene <i>ex</i> Pinaceae bark	Bark beetle (<i>Ips paraconfusus</i>) aggregation inhibitor; <i>Ips pini</i> aggregation pheromone

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) plant part/	Organism affected
Laserolide (germacranolide sesquiterpene lactone)	<i>Laser trilobum</i> (Apiaceae)	Insect antifeedant
Lavender oil (= oil of Lavender) (mostly monoterpenes)	<i>Lavandula officinalis</i> (Lavender oil) Lamiaceae] [leaf, tops]	Major components Linalol & Linalyl acetate [sedative, anti- insomniac, increases singer's pitch]
Ligulatin B (= Incanin) (pseudoguaianolide sesquiterpene lactone)	<i>Parthenium ligulatum</i> , <i>P. spp.</i> (Asteraceae)	Insect antifeedant
Limonene (monoterpene)	<i>Apium graveolens</i> (Apiaceae), <i>Prunus spp.</i> (Rosaceae), <i>Citrus limon</i> (Rutaceae); total global plant hydrocarbon emission ≈ 10× >anthropogenic non-methane hydrocarbon emission	Plum curculio (<i>Conotrachelus nenufar</i>) adult attractant
(+)-Limonene (monoterpene)	<i>Anethum graveolens</i> , <i>Apium graveolens</i> (Apiaceae), <i>Mosla dianthera</i> (Lamiaceae), <i>Citrus aurantium</i> , <i>C. limonum</i> , <i>C. vulgaris</i> , <i>C. spp.</i> (Rutaceae) [fruit peel oil]	OD-R (citrus, orange); relaxes female dental patients [expectorant, irritant, sedative]
Linalol (= Linalool) (monoterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [induction by wound-induced Methyljasmonate]; <i>Malus domestica</i> (apple) (Rosaceae), <i>Vitis vinifera</i> (Vitaceae)	Likely attractant for predators on insect cotton herbivores; antennal response by female codling moth (<i>Cydia pomonella</i>) (apple) (OD-R)
Lipiferolide (germacranolide sesquiterpene lactone)	<i>Liriodendron tulipifera</i> (Magnoliaceae)	Insect antifeedant
Melampodin A (germacranolide sesquiterpene lactone)	<i>Melampodium heterophyllum</i> , <i>M. leucanthum</i> (Asteraceae)	Insect antifeedant
Melampodin B (germacranolide sesquiterpene lactone)	<i>Melampodium americanum</i> , <i>M. spp.</i> (Asteraceae)	Insect antifeedant
Muzigadiol (sesquiterpene)	<i>Warburgia salutaris</i> (Muziga tree) (Canellaceae) [bark]	Antifeedant against armyworm (<i>Spodoptera</i>)
Neocembrene (macrocyclic diterpene)	<i>Picea spp.</i> (Pinaceae)	Termite (<i>Nasutitermis</i>) trail pheromone
Nepetalactone (isomeric mixture) (iridoid monoterpene lactone)	<i>Nepeta cataria</i> (catnip) (Lamiaceae) [leaf]	Insect repellent; excites cats (Felidae) (lions but not tigers)

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) plant part	Organism affected
Nerolidol (sesquiterpene)	Induced in <i>Zea mays</i> (corn) (Poaceae) [leaf] by wounding-inducible Jasmonic acid & by beet armyworm <i>Spodoptora exigua</i>	Likely attractant for predators on insect herbivores
β -Ocimene (monoterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [systemic induction by wound-induced Methyljasmonate]	Likely attractant for predators on insect herbivores (OD-R)
Parthenin (= Parthenicin) (pseudoguaianolide sesquiterpene lactone)	<i>Ambrosia psilostachya</i> , <i>Iva nevadensis</i> , <i>Parthenium hysterophorus</i> (Asteraceae)	Antifeedant [dermatitic, genotoxic]
α -Pinene (monoterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [stored odorant released by damage from beet armyworm, other insect herbivores]; <i>Picea abies</i> (spruce), <i>Pinus sylvestris</i> (Scots pine) (Pinaceae) [bark, needle]	Attractant for cotton pest predators; reduced attraction of (pine) bark beetle (<i>Pityogenes bidentatus</i>) by pheromones
β -Pinene (monoterpene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [stored odorant released by damage from beet armyworm, other insect herbivores]; <i>Picea abies</i> (spruce), <i>Pinus sylvestris</i> (Scots pine) (Pinaceae) [bark, needle]	Attractant for cotton pest predators; reduced attraction of bark beetle (<i>Pityogenes bidentatus</i>) by pheromones
Pinguicene (sesquiterpene)	<i>Aneura pinguis</i> (liverwort)	Insect antifeedant
Polhovolide (guaianolide sesquiterpene lactone)	<i>Laserpitium siler</i> (Apiaceae)	Insect antifeedant
Polygodial (= Tadeonal) (sesquiterpene)	<i>Warburgia stuhlmanii</i> (Canellaceae), <i>Polygonum hydroppiper</i> (Polygonaceae), <i>Drymis aromatica</i> (Winteraceae)	Insect antifeedant [pepper taste]
β -Santolin (eudesmanolide sesquiterpene lactone)	<i>Artemisia</i> spp. (Asteraceae)	Insect antifeedant
Santonin (= α -Santonin) (eudesmanolide)	<i>Artemisia absinthium</i> (wormwood), <i>A.</i> spp. (Asteraceae); xanthopsia from absinthe use affected Van Gogh's "yellow" period?	Insect antifeedant
Siromodiol diacetate (sesquiterpene)	<i>Lindera triloba</i> (Lauraceae) [leaf]	Insect antifeedant
Terpinolene (monoterpene)	<i>Picea abies</i> (spruce), <i>Pinus sylvestris</i> (Scots pine) (Pinaceae) [bark, needle]	Reduced attraction of bark beetle (<i>Pityogenes bidentatus</i>) by pheromones
Tetraneurin A (pseudoguaianolide sesquiterpene lactone)	<i>Parthenium alpinum</i> , <i>P.</i> spp. (Asteraceae)	Insect antifeedant [dermatitic]
Trilobolide (guaianolide sesquiterpene lactone)	<i>Laser trilobum</i> (Apiaceae)	Insect antifeedant [antitumour, cytotoxic]

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) plant part	Organism affected
4,8,12-Trimethyl-1,3E,7E,11-tridecatetraene (= Homoterpene II) (diterpene)	<i>Phaseolus lunatus</i> (Fabaceae) [leaf; induced by β -galactosidase application & by red spotted spider mite (<i>Tetranychus urticae</i>); induced in <i>Zea mays</i> (corn) (Poaceae) [leaf] by wounding-inducible Jasmonic acid & by beet armyworm <i>Spodoptera exigua</i>	Likely attractant for predators on insect herbivores
<i>epi</i> -Tulipinolide (germacranolide sesquiterpene lactone)	<i>Ambrosia</i> spp., <i>Zaluzania pringlei</i> (Asteraceae), <i>Liriodendron tulipifera</i> (Magnoliaceae)	Insect antifeedant [antitumour, cytotoxic]
[(+)- <i>cis</i> -Verbenol (= (+)- <i>cis</i> -Pin-2-en-4-ol)] (monoterpene)	Product from precursor (+)- α -Pinene <i>ex Picea abies</i> (Norway spruce) (Pinaceae) by bark beetle (<i>Ips typographica</i>)	Bark beetle (<i>Ips typographica</i>) aggregation pheromone
[(+)-&(-)-Verbenone (= Pin-2-en-4-one)] (monoterpene)	<i>Verbena triphylla</i> (Verbena oil) (Verbenaceae); products from plant precursor α -Pinene <i>ex Picea abies</i> (Pinaceae) & thence Verbenol by bark beetle (<i>Ips typographica</i>)	<i>Ips typographica</i> (bark beetle) anti-aggregation (dispersal) pheromones
Vernodalinal (eudesmanolide sesquiterpene lactone)	<i>Vernonia amygdalina</i> , <i>V. anthelmintica</i> , <i>V. guinensis</i> (Asteraceae)	Insect antifeedant
Warburganal (sesquiterpene)	<i>Warburgia salutaris</i> (muziga tree) (Canellaceae) [bark]	Antifeedant against armyworms (<i>Spodoptera</i> spp.) [antifungal]
Xanthumin (secoguaianolide sesquiterpene lactone)	<i>Xanthium</i> spp. (Asteraceae)	Insect antifeedant
Xerantholide (guaianolide sesquiterpene lactone)	<i>Xeranthemum cylindraceae</i> (Asteraceae)	Insect antifeedant
Other		10.6o
Dimethyl disulfide (alkyl disulfide)	Scent of bat-pollinated flowers	Nectarivorous bat (<i>Glossophaga soricina</i>) attractant
(3E)-4,8-Dimethyl-1,3,7-nonatriene (alkene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [systemic induction by wound-induced Methyljasmonate]; <i>Malus domestica</i> (apple) (Rosaceae)	Likely attractant for predators on insect herbivores (cotton); antennal response by female codling moth (<i>Cydia pomonella</i>) (apple) (OD-R)
2,4-Dithiapentane (alkane thioether)	Scent of bat-pollinated flowers	Nectarivorous bat (<i>Glossophaga soricina</i>) attractant
Ethanol (alkane alcohol)	From fermentation of plant-derived starch; desire for fermentable ethanol precursors a likely key stimulus for development of human agriculture & hence civilization; global ethanol production 33 billion litres (1998) (5% beverage use); Greenhouse gas lowering potential fuel use; lowers caution and although generally perceived as an aphrodisiac by males & females is not	Reduced attraction of bark beetle (<i>Pityogenes bidentatus</i>) by pheromones [hypoglycaemic – ↓ gluconeogenesis; sedative; excess → alcoholic hepatitis, cirrhosis, neuronal damage]

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) plant part	Organism affected
Ethyl isovalerate (alkyl ester)	<i>Artemisia salsoloides</i> (Asteraceae), <i>Prunus</i> spp. (plum) (Rosaceae) [unripe fruit]	Plum curculio (<i>Conotrachelus nenuphar</i>) adult attractant
(E,E)- α -Farnesene (sesquiterpene)	<i>Brassica napus</i> (oilseed rape) (Brassicaceae) [flower]	Bees stimulated
Formic acid (carboxylic acid)	Widespread (low); <i>Urtica dioica</i> (stinging nettle) (Urticaceae)	Alarm pheromone & defensive agent (<i>Formica</i> , ants) [toxic]
Glucosinolates (alkyl- and aryl- thioglycosides)	<i>Brassica</i> spp. & other Brassicaceae species	Feeding deterrents (through generation of reactive isothiocyanates, R=N=C=S)
Hexadecanal (alkane aldehyde)	<i>Cucumis sativus</i> (cucumber) (Cucurbitaceae) [fruit], <i>Citrus limon</i> (Rutaceae)	Sphacid wasp (<i>Phylanthus</i> spp.) male territory marker, female attractant
1-Hexanol (alkane alcohol)	<i>Brassica oleracea</i> (Brassicaceae) [leaf]; <i>Solanum tuberosum</i> (potato) (Solanaceae) [leaf, "green odour"]	Reduced attraction of bark beetle (<i>Pityogenes bidentatus</i>) by pheromones; diamondback moth (<i>Plutella xylostella</i>) attractant; Colorado potato beetle (<i>Leptinotarsa decemlineata</i>) attractant
(E)-2-Hexenal (= <i>trans</i> - Hex-2-en-1-al; Leaf aldehyde) (aliphatic aldehyde); major damaged leaf "green odour" & insect herbivore attractant	Damaged leaf tissue; e.g. <i>Brassica oleracea</i> (Brassicaceae), <i>Dianthus caryophyllus</i> (Caryophyllaceae), <i>Quercus rubra</i> (Fagaceae), <i>Aloe arborescens</i> (Liliaceae), <i>Musa acuminata</i> , <i>M. paradisiaca</i> (Musaceae), <i>Olea europaea</i> (Oleaceae), <i>Solanum tuberosum</i> (Solanaceae), <i>Vitis vinifera</i> (Vitaceae); modified by male olfactory sensilla-specific, sphinx moth (<i>Manduca sexta</i>) glutathione S-transferase; Colorado potato beetle (<i>Leptinotarsa decemlineata</i>) attractant	Sphinx moth (<i>Manduca sexta</i>) stimulated; diamondback moth (<i>Plutella xylostella</i>) attractant; stimulates female polyphemus moth <i>Anthera polyphemus</i> male attractant release (oak leaf needed for mating)
(Z)-3-Hexenal (alkene aldehyde)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [induced by beet armyworm]; <i>Malus domestica</i> (apple) (Rosaceae)	Attractant for cotton pest predators; antennal response by female codling moth (<i>Cydia pomonella</i>)
1-Hexen-3-ol (alkene alcohol)	<i>Brassica oleracea</i> (Brassicaceae) [leaf]	Diamondback moth (<i>Plutella xylostella</i>) attractant
<i>trans</i> -2-Hexen-1-ol (alkene alcohol)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [leaf, "green odour"]	Colorado potato beetle (<i>Leptinotarsa decemlineata</i>) attractant
(Z)-3-Hexen-1-ol (= <i>cis</i> - Hex-3-en-1-ol; Leaf alcohol) (alkene alcohol); major damaged leaf "green odour" & insect herbivore attractant	<i>Brassica oleracea</i> (Brassicaceae), <i>Robinia pseudacacia</i> (Fabaceae), <i>Mosla dianthera</i> (Lamiaceae), <i>Morus</i> spp. (Moraceae), <i>Aloe arborescens</i> (Liliaceae), <i>Solanum tuberosum</i> (Solanaceae), <i>Vitis vinifera</i> (Vitaceae); Colorado potato beetle (<i>Leptinotarsa decemlineata</i>) attractant	Reduced attraction of bark beetle (<i>Pityogenes bidentatus</i>) by pheromones; diamondback moth (<i>Plutella xylostella</i>) attractant

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) plant part/	Organism affected
(<i>Z</i>)-3-Hexenyl acetate (alkene ester); green leaf odour	<i>Brassica oleracea</i> (Brassicaceae); <i>Gossypium hirsutum</i> (cotton) (Malvaceae) [induced by beet armyworm & by wound-induced Methyljasmonate]; <i>Solanum tuberosum</i> (potato) (Solanaceae)	Diamondback moth (<i>Plutella xylostella</i>) attractant; attractant for cotton pest predators; Colorado potato beetle (<i>Leptinotarsa decemlineata</i>) attractant
Hexyl acetate (alkyl ester)	<i>Brassica oleracea</i> (Brassicaceae) [leaf], <i>Avena sativa</i> (oats) (Poaceae)	Diamondback moth (<i>Plutella xylostella</i>) attractant
Isovaleric acid (alkyl carboxylic acid)	<i>Mentha arvensis</i> (field mint) (Lamiaceae) [leaf], <i>Pavonia odorata</i> (Malvaceae)	Human brain response (NMR imaging) OD-R (unpleasant)
(<i>Z</i>)-Jasmone (= <i>cis</i> -Jasmone) (alicyclic ketone)	<i>Jasminum officinale</i> (Oleaceae) [flower]	Insect repellent (damson-hop & cereal aphids), insect attractant (seven-spot ladybird & aphid parasitoid)
Methyl anthranilate (= Methyl 2-aminobenzoate) (aryl ester)	<i>Cananga odorata</i> (Annonaceae), <i>Jasminum officinale</i> , <i>J. sambac</i> (Oleaceae), <i>Citrus aurantium</i> , <i>Citrus paradisi</i> (Rutaceae), <i>Vitis vinifera</i> (Vitaceae)	Ant (<i>Camponotus</i> spp.) male pheromone (OD-R)
Methyl mercaptan (= Methane thiol) (alkyl thiol)	<i>Raphanus sativus</i> (radish) (Brassicaceae) [root]; widespread from bacterial action on Cysteine & Methionine & as trace plant volatile	Sheep blowfly (<i>Lucilia cuprina</i> , <i>L. sericata</i>) attractant; sheep blowfly strike horrible in Australia
Naphthalene (naphthalene)	<i>Cynodon dactylon</i> (Bermuda grass), <i>Zea mays</i> (maize) (Poaceae) [fermented]	Mosquito (<i>Culex quinquefasciatus</i> <i>C. tarsalis</i>) responses
Nonanal (alkane aldehyde)	<i>Cynodon dactylon</i> (Bermuda grass) (Poaceae) [fermented], <i>Zingiber officinale</i> (Zingiberaceae)	Mosquito (<i>Culex quinquefasciatus</i> <i>C. tarsalis</i>) responses
Pentadecanal (alkane aldehyde)	<i>Cucumis sativus</i> (cucumber) (Cucurbitaceae) [fruit], <i>Mitracarpus scaber</i> (Rubiaceae)	Sphecid wasp (<i>Philanthus</i> spp.) male territory marker, female attractant
2-Phenylethanol (aryl alcohol)	<i>Asclepias syriaca</i> (milkweed) (Asteraceae) [flower], <i>Humulus lupulus</i> (Cannabaceae), <i>Beta vulgaris</i> (processed sugar beet) (Chenopodiaceae), <i>Jasminum sambac</i> (Oleaceae), <i>Citrus aurantium</i> (Rutaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	Bee (<i>Panurgus banksianus</i>) male attractant
2-Tridecanone (alkane ketone)	<i>Cynodon dactylon</i> (Bermuda grass) (Poaceae) [fermented]	Mosquito (<i>Culex quinquefasciatus</i> <i>C. tarsalis</i>) responses
(<i>E,E</i>)-4,8,12-Trimethyl-1,3,7,11-tridecatetraene (alkene)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [systemic induction by wound-induced Methyljasmonate]	Likely attractant for predators on insect herbivores (OD-R)
Undecane (alkane)	Tobacco smoke ex <i>Nicotiana tabacum</i> (Solanaceae), <i>Citrus aurantiifolia</i> (Rutaceae)	Ant (<i>Formica lugubris</i>) male pheromone
2-Undecanone (alkane ketone)	<i>Cynodon dactylon</i> (Bermuda grass) (Poaceae) [fermented]	Mosquito (<i>Culex quinquefasciatus</i> , <i>C. tarsalis</i>) responses

(continued)

Table 10.6 (Continued)

Compound (details)	Plant source (family) / plant part/	Organism affected
Valeric acid (= Pentanoic acid) (aliphatic carboxylic acid)	<i>Apium graveolens</i> (Apiaceae), <i>Valeriana officinalis</i> (valerian) (Valerianaceae) [oil]; other essential oils	Insect pheromone (<i>Limonius californicus</i> , sugar beet wireworm)

Table 10.7 Odoriferous human products of ingested plant compounds

Compound (class)	Plant source (family) / plant part/	Odour (other details)
Other		10.7o
Allyl mercaptan (= Allyl thiol) (aliphatic thiol)	<i>Allium sativum</i> , <i>A. schoenoprasum</i> (garlic) (Liliaceae) [bulb]	Unpleasant (breath)
Allyl methyl sulfide (aliphatic thiol)	<i>Allium sativum</i> (garlic) (Liliaceae) [bulb]	Unpleasant (breath)
Bis-(methylthio)methane (aliphatic thiol)	<i>Asparagus officinalis</i> (Liliaceae) (asparagus) [aerial]; reputed aphrodisiac	Pungent (urine)
Dimethyl sulfide (aliphatic sulfide)	<i>Asparagus officinalis</i> (Liliaceae) (asparagus) [aerial]; reputed aphrodisiac	Pungent (urine, flatus)
Dimethyl sulfone (= Methylsulfonylmethane) (aliphatic sulfone)	<i>Asparagus officinalis</i> (Liliaceae) (asparagus) [aerial]; reputed aphrodisiac	Pungent (urine)
Dimethyl sulfoxide (aliphatic sulfone)	<i>Asparagus officinalis</i> (Liliaceae) (asparagus) [aerial]; reputed aphrodisiac	Pungent (urine)
Hydrogen sulfide (= H ₂ S) (hydrogen sulfide)	Flatulence from anaerobic bacterial metabolizing of indigestible oligosaccharides esp. from legume seed e.g. <i>Glycine max</i> (soya bean), <i>Vigna anguiculata</i> (cowpea)	Malodorous [highly toxic; reactive so that odour reception declines]; low indigestible oligosaccharide soya bean decreases flatulence; malodour (periodontal disease)
Methanethiol (= Methyl mercaptan) (aliphatic thiol)	<i>Brassica oleracea</i> (Brassicaceae), <i>Allium sativum</i> (garlic, bulb), <i>Asparagus officinalis</i> (asparagus, aerial, reputed aphrodisiac) (Liliaceae), <i>Solanum tuberosum</i> (Solanaceae); intestinal gas (flatulence) (see Hydrogen sulfide)	Unpleasant (garlic breath), pungent (urine after asparagus), malodorous (flatulence), putrid (periodontal disease)
S-Methyl 3- (methylthio)thiopropionate (thioester)	<i>Asparagus officinalis</i> (Liliaceae) (asparagus) [aerial]; reputed aphrodisiac	Pungent (urine)
S-Methyl thioacrylate (aliphatic thioester)	<i>Asparagus officinalis</i> (Liliaceae) (asparagus) [aerial]; reputed aphrodisiac	Pungent (urine)

11 Agonists and antagonists of cytosolic hormone receptors

11.1 Introduction

The superfamily of cytosolic hormone receptors include receptors for steroid hormones including (some agonists in parentheses): androgen receptors (testosterone and 5 α -dihydrotestosterone), insect moulting hormone receptors (β -ecdysone), mineralocorticoid receptors (aldosterone), glucocorticosteroid receptors (cortisol), oestrogen receptors (β -oestradiol) and receptors for progesterone (Table 11.1). This superfamily also includes cytosolic receptors for non-steroid hormones such as (some ligands in parentheses): peroxisome proliferator activated receptors (unsaturated fatty acids), retinoic acid receptors (retinoic acid), thyroid hormone receptors (triiodothyronine (T₃) and tetraiodothyronine or thyroxine (T₄)), vitamin D receptors (1,25-dihydroxyvitamin D₃) and so-called “orphan” members of the superfamily presently lacking identified agonists, such as the steroid X receptors and the chicken ovalbumin upstream promoter transcription factors (COUP-TFs) (Table 11.2).

The members of the cytosolic hormone receptor family are homologous proteins and the mechanism of action involves translocation of the receptor with hormone bound to the nucleus, where it homodimerizes (or heterodimerizes with related activated receptors) and binds to specific promoters to “switch on” transcription of particular genes. The ultimate response to the hormonal stimulus is expression of particular proteins that variously influence development and metabolism as briefly outlined below.

11.2 Steroid hormones

The androgen testosterone is made in the testis and directs developmental maturation of male sex characteristics and normal function of male sex organs. Anabolic–androgenic steroid analogue drugs have been developed for increasing muscle mass.

The oestrogen β -oestradiol derives from the ovary (levels rising and falling successively in two peaks during the menstrual cycle associated with Graafian follicle development culminating in ovulation and post-ovulation corpus luteum development, respectively) and from the placenta. β -Oestradiol is involved in the differentiation of uterine endometrium and other female organs, the maintenance of female characteristics, the regulation of the normal ovarian maturation and release cycle, of anterior pituitary secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and of mammary gland duct development. The oestrogen receptor antagonist drug tamoxifen blocks oestrogen-dependent cell division in some types of breast cancer.

Progesterone derives from the ovary (mainly from the corpus luteum) and from the placenta and is involved in uterine endometrium differentiation for embryo implantation,

maintenance of early pregnancy and mammary alveolar development. After fertilization progesterone promotes placental chorionic gonadotropin production, which in turn promotes corpus luteum integrity, progesterone production and increased endometrial blood supply for the embryo. The early abortion drug RU486 (mifepristone) is a progesterone antagonist and acts by blocking progesterone-dependent development required for proper ovum implantation and embryo development.

The sterol moulting hormones such as β -ecdysone regulate insect and crustacean development. Accordingly, many plants have evolved elaboration of moulting hormone agonists (phytoecdysones) to interfere with normal development of the larvae of insect herbivores. Some two hundred and fifty phytoecdysones have been identified and there may be a thousand variants in nature. Phytoecdysones are of interest for insect control, pharmacological effects (anabolic, spermicidal, cancer chemopreventative, antihepatotoxic and antidepressant effects) and as benign gene switches for human gene replacement therapy.

The glucocorticoid cortisol is secreted from the adrenal cortex as a stress response: stress \rightarrow CNS \rightarrow hypothalamic corticotropin release factor secreted \rightarrow stimulation of anterior pituitary production of corticotropin (adrenocorticotrophic hormone or ACTH) \rightarrow adrenal cortex stimulated by ACTH to produce cortisol. Cortisol decreases inflammation and immune responses and enhances stress responses involving epinephrine. Cortisol acts to inhibit the action of pro-inflammatory transcription factors such as activator protein 1 (AP-1), signal transducers and activators of transcription (STATs), nuclear factor of activated T cells (NFAT) and nuclear factor κ B (NF κ B). Accordingly, the adrenocortical steroids cortisol and prednisone and their synthetic analogues such as prednisolone and dexamethasone are variously used as anti-inflammatory agents (e.g. for inflammatory autoimmune diseases such as multiple sclerosis and ulcerative colitis). Cortisol is a catabolic hormone, increasing expression of the key gluconeogenesis enzyme phosphoenolpyruvate carboxykinase (PEPCK), increasing gluconeogenesis, fatty acid mobilization and glucagon secretion and decreasing protein synthesis. Cushing's disease involves excess cortisol production and Addison's disease involves cortisol deficiency.

The mineralocorticoid aldosterone is also produced by the adrenal cortex and promotes retention of H_2O and Na^+ and loss of K^+ by the kidney. Cortisol is also an agonist of the aldosterone receptor but the level of cortisol is kept low by type 2 11β -hydroxysteroid dehydrogenase, which converts cortisol to the inactive cortisone (11-dehydrocortisol). Accordingly inhibition of this enzyme by 18β -glycyrrhetic acid (from liquorice) elevates cortisol with consequent effects of H_2O and Na^+ retention, oedema and hypertension. Further potential sites of interference by plant substances with steroid hormone metabolism include enzymes involved in steroid hormone synthesis such as the cytochrome P450-linked 11β -hydroxylase that catalyses the last step of corticosterone synthesis.

The steroid hormones are hydrophobic, this property enabling them to readily cross the plasma membrane to bind their respective cytosolic receptors. However, transport of such hydrophobic hormones through the blood stream requires hormone-binding proteins such as the steroid-binding globulins and corticosteroid-binding globulins.

11.3 Non-steroid cytosolic hormone receptor ligands

The aryl hydrocarbon receptor (ARH-R or dioxin receptor) is activated by xenobiotics such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin with resultant adverse effects. The activated receptor binds to a xenobiotic-responsive element with the consequent activation of the transcription of particular genes. Cell cycle progression is inhibited by naturally occurring and synthetic flavonoids at concentrations at which they act as agonists of the ARH-R.

The peroxisome proliferator-activated receptors (PPA-Rs) are involved in peroxisome synthesis, adipogenesis and glucose homeostasis and can be activated by particular long chain polyunsaturated fatty acids. PPA-Rs are involved in metabolic changes leading to obesity, syndrome X, type 2 diabetes and atherosclerosis. PPA-Rs of the α , β , γ and δ types have been identified and are variously targets for synthetic antihyperlipoproteinaemic drugs such as clofibrate. The antihyperglycaemic and insulin-sensitizing thiazolidinedione drugs for type 2 diabetes such as ciglitazone and troglitazone act via γ -type PPA-Rs.

Retinoids (e.g. retinoic acid) are involved in development and in metabolic regulation (e.g. through induction of expression of PEPCK, the rate limiting enzyme in gluconeogenesis). Retinoic acid derives from retinol, which in turn derives from ingestion of plant α -, β - and γ -carotenes and other carotenes. Retinoic acid acts via retinoic acid receptors and retinoid X receptors; note that these receptors can heterodimerize in the nucleus with other related hormone receptors such as PPA-Rs. The developmental importance of retinoic acid is underscored by the teratogenicity of retinoic acid and other vitamin A related compounds, notably some compounds developed for anti-acne properties.

The thyroid hormones thyroxine (tetraiodothyronine, T4) and triiodothyronine (T3) are iodinated tyrosine derivatives and their synthesis is effected via the following successive processes: hypothalamic thyrotropin release hormone (TRH) secretion \rightarrow anterior pituitary thyrotropin production \rightarrow thyroid \rightarrow thyroglobulin iodination by thyroid peroxidase and degradation \rightarrow thyroxine (T4) \rightarrow T3 via iodothyronine deiodinase. T4 and T3 exert a negative feedback on TRH and thyrotropin production. The thyroid hormones are transported by the protein transthyretin and act via cytosolic thyroid receptors to induce expression of particular proteins resulting in increased oxidation of glucose and other fuels with consequent thermogenesis. Thyroid hormones (like cortisol and retinoids) induce PEPCK expression and hence promote gluconeogenesis. Thyroid diseases variously derive from genetic defects, iodide insufficiency or ingestion of goitrogenic plants leading to enlargement of the thyroid (or goitre). Grave's disease involves excess thyroxine (thyrotoxicosis) and hypothyroidism (myxoedema) derives from insufficient thyroxine.

Vitamin D₃ (cholecalciferol) derives from the photochemical cleavage of 7-dehydrocholesterol and subsequent successive hydroxylations yield the active vitamin D receptor agonist 1,25-dihydroxyvitamin D₃ (1,25-dihydroxycholecalciferol). Activation of the receptor leads to expression of particular proteins, notably an intestinal Ca²⁺ binding protein, and regulation of intestinal Ca²⁺ uptake and Ca²⁺ sequestration in kidney and bone. Vitamin D₂ (ergocalciferol) is industrially obtained from irradiation of yeast-derived ergosterol and is hydroxylated to form an active vitamin D receptor agonist. Vitamin D deficiency causes rickets.

Finally, there are some so-called "orphan" cytosolic receptor family receptors for which the physiological agonists are uncertain. However, as detailed in Table 11.2 some plant-derived substances can bind to these receptors.

11.4 Plant bioactives affecting cytosolic receptor-mediated signalling

Plant bioactives potentially can interact with the hormonally regulated synthesis of hormone agonists and affect further metabolism and transport of agonists as well as acting as agonists or antagonists of the hormone receptors. Thus, in addition to plant-derived agonists and antagonists of particular cytosolic hormone receptors, plant inhibitors have been resolved which variously interact with testosterone 5 α -reductase (which generates the more

active androgen receptor agonist 5 α -dihydrotestosterone), type 2 cortisol 11- β -hydroxysteroid dehydrogenase (which generates the inactive cortisone), 17 β -hydroxysteroid oxidoreductase (which converts oestrone to the more active 17 β -oestradiol), cytochrome P450-linked ecdysone 20-monooxygenase (which converts ecdysone to the more active 20-hydroxyecdysone), cytochrome P450-linked aromatase enzymes (which convert androgen to oestrogen, for example, androstenedione to oestrone), steroid transport proteins, thyroid peroxidase and iodothyronine deiodinase (Tables 11.1 and 11.2).

Table 11.1 Agonists and antagonists of cytosolic steroid hormone receptors

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects
Androgen receptor (AND-R)		11.1A
Phenolic		11.1Ap
Cannabinol (dibenzopyran)	<i>Cannabis sativa</i> (marijuana) (Cannabaceae) [cannabis resin, marijuana leaf]	AND-R antagonist [0.6] [anti-androgen; inactive as CB-R ligand]
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	[\downarrow AND-R expression] (PK) [oxidation products give tea taste]
9-Hydroxy-6,7-dimethoxydalbergiquinol (phenolic, quinol)	<i>Dalbergia cochinchinensis</i> (Fabaceae)	AND-R antagonist [anti-androgen]
6-Hydroxy-2,7-dimethoxyneoflavene (phenolic, neoflavene)	<i>Dalbergia cochinchinensis</i> (Fabaceae)	AND-R antagonist [anti-androgen]
Palodesangrens A-E (phenolic adducts)	<i>Brosimum rubescens</i> (Moraceae)	AND-R antagonists
Δ^1 -Tetrahydrocannabinol (= Dronabinol; Δ^9 -Tetrahydrocannabinol; (-)- Δ^1 -3,4- <i>trans</i> -Tetrahydrocannabinol (dibenzopyranol)	<i>Cannabis sativa</i> (marijuana) (Cannabaceae) [cannabis resin, marijuana leaf]	AND-R antagonist [0.2] (CBR, H-R) [AI, antiemetic, hallucinogenic, psychotropic]
Terpene		11.1At
Androstenedione (= Androtex) (terpene, sterol)	<i>Pinus sylvestris</i> (Scots pine) (Pinaceae) [pollen]	AND-R agonist [androgen cf. Testosterone]
Dehydro- <i>epi</i> -androsterone (steroid)	Metabolite of Protodioscin	AND-R agonist
Permixon (liposterolic extract) (fatty acids & terpenes)	<i>Serenoa repens</i> (Palmae); used for treatment of benign prostatic hyperplasia due to dihydrotestosterone accumulation	AND-R antagonist, (-) 5 α -Testosterone reductase (6ng/L); \downarrow testosterone & dihydrotestosterone binding; used for breast enlargement
Protodioscin (steroid saponin)	<i>Dioscorea gracillima</i> , (Dioscoreaceae); <i>Tribulus terrestris</i> (puncture vine) (Zygophyllaceae) – aphrodisiac (but plant efficacy varies with growth conditions)	Metabolized to Dehydro- <i>epi</i> -androsterone [aphrodisiac – improves libido & enhances erection]; aglycone Diosgenin

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Testosterone (terpene, sterol)	<i>Vitex agnus-castus</i> (Lamiaceae), <i>Pinus sylvestris</i> (Scots pine) (Pinaceae) [pollen]; animals; <i>ex</i> interstitial cells of testes; Leopold Ruzicka (Croatia/Switzerland, Nobel Prize, Chemistry, 1939, terpenes)	AND-R agonist; converted via 5 α -reductase to more potent 5 α -Dihydro-testosterone [androgen; male development]
Non-plant reference		11.1An
[Androsterone] (sterol); Adolph Butenandt (Germany, Nobel Prize, Chemistry, 1939, sex hormones, acceptance forbidden by Nazis)	Animals; Leopold Ruzicka (synthesis) (Croatia/Switzerland, Nobel Prize, Chemistry, 1939, terpenes)	AND-R agonist
[5 α -Dihydrotestosterone] (sterol)	Animals; product of Testosterone via 5 α -reductase	AND-R agonist [androgen]
Androgen conversion – Testosterone 5α-reductase (5αR)		11.1B
Phenolic		11.1Bp
Artocarpin (phenolic)	<i>Artocarpus incisus</i> (Moraceae) [leaf]	5 α R (85)
Butein (= 2',4',3,4-Tetrahydrochalcone) (chalcone, phenolic)	<i>Dalbergia odorifera</i> , <i>Robinia pseudoacacia</i> , <i>Vicia faba</i> (Fabaceae); glycosides in <i>Coreopsis douglasii</i> , <i>Bidens</i> spp. (Asteraceae), <i>Butea monosperma</i> , <i>B. frondosa</i> (Fabaceae) [flower]	5 α R (217) (EGF-RTK, F ₁ -ATPase, p60 ^{c-src} TK) [antioxidant]
(+)-Catechin-3-gallate (= CG) (phenolic, hydrolysable tannin)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	5 α R ligand (20)
Chlorophorin (= 2,4,3',5'-Tetrahydroxy-4'-geranylstilbene) (stilbene, phenolic)	<i>Artocarpus incisus</i> (Moraceae) [leaf]	5 α R (37)
(-)-Epicatechin 3-gallate (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	5 α R (12) (collagenase, EGF-RTK, EST-R)
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	5 α R (15) (EGF-RTK, EST-R, PDGF-RTK, FGF-RTK, pp60 ^{v-src} , PKA, PKC) [oxidation products give tea taste]
3'-Geranyl-3,4,2',4'-tetrahydrochalcone (chalcone, phenolic)	<i>Artocarpus incisus</i> (Moraceae) [leaf]	5 α R (104)
Impatiinol (= 3-Hydroxy-2-[3-hydroxy-1,4-dioxo(2-naphthyl)]ethyl-naphthalene-1,4-dione) (naphthoquinone)	<i>Impatiens balsamina</i> (Balsaminaceae) [aerial]	5 α R

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects
Myricanol (diarylheptanoid)	<i>Pimpinella anisum</i> (Apiaceae), <i>Myrica rubra</i> (Myricaceae) [bark]	5 α R
Myricanone (diarylheptanoid)	<i>Myrica rubra</i> (Myricaceae) [bark]	5 α R
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplopappus canescens</i> (Asteraceae) [aerial]	5 α R (F ₁ -ATPase, IKK, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TOPII) [antibacterial, antigonadotropic]
Oenothem A (ellagitannin)	<i>Epilobium</i> spp. (Onagraceae)	5 α R (0.2; 1) (AROM)
Oenothem B (macrocircular dimeric ellagitannin)	<i>Cuphea hyssopifolia</i> (Lythraceae), <i>Eucalyptus considemiana</i> , <i>E. viminalis</i> (Myrtaceae), <i>Epilobium</i> spp., <i>Oenothera laciniata</i> (Onagraceae)	5 α R (0.2; 0.4) AROM, PADPRH) [antitumour, inhibits glucocorticoid-induced de-polyADP-ribosylation]
Other		11.1Bo
Elaidic acid (= <i>trans</i> -9-Octadecenoic acid) (C ₁₈ unsaturated FA)	<i>Punica granatum</i> (Punicaceae), <i>Boehmeria nipooniviva</i> (Urticaceae)	5 α R [hair regrowth]
Linoleic acid (= all <i>cis</i> -9,12-Octadecadienoic acid) (C ₁₈ unsaturated FA)	Widespread; <i>Helianthus annuus</i> (Asteraceae), <i>Cucumis melo</i> (Cucurbitaceae), <i>Arachis hypogaea</i> , <i>Glycine max</i> (Fabaceae), <i>Linum usitatissimum</i> (Linaceae), <i>Gossypium hirsutum</i> (Malvaceae) [oil]	5 α R
α -Linolenic acid (= all <i>cis</i> -9,12,15-Octadecatrienoic acid) (C ₁₈ unsaturated FA)	Widespread; <i>Cucumis sativus</i> (cucumber) (Cucurbitaceae), <i>Linum usitatissimum</i> (flax, linseed) (Linaceae) [oil]	5 α R (116) [hair regrowth]
Oleic acid (= <i>cis</i> -9-Octadecenoic acid) (C ₁₈ unsaturated FA)	Widespread in plant fats & oils; <i>Helianthus annuus</i> (sunflower seed) (Asteraceae), <i>Arachis hypogaea</i> (peanut) (Fabaceae), <i>Persea americana</i> (avocado) (Lauraceae), <i>Olea europaea</i> (olive) (Oleraceae) [oil]	5 α R
Palmitic acid (= Hexadecanoic acid) (C ₁₆ saturated FA)	Widespread in plant lipids, oils & waxes; <i>Cucumis melo</i> (Cucurbitaceae), <i>Arachis hypogaea</i> (Fabaceae), <i>Gossypium hirsutum</i> (Malvaceae), <i>Olea europaea</i> (Oleraceae), <i>Cocos nucifera</i> (Palmae)	5 α R
Permixon (liposterolic extract) (fatty acids & terpenes)	<i>Serenoa repens</i> (Palmae)	5 α R (6ng/L) (AND-R) [treatment of benign prostatic hyperplasia due to dihydrotestosterone accumulation; for breast enlargement]
Stearic acid (= Octadecanoic acid) (C ₁₈ saturated FA)	Widespread in plant lipids, oils & waxes; <i>Carapa guianensis</i> (Meliaceae)	5 α R [hair regrowth]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) / part/	Protein target (other targets) / in vivo effects/
Non-plant reference [Finasteride] (androstene steroid)	Synthetic	11.1Bn 5 α R (3–10nM)
Androgen transport – Steroid binding globulin (SBG) 18 β -Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	11.1C SBG [0.5] (ALDO-R, CBG, CORT-R, EST-R, 11 β HSDH, SBG) [elevated cortisol, hypermineralocorticoidism, renin–angiotensin system depression]
Glycyrrhizic acid (= Glycyrrhinic acid; Glycyrrhizin; Glycyrrhizinic acid) (triterpene saponin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	SBG [0.5] (ALDO-R, CBG, CORT-R, EST-R, SBG) [anti-ulcerogenic, expectorant, sweet]
Paeoniflorin (phenolic related glycoside)	<i>Paeonia albiflora</i> , <i>P. lactiflora</i> , <i>P. moutan</i> , <i>P. officinalis</i> (Paeoniaceae)	SBG [0.5] (ALDO-R, CBG, CORT-R, EST-R, SBG) [antiallergic, anti-coagulant, PAI]
Non-plant reference [5 α -Dihydrotestosterone] (sterol)	Animals; product of Testosterone via 5 α -reductase	11.1Cn SBG [2nM] (AND-R agonist) [androgen]
Corticosteroid Receptors – Aldosterone receptor (ALDO-R) & Cortisol receptor (CORT-R)		11.1D
Cucurbitacin I (= Elatericin B; Ibamarin) (Cucurbitacin triterpene)	<i>Iberis</i> spp. (Brassicaceae), <i>Citrullus</i> spp. (Cucurbitaceae), <i>Gratiola officinalis</i> (Scrophulariaceae)	CORT-R antagonist [cytotoxic]
18 β -Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	ALDO-R [4nM], CORT-R [2nM] (CBG, FAD, EST-R, 11 β HSDH, SBG) [elevated cortisol, hypermineralocorticoidism]
Glycyrrhizic acid (= Glycyrrhinic acid; Glycyrrhizin; Glycyrrhizinic acid) (triterpene glycoside saponin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	ALDO-R [3nM], CORT-R [2nM] (CBG, FAD, EST-R, SBG) [anti-ulcerogenic, expectorant, sweet]
Paeoniflorin (phenolic related glycoside)	<i>Paeonia albiflora</i> , <i>P. lactiflora</i> , <i>P. moutan</i> , <i>P. officinalis</i> (Paeoniaceae)	ALDO-R [4nM], CORT-R [3nM] (CBG, EST-R, SBG) [antiallergic, anticoagulant, PAI]
β -Sitosterol (sterol)	Plant membranes	↓ Cortisol induction by stress [membrane fluidity; ↓ stressful exercise-induced immunosuppression]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) / part /	Protein target (other targets) / in vivo effects/
β -Sitosterol glucoside (sterol glycoside)	Plant membranes	↓ Cortisol induction by stress [membrane fluidity; ↓ stressful exercise-induced immunosuppression]
Non-plant reference		
[Aldosterone] (mineralocorticoid, steroid); isolated by Tadeusz Reichstein (Nobel Prize, Physiology/Medicine, 1950)	Animals <i>ex</i> adrenal cortex; semi-synthesis by Sir Derek Barton (UK, Nobel Prize, Chemistry, 1969, organic chemical conformation)	11.1Dn ALDO-R agonist [anti-diuresis, anti-natriuresis i.e. H ₂ O retention, Na ⁺ retention; K ⁺ loss from kidneys]
[Benzylidated Podophyllotoxin glycoside mixture (= CPH82)] (lignan glycosides)	Semi-synthetic from Podophyllotoxin	CORT-R agonist [AI, ↓ ACTH, ↓ cortisol, Cushing's side effects]
[Corticosterone] (glucocorticoid, steroid triterpene); isolated by Tadeusz Reichstein (Nobel Prize, Physiology/Medicine, 1950)	Animals; <i>ex</i> adrenal cortex (ACTH-induced); Tadeusz Reichstein (Poland/Switzerland) & Edward Kendall & Philip Hench (USA) (Nobel Prize, Physiology/Medicine, 1950, glucocorticoids)	CORT-R agonist [AI]
[Cortisol (= Hydrocortisone; 17-Hydroxycorticosterone)] (glucocorticoid, steroid); Tadeusz Reichstein (Poland/Switzerland) & Edward Kendall & Philip Hench (USA) Nobel Prize, Physiology/Medicine, 1950, glucocorticoids)	Animals; <i>ex</i> adrenal cortex (stress-, ACTH-induced); ↓ synthesis in Addison's disease (sufferers Jane Austen, John F. Kennedy); ↑ synthesis in Cushing's syndrome (moon-face)	Cortisol-R agonist & ALDO-R agonist [AI, anti-insulin, catabolic, H ₂ O & Na ⁺ retention & K ⁺ loss; inhibits action of pro-inflammatory TFs AP-1, STATs, NFAT & NFκB]
[Cortisone (= 17-Hydroxy-11-dehydrocorticosterone)] (glucocorticoid, steroid)	Animals; 11-Dehydrocortisol; Cortisone isolated by Edward Kendall (USA, Nobel Prize, Physiology/Medicine, with T. Reichstein & P. Hench) & synthesized (1951) by Robert Burns Woodward (USA, chemist; Nobel Prize, 1965)	Oxidation product of Cortisol (unidirectional via NAD-dependent 11βHSDH type 2)
[Dexamethasone (= 9α-Fluoro-16α-methylprednisolone)] (glucocorticoid; steroid)	Synthetic	CORT-R agonist [AI, immunosuppressive]
[Prednisolone (= Δ ¹ -Dehydrocortisol)] (glucocorticoid, steroid)	Synthetic	CORT-R agonist [AI, immunosuppressive]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
[Prednisone (= Δ^1 -Dehydrocortisone)] (glucocorticoid, steroid triterpene)	Adrenocortical	CORT-R agonist [AI, immunosuppressive]
Corticosteroid metabolism – 11-β-Hydroxysteroid Dehydrogenase (11βHSDH)		11.1E
[Carbenoxolone (= 18 β -Glycyrrhetic acid hydrogen succinate)] (triterpene)	Metabolite of 18 β -Glycyrrhetic acid	11 β HSDH (Na^+ , K^+ -ATPase) [sodium retention per \uparrow cortisol & ALDO-R activation as with 18 β -Glycyrrhetic acid]
18 β -Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	11 β HSDH (esp. cortisone-generating type 2) (ALDO-R, CBG, CORT-R, EST-R, Na^+ , K^+ -ATPase, SBG) [elevated cortisol, hypermineralo-corticoidism]
Glycyrrhizic acid (= Glycyrrhinic acid; Glycyrrhizin; Glycyrrhizinic acid) (triterpene glycoside saponin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	Glycosylated precursor of 11 β HSDH inhibitor Glycyrrhetic acid (ALDO-R, CBG, CORT-R, EST-R, Na^+ , K^+ -ATPase, SBG) [anti-ulcerogenic, expectorant, sweet]
Gossypol (dimeric phenolic sesquiterpenoid)	<i>Gossypium</i> spp. (cotton), <i>Montezuma speciosissima</i> , <i>Thespesia populnea</i> (Malvaceae) [seed]	11 β HSDH (Ca^{2+} -ATPase, CAMA, PK) [antifungal, antitumour, inhibits spermatogenesis]
4-Hydroxyacetophenone (phenolic ketone)	<i>Salsola tuberculatiformis</i> (Chenopodiaceae) [aerial]	11 β HSDH
4-Hydroxy-3-methoxyacetophenone (phenolic ketone)	<i>Salsola tuberculatiformis</i> (Chenopodiaceae) [aerial]	11 β HSDH
Magnolol (lignan phenolic)	<i>Sassafras randaiense</i> (Lauraceae) [root], <i>Magnolia officinalis</i> (Magnoliaceae) [bark]	11 β HSDH (type 2) [antibacterial, antidepressant]
3-Monoglucuronyl-glycyrrhetic acid (triterpene glycoside)	Metabolite of Glycyrrhizic acid <i>ex Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	11 β HSDH [sodium retention per \uparrow cortisol & ALDO-R activation as with 18 β -Glycyrrhetic acid]
Naringenin (= 5,7,4'-Trihydroxyflavone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia</i> spp. (Asteraceae), <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice]	11 β HSDH

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae), Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; widespread as glycosides	11 β HSDH (AR, cAMP PDE, F ₁ -ATPase, LOX, MDR-TR, MLCK, Na ⁺ , K ⁺ -ATPase, NEP, PK, PS – EF-1 α , TOPII) [allergenic, antibacterial, AI, antiviral]
Cortisol transport – Cortisol binding globulin (CBG)		11.1F
[Cortisol (= Hydrocortisone; 17-Hydroxycorticosterone)] (glucocorticoid, steroid, triterpene)	Animals; <i>ex</i> adrenal cortex (stress-, ACTH-induced); ↓ synthesis in Addison's disease (sufferers Jane Austen, John F. Kennedy); ↑ synthesis in Cushing's syndrome	CBG [2nM] (CORT-R, ALDO-R) [anti-insulin, catabolic, H ₂ O & Na ⁺ retention & K ⁺ loss]
18 β -Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	CBG [10] (ALDO-R, CORT-R, EST-R, 11 β HSDH, SBG) [elevated cortisol, hyper-mineralocorticoidism, renin-angiotensin system depression]
Glycyrrhizic acid (= Glycyrrhinic acid; Glycyrrhizin; Glycyrrhizinic acid) (triterpene glycoside saponin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	CBG [10] (ALDO-R, CORT-R, EST-R, SBG) [anti-ulcerogenic, expectorant, sweet]
Paconiflorin (phenolic related glycoside)	<i>Paeonia albiflora</i> , <i>P. lactiflora</i> , <i>P. moutan</i> , <i>P. officinalis</i> (Paeoniaceae)	CBG [10] (ALDO-R, CORT-R, EST-R, SBG) [antiallergic, anticoagulant, PAI]
Ecdysone receptor (ECDY-R)		11.1G
Phenolic		11.1Gp
Ampelopsin B (oligostilbene)	<i>Iris clarkei</i> (Liliaceae) [seed]	ECDY-R antagonist (33)
Coumestrol (coumestan isoflavone)	<i>Brassica oleracea</i> (Brassicaceae), <i>Spinacia oleracea</i> (Chenopodiaceae), <i>Medicago</i> spp., <i>Pisum sativum</i> , <i>Trifolium</i> spp. (clover) (Fabaceae); induced phytoalexin in <i>Glycine max</i> , <i>Phaseolus lunatus</i> , <i>P. vulgaris</i> , <i>Vigna unguiculata</i> (Fabaceae)	ECDY-R mixed agonist/antagonist (EST-R agonist) [phytoestrogen]
Kobophenol B (oligostilbene)	<i>Carex pendula</i> (Cyperaceae) [seed]	ECDY-R antagonist (37)
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium graveolens</i> (Apiaceae); widespread as glycosides in Cruciferae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	ECDY-R-dependent transcription (ACE, AR, ITDI, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TOPII, TPO) [antibacterial, AI, nodulation signal]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
<i>cis</i> -Miyabenol A (tetrastilbene)	<i>Carex pendula</i> (Cyperaceae) [seed]	ECDY-R antagonist (31)
<i>cis</i> -Miyabenol C (tetrastilbene)	<i>Carex pendula</i> (Cyperaceae) [seed]	ECDY-R antagonist (19)
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koeleria henryi</i> (Sapindaceae), Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; widespread as glycosides	ECDY-R-dependent transcription (AR, cAMP PDE, F ₁ -ATPase, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, NEP, PK, PS – EF-1 α , TOPII) [allergenic, antibacterial, AI, antiviral]
α -Viniferin (oligostilbene)	<i>Caragana sinica</i> (Fabaceae), <i>Iris clarkei</i> (Liliaceae) [seed], <i>Vitis vinifera</i> (Vitaceae)	ECDY-R antagonist (10)
Terpene		11.1Gt
Abutasterone (sterol)	<i>Lamium</i> spp. (Lamiaceae)	ECDY-R agonist
8- <i>O</i> -Acetylharpagide (iridoid monoterpene glycoside)	<i>Ajuga reptans</i> (Lamiaceae)	ECDY-R agonist
Ajugalactone (sterol)	<i>Ajuga chamaepitys</i> , <i>A. reptans</i> (Lamiaceae)	ECDY-R agonist
Ajugasterone C (sterol)	<i>Rhaponticum</i> spp., <i>Serratula coronata</i> (Asteraceae), <i>A. nipponensis</i> (Lamiaceae), <i>Vitex madiensis</i> (Verbenaceae)	ECDY-R agonist (62 nM)
Brassinolide (sterol)	<i>Helianthus annuus</i> (Asteraceae), <i>Alnus glutinosa</i> (Betulaceae), <i>Brassica napus</i> (Brassicaceae), <i>Camellia sinensis</i> (Theaceae)	ECDY-R antagonist
24- <i>epi</i> -Brassinolide (sterol)	Brassicaceae	ECDY-R ligand
24- <i>epi</i> -Castasterone (sterol)	Brassicaceae	ECDY-R ligand
Commisterone (sterol)	<i>Cyanotis vaga</i> (Commalinaceae)	ECDY-R agonist
Cucurbitacin B (= Amarin; 1,2-Dihydro- α -elaterin) (cucurbitacin triterpene)	<i>Iberis umbellata</i> (Brassicaceae) [seed], <i>Cucumis africanus</i> (Cucurbitaceae)	ECDY-R antagonist [5]
Cucurbitacin D (= Elatericin A) (cucurbitacin triterpene)	<i>Iberis umbellata</i> (Brassicaceae) [seed], <i>Crinodendron hookerianum</i> (Elaeocarpaceae)	ECDY-R antagonist [50]
Cyasterone (sterol)	<i>Ajuga chamaepitys</i> , <i>A. nipponensis</i> , <i>A. reptans</i> (Lamiaceae)	ECDY-R agonist
24(24(1))[\mathcal{Z}]-Dehydroamarasterone B (sterol)	<i>Rhaponticum carthamoides</i> (Asteraceae)	ECDY-R agonist (0.5)
(20 <i>R</i>)-22-Deoxy-20,21-Dihydroxyecdysone (sterol)	<i>Rhagodia baccata</i> (Chenopodiaceae)	ECDY-R agonist (0.2)

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects
1 α , 20R-Dihydroxyecdysone (= 1- <i>epi</i> -Integristerone A) (sterol)	<i>Axyris amaranthoides</i> (Chenopodiaceae) [seed]	ECDY-R agonist
Ecdysone (= α -Ecdysone) (sterol)	<i>Lychnis fulgens</i> (Caryophyllaceae), <i>Polypodium aureum</i> (Polypodiaceae); <i>Pteris aquilina</i> (bracken fern) [leaf]; insects, crustacea	ECDY-R agonist [bracken fern carcinogen, moulting hormone]
20-Hydroxyecdysone (= β -Ecdysone; Ecdysterone) (sterol)	Widespread in plants; <i>Serratula</i> (Asteraceae), <i>Atriplex</i> , <i>Axyris</i> , <i>Rhagodia</i> (Chenopodiaceae), <i>Lamium</i> (Lamiaceae), <i>Ipheion</i> , <i>Lloydia</i> (Liliaceae), <i>Diploclisia</i> (Menispermaceae), <i>Podocarpus</i> (Podocarpaceae) spp.; ferns; insects, crustacea	ECDY-R agonist (8 nM) (ECMOX) [moulting hormone – the major invertebrate ecdysteroid]
3- <i>epi</i> -20-Hydroxyecdysone (sterol)	<i>Serratula coronata</i> (Asteraceae)	ECDY-R agonist (0.2)
20-Hydroxyecdysone 22-acetate (sterol)	<i>Serratula coronata</i> (Asteraceae)	ECDY-R agonist
Inokosterone (sterol)	<i>Achyranthes bidentata</i> , <i>A. fauriei</i> (Amaranthaceae) [root], <i>Lamium</i> spp. (Lamiaceae), <i>Morus alba</i> (Moraceae)	ECDY-R agonist
Makisterone A, D (sterols)	<i>Diplazium donianum</i> (fern) (Woodsiaceae)	ECDY-R agonists
Makisterone B (= Callinecdysone B) (sterol)	<i>Ajuga chamaepitys</i> (Lamiaceae), <i>Diploclisia glaucescens</i> (Menispermaceae) [seed], <i>Diplazium donianum</i> (fern) (Woodsiaceae)	ECDY-R agonist
Podecdysone B (sterol)	<i>Podocarpus</i> spp. (Podocarpaceae)	ECDY-R agonist
Polypodine B (= 5 β , 20-Dihydroxyecdysone) (sterol)	<i>Rhaphonticum</i> (Asteraceae), <i>Pfaffia</i> (Amaranthaceae), <i>Lychnis</i> (Caryophyllaceae), <i>Atriplex</i> , <i>Axyris</i> , <i>Chenopodium</i> , <i>Rhagodia</i> , <i>Spinacia</i> (Chenopodiaceae), <i>Ajuga</i> , <i>Lamium</i> (Lamiaceae), <i>Lloydia</i> (Liliaceae), <i>Polypodium</i> (Polypodiaceae) spp.	ECDY-R agonist
Ponasterones A, B, C & D (sterols)	<i>Podocarpus nakaii</i> (Podocarpaceae); ferns	ECDY-R agonists
Prieurianin (prieurianin limonoid nortriterpene)	<i>Turraea obtusifolia</i> (Meliaceae) [seed]	ECDY-R antagonist (10)
Pterosterone (sterol)	<i>Pfaffia iresinoides</i> (Amaranthaceae) [root], <i>Lamium</i> spp. (Lamiaceae), <i>Diploclisia glaucescens</i> (Menispermaceae) [seed]	ECDY-R agonist
Rhapontisterone (sterol)	<i>Rhaphonticum uniflorum</i> (Asteraceae) [root]	ECDY-R agonist
Rhapontisterone R1 (sterol)	<i>Rhaphonticum uniflorum</i> (Asteraceae) [root]	ECDY-R agonist

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) / part /	Protein target (other targets) / in vivo effects /
Rohitukin (prieurianin limonoid nortriterpene)	<i>Turraea obtusifolia</i> (Meliaceae) [seed]	ECDY-R antagonist (125)
Schottenol (sterol)	<i>Lophocereus schottii</i> (Senita cactus) (Cactaceae)	[Precursor for fruit fly ecdysone]
Taxisterone (sterol)	<i>Serratala coronata</i> (Asteraceae)	ECDY-R agonist (95 nM)
Turkesterone (sterol)	<i>Rhaponticum uniflorum</i> (Asteraceae) [root]	ECDY-R agonist
Ecdysone metabolism – cytochrome P450- dependent ecdysone 20-monooxygenase (ECMOX)		11.1H
Alkaloid		11.1Ha
Corynanthine (=Rauhimbine) (indole)	<i>Corynanthe johimbe</i> , <i>Pausinystalia johimbe</i> , <i>Pseudocinchona africana</i> (Rubiaceae) [bark], <i>Rauwolfia serpentina</i> , <i>R. tetraphylla</i> (Apocynaceae)	ECMOX
Quinidine (= β-Quinine) (quinoline)	<i>Cinchona officinalis</i> , <i>C. spp.</i> , <i>Remijia pedunculata</i> (Rubiaceae)	ECMOX [antitumour, immunosuppressive]
Quinine (quinoline)	<i>Cinchona officinalis</i> [bark], <i>Cinchona spp.</i> , <i>Remijia pedunculata</i> (Rubiaceae)	ECMOX [abortefacient, analgesic, antimalarial, bitter, cardiac depressant, spermicidal]
Phenolic		11.1Hp
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	Lamiaceae, [leaf surface]; <i>Apium</i> , <i>Daucus</i> (Apiaceae), <i>Achillea</i> , <i>Artemisia</i> (Asteraceae), <i>Mentha</i> , <i>Thymus</i> (Lamiaceae), ferns [leaf surface], <i>Buddleja officinalis</i> (Loganiaceae), <i>Digitaria exilis</i> (Poaceae); as glycoside in <i>Apium</i> , <i>Petroselinum</i> (Apiaceae), <i>Cosmos</i> , <i>Erigeron</i> , <i>Dahlia</i> (Asteraceae), <i>Amorpha</i> (Fabaceae) spp.	ECMOX (BZ-R-like R, CDK2, EGF-RTK, EST-R MLCK, PKA, PKC, RTK, TPO) [antibacterial, AI, diuretic, hypotensive, nodulation stimulant]
Chrysin (= 5,7- Dihydroxyflavone) (flavone)	<i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (poplar) (Salicaceae) [leaf bud], <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	ECMOX (AR, cAMP PDE, ITDI) [antibacterial, AI, inhibits histamine release]
Flavone (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	ECMOX (COX, 5-LOX) [AI, PAI, inhibits basophil histamine release]
Juglone (= 5-Hydroxy-1,4- naphthalenedione; Mucin; Natural Brown 7; Regianin) (naphthoquinone)	<i>Juglans cinerea</i> , <i>J. nigra</i> [stem bark], <i>J. regia</i> , <i>Carya ovata</i> , <i>C. illinoensis</i> [leaf, nut] (Juglandaceae), <i>Lomatia</i> spp. (Proteaceae)	ECMOX (100) (MLCK, PKA, PKC, pp60 ^{c-src}) [antifungal, antiviral, molluscicidal, feeding deterrent, walnut allelopathic]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread; <i>Hypericum brasiliense</i> (Guttiferaceae) [leaf, flower]; widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae) [seed, stem], <i>Pisum sativum</i> (Fabaceae), <i>Thespesia populnea</i> (Malvaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koelreuteria henryi</i> (Sapindaceae)	ECMOX (AR, ITDI, MLCK, PKA, RTK (p56lck)) [antibacterial, antioxidant, AI, mutagenic]
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> , <i>Chlorophora tinctoria</i> , <i>Morus alba</i> (mulberry), <i>M. spp.</i> (Moraceae)	ECMOX (AR, ITD, 5-LOX, MLCK, PKA) [allergenic, antibacterial, antiviral, feeding attractant]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplopappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	ECMOX (AR, CDPK, IKK, LOX, MLCK, NADH DH, PKA, succinate DH) [antibacterial, antionadotropic]
Phloretin (= 2',4,4',6'-Tetrahydroxy-dihydrochalcone) (dihydrochalcone)	<i>Malus domestica</i> (Rosaceae); as 2'-glucoside (Phloridzin) in <i>Kalmia latifolia</i> , <i>Pieris japonica</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>M. spp.</i> (Rosaceae), <i>Symplocos</i> spp. (Symplocaceae)	ECMOX (PKC, ITD, ox. phos. uncoupler) [antibacterial, AI, feeding deterrent]
Plumbagin (naphthoquinone)	<i>Dionaea muscipula</i> (Venus fly trap; 2 action potential-initiating stimulus events required before trap closure), <i>Drosera</i> (Droseraceae), <i>Aristea</i> , <i>Sisyrinchium</i> , <i>Sparaxis</i> (Iridaceae), <i>Diospyros</i> (Ebenaceae), <i>Pera</i> (Euphorbiaceae) spp.; <i>Plumbago europaea</i> (Plumbaginaceae) [root]	ECMOX (100) (MLCK, PKA, TOPII)
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae), Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; widespread as glycosides	ECMOX (AR, CDPK, β HSOR, MLCK, PKA, PKC, RTK, RTK (p56lck)) [antibacterial, antiviral, AI]
Terpene		11.1Ht
Azadirachtin (limonoid nortriterpene)	<i>Azadirachta indica</i> (neem tree) (Meliaceae)	ECMOX (100) [insect antifeedant]
6-Desacetylnimbicin (limonoid nortriterpene)	<i>Azadirachta indica</i> (neem tree) (Meliaceae) [oil]	ECMOX [insect antifeedant]
1,9- Dideoxyforskolin (labdane diterpene)	Semi-synthetic from Forskolin	ECMOX (at 10–100) (inactive as AC activator)

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Ecdysterone (sterol)	<i>Ipehion uniflorum</i> (Liliaceae) [bulb], <i>Diploclisia glaucescens</i> (Menispermaceae) [root]	ECMOX [0.8] (ECDY-R)
Forskolin (labdane diterpene)	<i>Coleus forskohlii</i> (Lamiaceae) [root]	ECMOX (at 10–100) (AC) [increases cytosolic cAMP]
Nimbin (limonoid nortriterpene)	<i>Azadirachta indica</i> (neem tree) (Meliaceae) [oil]	ECMOX
Salannin (limonoid nortriterpene)	<i>Azadirachta indica</i> (neem tree) (Meliaceae) [oil]	ECMOX [insect antifeedant]
Oestrogen receptor (EST-R), acting via Oestrogen Response Element (ERE)		11.II
Phenolic		11.IIp
Apigenin (5,7,4'-Trihydroxyflavone) (flavone)	<i>Apium graveolens</i> (Apiaceae), Lamiaceae, ferns [leaf surface]; glucosides in <i>Apium graveolens</i> , <i>Petroselinum</i> (Apiaceae), <i>Amorpha fruticosa</i> , <i>Cosmos bipennatus</i> , <i>Erigeron annuus</i> , <i>Dahlia variabilis</i> (Asteraceae)	EST-R (18) [10] (BZ-R-like R, PK) [antibacterial, AI, diuretic, hypotensive, phytoestrogen, <i>Rhizobium</i> nodulation stimulant
Biochanin A (= 5,7-Dihydroxy-4'-methoxyisoflavone; Pratensol) (isoflavone)	<i>Cicer arietum</i> , <i>Trifolium pratense</i> , <i>T. spp.</i> , <i>Baptisia spp.</i> , <i>Dalbergia spp.</i> (Fabaceae), <i>Virola cadudifolia</i> (Myristicaceae) [wood], <i>Cotoneaster pannosa</i> (Rosaceae) [fruit]	EST-R antagonist (0.5) (EST β -R selective), EST-R ligand (53) (AROM, EGF-RTK, 17 β HSOR, MLCK) [hypolipidaemic, phytoestrogen]
Coumestrol (coumestan isoflavone)	<i>Brassica oleracea</i> (Brassicaceae), <i>Spinacia oleracea</i> (Chenopodiaceae), <i>Medicago spp.</i> (alfalfa), <i>Pisum sativum</i> , <i>Trifolium pratense</i> (Fabaceae); induced phytoalexin in <i>Glycine max</i> , <i>Phaseolus lunatus</i> , <i>P. vulgaris</i> , <i>Vigna unguiculata</i> (Fabaceae)	EST-R agonist – ER α (0.1–1 nM; 109 nM), ER β (35 nM) (AROM, ECDY-R, 17 β HSOR) [phytoestrogen]
Daidzein (= 4',7-Dihydroxyisoflavone) (isoflavone)	<i>Glycine max</i> , <i>Trifolium repens</i> (clover), <i>Ulex europaeus</i> (gorse) (Fabaceae); 7-O-glucoside (Daidzin) in <i>Baptisia spp.</i> , <i>Glycine max</i> , <i>Pueraria spp.</i> , <i>Trifolium pratense</i> (Fabaceae)	EST-R agonist (3; 4) (EST β -R selective) – ER α (7), ER β (0.7) (DNAPOL, GABAA-R, lipase, TOPII) [antifungal, phytoestrogen]
3,4-Dihydro-4-(4'-hydroxyphenyl)-7-hydroxycoumarin 3,3''-dimers I & II (4-aryl-coumarins, neoflavones)	<i>Pistacia chinensis</i> (Anacardiaceae)	EST-R agonist
5,7-Dihydroxy-3-(4-hydroxybenzyl)-4-chromanone (chromanone)	<i>Dracaena loureiri</i> (Agavaceae) [stem wood]; used against infection & GI upset (Thailand)	EST-R agonist (0.4)
4,4'-Dihydroxy-2,6-dimethoxy-dihydrochalcone (dihydrochalcone)	<i>Dracaena loureiri</i> (Agavaceae) [stem wood]; used against infection & GI upset (Thailand)	EST-R agonist (0.9)

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects
2,4'-Dihydroxy-4,6-dimethoxy-dihydrochalcone (dihydrochalcone)	<i>Dracaena loureiri</i> (Agavaceae) [stem wood]; used against infection & GI upset (Thailand)	EST-R agonist (15)
5,7-Dihydroxyflavone (= Chrysin) (flavone)	Widespread; <i>Passiflora coerulea</i> (Passifloraceae), <i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (Salicaceae), <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	EST-R antagonist (10) (CBZ-R, CKII, MLCK, PBZ-R, PKA) [phytoestrogen]
6,8-Diprenylnaringenin (flavanone)	<i>Humulus lupulus</i> (hops) (Cannabaceae)	EST-R agonist (~10)
Ebenfuran I (= 2-(2,4-Dihydroxyphenyl)-5-hydroxy-6-methoxy-benzofuran) (benzofuran)	<i>Onobrychis eboides</i> (Fabaceae)	EST-R agonist (46 nM) [phytoestrogen]
Ebenfuran II (= 2-(2,4-Dihydroxyphenyl)-3-formyl-4-hydroxy-6-methoxy-benzofuran) (benzofuran)	<i>Onobrychis eboides</i> (Fabaceae)	EST-R agonist (43 nM) [phytoestrogen]
Ebenfuran III (= 2-(2,4-Dihydroxyphenyl)-3-formyl-4-hydroxy-6-methoxy-5-(3-methylbuten-2-yl)-benzofuran) (benzofuran)	<i>Onobrychis eboides</i> (Fabaceae)	Inactive as EST-R agonist [phytoestrogen]
(-)-Epicatechin 3-gallate (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae)	[EST-R antagonist (> 5)] (collagenase, EGF-RTK)
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae), <i>Camellia sinensis</i> (Theaceae)	[EST-R antagonist (5)] (PKA, PKC, RTK) [oxidation products give tea taste]
[Equol (= 4',7-Dihydroxyisoflavan)] (isoflavan)	Metabolic product from Formononetin & Genistein <i>ex clover</i> consumed by stock	EST-R agonist (2) [oestrogen, causes "clover disease" (infertility disease) of ewes]
Eriodictyol (= 5,7,3',4'-Tetrahydroxyflavanone) (flavanone)	<i>Eriodictyon californicum</i> (Hydrophyllaceae); Asteraceae, Fabaceae, Lamiaceae; 7-rhamnoside (Eriodictin) in <i>Citrus</i> spp. (Rutaceae)	EST-R (87)
Flavone (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	EST-R (2) antagonist (COX, EGF-RTK, 5-LOX) [allergenic, antibacterial, AI, inhibits histamine release, PAI, phytoestrogen]
Formononetin (= Biochanin B; Daidzein 4'-methyl ether; Neochanin; Pratol) (isoflavone)	<i>Baptisia</i> spp., <i>Cicer arietinum</i> , <i>Trifolium pratense</i> , <i>T.</i> spp. (clover) (Fabaceae) [leaf]	EST-R agonist (yields the more potent oestrogen Equol after ingestion → "clover disease" of ewes) [antifungal, hypolipidaemic, phytoestrogen]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Phaseolus lunatus</i> , <i>Trifolium brachycalycinum</i> , <i>T. subterraneum</i> (clover) (Fabaceae); glucosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Sophora japonica</i> , <i>Ulex nanus</i> (Fabaceae)	EST-R agonist [0.2–15 nM] (EST-R β -selective) – EST-R α (0.1–1), ER β (12 nM) (AROM, HISK, 17 β HSOR, lipase, peroxidase, PK) [phytoestrogen; inhibits breast cancer cell proliferation, antifungal, oestrogenic]
8-Geranylneringenin (flavanone)	<i>Humulus lupulus</i> (hops) (Cannabaceae)	EST-R agonist (~10)
Glabrene (isoflaven)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root]	EST-R agonist (1) [oestrogenic]
Glabridin (isoflavan)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root]	EST-R agonist (5) [antiproliferative, oestrogenic]
(–)-Glyceollin I (pterocarpan isoflavanone)	<i>Glycine</i> spp., <i>Psoralea</i> spp. (Fabaceae) [leaf phytoalexin]	EST-R antagonist (α & β) – ER α (6), ER β (16) (ETC) [antibacterial, antifungal]
(–)-Glyceollin II (pterocarpan isoflavanone)	<i>Glycine</i> spp., <i>Psoralea</i> spp. (Fabaceae) [leaf phytoalexin]	EST-R antagonist (α & β) (ETC) [antibacterial, antifungal]
Glycitein (4',7-Dihydroxy-6-methoxyisoflavone) (isoflavone)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	EST-R agonist (0.4) [phytoestrogen]
<i>cis</i> -Hinokiresinol (= Nyasol) (lignan, phenylpropanoid)	<i>Araucaria angustifolia</i> (Araucariaceae), <i>Chamaecyparis obtusa</i> (Cupressaceae), <i>Anemarrhena asphodeloides</i> (Liliaceae) [rhizome]	EST-R agonist (0.4) (cAMP PDE) [phytoestrogen]
3(<i>R</i>)- <i>cis</i> -Hinokiresinol (= Nyasol) (lignan, phenylpropanoid)	<i>Araucaria angustifolia</i> (Araucariaceae), <i>Chamaecyparis obtusa</i> (Cupressaceae), <i>Anemarrhena asphodeloides</i> (Liliaceae) [rhizome]	EST-R agonist (0.4) (cAMP PDE) [phytoestrogen]
3(<i>S</i>)- <i>cis</i> -Hinokiresinol (= Nyasol) (lignan, phenylpropanoid)	<i>Araucaria angustifolia</i> (Araucariaceae), <i>Chamaecyparis obtusa</i> (Cupressaceae), <i>Anemarrhena asphodeloides</i> (Liliaceae) [rhizome]	EST-R agonist (60 nM) (cAMP PDE) [phytoestrogen]
<i>trans</i> -Hinokiresinol (lignan, phenylpropanoid)	<i>Chamaecyparis obtusa</i> (Cupressaceae) [heartwood]	EST-R agonist (2) [phytoestrogen]
Isoliquiritigenin (= 2',4',4'-Trihydroxychalcone) (chalcone)	<i>Glycyrrhiza glabra</i> (Fabaceae); glycoside in <i>Dahlia variabilis</i> (Asteraceae), <i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root, rhizome]	EST-R agonist (0.5; 7) [3] (AR, COX, 5-LOX, MAO, MLCK, ox. phos. uncoupler) [PAI, yellow pigment]
8-Isopentenylapigenin (prenylated flavone)	<i>Anaxagorea luzonensis</i> (Annonaceae) [heartwood]	EST-R agonist (40 nM) [phytoestrogen]
8-Isopentenylneringenin (prenylated flavone)	<i>Anaxagorea luzonensis</i> (Annonaceae) [heartwood]	EST-R agonist (33 nM) [phytoestrogen]
8-Isopentenylquercetin (prenylated flavone)	<i>Anaxagorea luzonensis</i> (Annonaceae) [heartwood]	EST-R agonist (50 nM) [phytoestrogen]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Azadirachta indica</i> (Meliaceae), <i>Cuscuta reflexa</i> (Convolvulaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koeboutenia henryi</i> (Sapindaceae); glycosides in Hippocastanaceae, Fabaceae [wood, leaf]	EST-R (23) (CDPK, EGF-RTK, MLCK, PKA, p56 ^{lck} TK) [neuroprotective versus amyloid-induced toxicity (AD), phytoestrogen]
Kievitone (= 2',4',5,7-Tetrahydroxy-8-isoprenylisoflavanone) (isoflavanone)	<i>Dolichos biflorus</i> , <i>Lablab niger</i> , <i>Phaseolus coccineus</i> , <i>P. spp.</i> (Fabaceae)	EST-R agonist (EGF-RTK) [phytoestrogen; inhibits breast cancer cell proliferation, antibacterial, antifungal, oestrogenic, phytoalexin]
Loureirin B (= 4'-Hydroxy-2,4,6-trimethoxy-dihydrochalcone) (dihydrochalcone)	<i>Dracaena loureiri</i> (Agavaceae) [stem wood]; used against infection & GI upset (Thailand)	EST-R agonist (10)
Loureirin D (= 4',4,6-Trihydroxy-2-methoxy-dihydrochalcone) (dihydrochalcone)	<i>Dracaena loureiri</i> (Agavaceae) [stem wood]; used against infection & GI upset (Thailand)	EST-R agonist (9)
Liquiritigenin (= 7,4'-Dihydroxyflavanone) (flavanone)	<i>Cicer arietinum</i> , <i>Glycyrrhiza glabra</i> , <i>Medicago sativa</i> , <i>M. lupulina</i> [phytoalexin] (Fabaceae); glycosides in <i>Dahlia variabilis</i> (Asteraceae), <i>Glycyrrhiza spp.</i> (liquorice) (Fabaceae)	EST-R agonist (> 10) (antifungal, MAO)
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium graveolens</i> (Apiaceae); widespread as glycosides in Brassicaceae, Fabaceae, Lamiaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	EST-R (37) (ACE, AR, AROM, CDPK, ITDI, MLCK, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PKA, PKC, succinate DH, TOPII, TPO) [antibacterial, AI, nodulation signal]
α-Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	EST-R agonist (Ca ²⁺ ATPase, CDPK, HIV-1 PR, MLCK, PKA, HIS-R) [antibacterial, AI, antiulcer, phytoestrogen]
Naringenin (= 5,7,4'-Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia spp.</i> , (Asteraceae), <i>Citrus paradisi</i> , <i>C. sinensis</i> (Rutaceae) [grapefruit juice]	EST-R agonist (33) (> 10), EST-Rα (~10), (AR, AROM, cAMP PDE, TPO) [antibacterial, antifungal, phytoestrogen]
Paeoniflorin (phenolic related glycoside)	<i>Paeonia albiflora</i> , <i>P. lactiflora</i> , <i>P. moutan</i> , <i>P. officinalis</i> (Paeoniaceae)	EST-R [0.9] (ALDO-R, CBG, CORT-R, SBG) [antiallergic, anticoagulant, PAI]
Phloretin (= 2',4,4',6'-Tetrahydroxy-dihydrochalcone) (dihydrochalcone)	<i>Malus domestica</i> (Rosaceae); as 2'-glucoside (Phloridzin) in <i>Kalmia latifolia</i> , <i>Pieris japonica</i> , <i>Rhododendron spp.</i> (Ericaceae), <i>Malus spp.</i> (Rosaceae), <i>Symplocos spp.</i> (Symplocaceae)	EST-R (12) (ECMOX, EGF-RTK, F ₁ -ATPase, ITD, ox. phos. (uncoupler), PKC) [antibacterial, AI, feeding deterrent]

(continued)

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Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects
6-Prenylnaringenin (flavanone)	<i>Humulus lupulus</i> (hops) (Cannabaceae)	EST-R agonist (~1)
8-Prenylnaringenin (flavanone)	<i>Humulus lupulus</i> (hops) (Cannabaceae)	EST-R agonist (10–100nM)
<i>cis</i> - & <i>trans</i> -Resveratrol (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum</i> (Liliaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae) spp.; <i>Vitis vinifera</i> (Vitaceae) [root]	EST-R antagonist (at 5) & agonist (p56 lck TK) [inhibits growth of breast cancer cells]
Terpene		11.1It
Deoxymiroestrol (sterol)	<i>Pueraria mirifica</i> (kwao keur) (Fabaceae) [root]; rejuvenating Thai herbal medicine	EST-R agonist [oestrogen]
1 α ,25-Dihydroxyvitamin D3 (ring-opened sterol)	<i>Pinus nigra</i> , <i>P. sylvestris</i> (Pinaceae) [pollen], <i>Nicotiana glauca</i> , <i>Lycopersicon esculentum</i> (tomato), <i>Solanum glaucophyllum</i> , <i>S. malacoxylon</i> (Solanaceae) [leaf]; animals	Antioestrogenic at oestrogen response element level (VITD-R agonist) [antirachitic, promotes intestinal Ca ²⁺ transport]
β -Estradiol (= 17 β -Oestradiol; 17 β -Estradiol) (sterol); isolated by Edward Doisy (USA) (Nobel Prize, Medicine, 1943, with Henrik Dam, Vitamin K)	<i>Panax quinquefolius</i> (Araliaceae), <i>Humulus lupulus</i> (Cannabaceae), <i>Phaseolus vulgaris</i> (French bean) (Fabaceae) [seed], <i>Punica granatum</i> (Punicaceae); animals <i>ex ovary</i>	EST-R agonist (0.3–10nM) (ER α -R, ER β -R) – ER α (13nM), ER β (12nM) [oestrogen; female development, lactation, gonadotropin expression, ovulation, uterine changes]
Estriol (= Oestriol) (sterol)	<i>Glycyrrhiza glabra</i> (Fabaceae), <i>Salix</i> sp. (willow) (Salicaceae) [flower]; animals; Oestriol isolated by Edward Doisy (USA) (Nobel Prize, Medicine, 1943, with Henrik Dam, Vitamin K)	EST-R agonist [oestrogen; less active metabolite of Oestradiol]
Estrone (= Estrol; Folliculin; Oestrone) (sterol); Adolph Butenandt (Germany) & Leopold Ruzicka (Croatia/Switzerland) (Nobel Prize, Chemistry, 1939, sex hormones; Butenandt's acceptance forbidden by Nazis)	<i>Phoenix dactylifera</i> (date palm) (Palmae) [pollen, seed], <i>Zea mays</i> (Poaceae) [seed oil], <i>Punica granatum</i> (pomegranate) (Punicaceae) [seed], <i>Malus domestica</i> (Rosaceae); fruit & vegetable oil; animals; Oestrone isolated by Edward Doisy (USA) (Nobel Prize, Medicine, 1943, with Henrik Dam, Vitamin K)	EST-R agonist [oestrogen; less active metabolite of Oestradiol]
18 β -Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	EST-R [0.9] (ALDO-R, CBG, CORT-R, 11 β HSDH, 17 β SOR, SBG) [elevated cortisol, hypermineralocorticoidism]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Glycyrrhizic acid (= Glycyrrhinic acid; Glycyrrhizin; Glycyrrhizinic acid) (triterpene glycoside saponin)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	EST-R [0.9] (ALDO-R, CBG, CORT-R, SBG) [anti-ulcerogenic, expectorant, sweet]
[Miroestrol] (sterol)	<i>Pueraria mirifica</i> (kwao keur) (Fabaceae) [root]; rejuvenating Thai herbal medicine	EST-R agonist [oestrogen]; may derive from oxidation of Deoxymiroestrol
all <i>trans</i> -Retinoic acid (= Retinoic acid) (carotene)	Post-ingestion from α -, β - & γ -carotene & other carotenes	Anti-oestrogenic at oestrogen response element level (RA-R)
β -Sitosterol (= Sitosterin; Sitosterol) (phytosterol, sterol)	<i>Triticum</i> spp. (wheat), <i>Zea mays</i> (corn) (Poaceae) [together with Biochanin A in beer & bourbon]	EST-R agonist (weak) [plant membrane component, phytoestrogen]
Testosterone (terpene, sterol)	<i>Vitex agnus-castus</i> (Lamiaceae), <i>Pinus sylvestris</i> (Scots pine) (Pinaceae) [pollen]; animals; <i>ex</i> interstitial cells of testes	EST-R ligand (weak) – ER α (35), ER β (20) (AND-R) [androgen; male development]
Other		11.1Io
Segetalins A & B (cyclic peptides)	<i>Vaccaria segetalis</i> (Caryophyllaceae) [seed]	Oestrogen-like
Non-plant		11.1In
[DDT (= 1,1,1-Trichloro-2,2-bis(<i>p</i> -chlorophenyl)ethane)] (chlorinated biphenyl)	Synthetic; DDT ban in Sri Lanka led to resurgence of mosquitoes & hence of malaria	EST-R agonist [environmental pollutant oestrogen, insecticide]
[Diethylstilbestrol (= DES; 3,4-Bis(<i>p</i> -hydroxyphenyl)-3-hexene)] (stilbene phenolic)	Synthetic	EST-R agonist (1 nM) (17 β HSOR) [synthetic oestrogen; formerly in oestrogen therapy, cancer risk concerns]
[4,4'-Dihydroxychalcone] (chalcone)	Synthetic; derivatives in plants	EST-R agonist [3] [phytoestrogen]
[α -Estradiol] (sterol)	Animals <i>ex</i> ovary	EST-R agonist (weak) (ER α -R, ER β -R) [oestrogen]
[Ipriflavone] (isoflavone)	Synthetic	EST-R agonist/antagonist [anti-osteoporosis]
[Tamoxifen (= 1- <i>p</i> - β -Dimethylaminoethoxy-phenyl- <i>trans</i> -1,2-diphenylbut-1-ene) (aryl tertiary amine)]	Synthetic	[EST-R antagonist (<0.5)] [antioestrogen, therapy for oestrogen-promoted breast cancer]
[Zearalenol] (phenolic)	<i>Gibberella zeae</i> (fungus) on <i>Zea mays</i> (maize) (Poaceae)	EST-R agonist [oestrogenic]
[Zearalenone (= Mycotoxin F2; Toxin F2) (phenolic)]	<i>Gibberella zeae</i> (fungus) on <i>Zea mays</i> (maize) (Poaceae)	EST-R agonist – ER α (1–10 nM; 58 nM), ER β (16 nM); (17 β HSOR) [oestrogenic, \uparrow prolactin secretion]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Oestrogen metabolism – cytochrome P450- linked aromatase (AROM)		11.1J
Alkaloid		11.1Ja
<i>N</i> -(4-Hydroxyundecanoyl)- anabasine (piperidinyl pyridine)	Smoke of tobacco – <i>Nicotiana tabacum</i> (Solanaceae)	AROM (2; 20) [0.2]
<i>N</i> -n-Octanoylnornicotine (pyridine)	Smoke of tobacco – <i>Nicotiana tabacum</i> (Solanaceae)	AROM (310; 450)
Phenolic		11.1Jp
(2 <i>S</i>)-Abyssinone (flavonoid)	<i>Broussonetia papyrifera</i> (Moraceae)	AROM (0.4)
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	<i>Apium graveolens</i> (Apiaceae), Apiaceae, Asteraceae, Lamiaceae, ferns [leaf surface], <i>Buddleja officinalis</i> (Loganiaceae) [flower]	AROM (3) (AR, cAMP PDE, CDK2, 17βHSOR, PKA, MLCK, RTK) [antibacterial, AI, diuretic, hypotensive, nodulation signal for <i>Rhizobium</i>]
Baicalein (flavone)	<i>Oroxylum indicum</i> (Bognoniaceae) [leaf], <i>Scutellaria</i> spp. (Lamiaceae) [root, leaf], <i>Plantago major</i> (Plantaginaceae)	AROM (TOPII)
Biochanin A (= 5,7- Dihydroxy-4'- methoxyisoflavone; Pratensol) (isoflavone)	<i>Cicer arietum</i> , <i>Trifolium pratense</i> , <i>T.</i> spp., <i>Baptisia</i> spp., <i>Dalbergia</i> spp. (Fabaceae), <i>Viola cadudifolia</i> (Myristicaceae) [wood], <i>Cotoneaster pannosa</i> (Rosaceae) [fruit]	AROM (113) [49] (AROM, EGF-RTK, EST-R, 17βHSOR, MLCK) [hypolipidaemic, phytoestrogen]
Chrysin (= 5,7- Dihydroxyflavone) (flavone)	<i>Daucus carota</i> (Apiaceae), <i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (poplar) (Salicaceae) [leaf bud], <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	AROM (5) [2] [anxiolytic]
Coumestrol (coumestan isoflavone)	<i>Brassica oleracea</i> (Brassicaceae), <i>Spinacia oleracea</i> (Chenopodiaceae), <i>Medicago</i> spp., <i>Pisum sativum</i> , <i>Trifolium</i> spp. (Fabaceae); induced phytoalexin in <i>Glycine max</i> , <i>Phaseolus lunatus</i> , <i>P. vulgaris</i> , <i>Vigna unguiculata</i> (Fabaceae)	AROM (25) [1] (ECDY-R, EST-R, 17βHSOR) [phytoestrogen]
[3'-Demethoxy-3 <i>O</i> - demethylmatairesinol] (lignan)	Likely precursor of Enterolactone	AROM [5]
[Didemethoxymatairesinol] (lignan)	Likely precursor of Enterolactone	AROM [7]
7,8-Dihydroxyflavone (flavone)	Plant	AROM
2',4'-Dihydroxy-2''-(1- hydroxy-1- methylethyl)dihydrofuro- [2,3- <i>h</i>]flavanone (flavanone)	<i>Broussonetia papyrifera</i> (Moraceae)	AROM (0.1)

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) / part /	Protein target (other targets) / in vivo effects/
[Enterodiol] (lignan)	“Mammalian lignan” derived from intestinal bacterial modification of lignans from ingested <i>Secale cereale</i> (rye) (Poaceae)	AROM
[Enterolactone] (lignan)	“Mammalian lignan” derived from intestinal bacterial modification of lignans from ingested <i>Secale cereale</i> (rye) (Poaceae)	AROM [14]
Eriodictyol (= 5,7,3',4'-Tetrahydroxyflavanone) (flavanone)	<i>Eriodictyon californicum</i> (Hydrophyllaceae); Asteraceae, Fabaceae, Lamiaceae; as 7-rhamnoside (Eriocitrin) <i>Citrus</i> spp. (Rubiaceae)	AROM (0.6) (EST-R)
Eriodictyol chalcone (chalcone)	<i>Daucus carota</i> (Apiaceae)	AROM (3)
Flavone (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelacaceae)	AROM (49; 68) [22] (COX, EGF-RTK, EST-R, 5-LOX) [allergenic, antibacterial, AI, anxiolytic, inhibits histamine release, PAI, phytoestrogen]
Galangin (= 3,5,7-Trihydroxyflavone) (flavonol).	<i>Escallonia</i> spp. (Saxifrageaceae) [leaf], Betulaceae, Lamiaceae, Salicaceae [bud], ferns [leaf], <i>Alpinia officinarum</i> (Zingiberaceae)	AROM (CDPK, COX, MLCK, Na ⁺ , K ⁺ -ATPase, PKA) [antibacterial]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Genista</i> spp. (broom), <i>Trifolium brachycalycinum</i> , <i>T. subterraneum</i> , <i>T.</i> spp. (clover) (Fabaceae), <i>Prunus</i> spp. (Rosaceae) [wood]; glucosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Sophora japonica</i> , <i>Ulex nanus</i> (Fabaceae)	AROM (EGF-RTK, EST-R, HISK, 17βHSOR, lipase, MLCK, peroxidase, PKA) [phytoestrogen; inhibits breast cancer cell proliferation, antifungal, oestrogenic]
Hesperetin (= Eriodictyol 4'-methyl ether) (flavanone)	<i>Mentha aquatica</i> (Lamiaceae), <i>Citrus paradisi</i> , <i>C.</i> spp. (Rutaceae); glycosides in <i>Cordia obliqua</i> (Boraginaceae), <i>Prunus persica</i> (Rosaceae)	AROM (3) [antifeedant, nodulation gene expression induction]
4-Hydroxychalcone (chalcone)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root]	AROM
7-Hydroxyflavone (flavone)	<i>Clerodendron phlomidis</i> (Verbenaceae) [flower, leaf]	AROM (0.2) (ADH, 17βHSOR) [antinociceptive]
3'-(γ-Hydroxymethyl-γ-methylallyl)-2,4,2',4'-tetrahydroxychalcone-11'- <i>O</i> -coumarate (chalcone)	<i>Broussonetia papyrifera</i> (Moraceae)	AROM (0.5)
Isolicoflavone (flavone)	<i>Broussonetia papyrifera</i> (Moraceae)	AROM (0.1)
Isoliquiritigenin (= 2',4',4'-Trihydroxychalcone) (chalcone)	<i>Glycyrrhiza glabra</i> (Fabaceae); as glycoside in <i>Dahlia variabilis</i> (Asteraceae) [flower], <i>Glycyrrhiza glabra</i> (Fabaceae) [root, rhizome]	17βHSOR (34) (COX, AROM, 5-LOX, uncoupler) [PAI, yellow]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) / part /	Protein target (other targets) / in vivo effects /
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koelreuteria henryi</i> (Sapindaceae)	AROM-CYP IIIA4 (at 0.5), AROM (> 50) (CDPK, EGF-RTK, EST-R, MLCK, PKA, p56 ^{lck} TK, TPO)
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium graveolens</i> (Apiaceae); widespread as glycosides in Brassicaceae, Fabaceae, Lamiaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	AROM (1) [5] (ACE, AR, CDPK, EST-R, ITD, MLCK, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PKA, PKC, succinate DH, TOPII, TPO) [antibacterial, AI, nodulation signal]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplopappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	AROM (> 50) (AROM, DNAL, DNAP, F ₁ -ATPase, HIV-1 RT, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, Nase, NEP, PGK, PK, 5αR, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic, apoptotic]
Naringenin (= 5,7,4'-Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia</i> spp. (Asteraceae), <i>Citrus paradisi</i> [grapefruit juice], <i>Citrus sinensis</i> [orange] (Rutaceae)	AROM-CYP IIIA4 (at 0.5), AROM (9) (AR, cAMP PDE, EST-R, 17βHSOR, TPO) [antibacterial, antifungal, phytoestrogen]
Naringenin chalcone (chalcone)	<i>Dianthus caryophyllus</i> (carnation) (Caryophyllaceae)	AROM (3)
Oenotherin A (ellagitannin)	<i>Epilobium</i> spp. (Onagraceae)	AROM (< 50) (5αR)
Oenotherin B (macrocircular dimeric ellagitannin)	<i>Cuphea hyssopifolia</i> (Lythraceae), <i>Eucalyptus considetiana</i> , <i>E. viminalis</i> (Myrtaceae), <i>Epilobium</i> spp., <i>Oenothera laciniata</i> (Onagraceae)	AROM (> 50) (PADPRH, 5αR) [antitumour, inhibits glucocorticoid-induced de-polyADPriboseylation]
[Pinostrobin chalcone] (chalcone)	Bee propolis (<i>ex</i> plant nectar)	AROM (14)
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Oenothera biennis</i> (Onagraceae), <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice], <i>Koelreuteria henryi</i> (Sapindaceae)	AROM -CYP IIIA4 (at 0.5), AROM (> 50) (LOX, PK) [AI, feeding stimulant]
Terpene		11.1Jt
Achalensolide (guaianolide sesquiterpene lactone)	<i>Stevia achalensis</i> (Asteraceae)	AROM (110)
Dehydroleucodinin (germacranolide sesquiterpene lactone)	<i>Artemisia douglasiana</i> , <i>Stevia yaconensis</i> (Asteraceae)	AROM (15)
10- <i>epi</i> -10-Deoxycumambrin B (germacranolide sesquiterpene lactone)	<i>Chrysanthemum</i> sp. (Asteraceae)	AROM (7) [dermatitic]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects
Eupahakenin B (sesquiterpene lactone)	Asteraceae	AROM (> 200)
Helenalin (pseudoguaianolide sesquiterpene lactone)	<i>Anaphalis</i> , <i>Arnica</i> , <i>Baldwinia</i> , <i>Eupatorium</i> <i>Gaillardia</i> , <i>Helenium</i> spp., <i>Inula helenium</i> (Asteraceae)	AROM (70)
Inflexin (kaurane diterpene)	<i>Isodon excisus</i> , <i>I. lungshengensis</i> (Lamiaceae)	AROM (21) [antifeedant, cytotoxic]
Ludartin (germacranolide sesquiterpene lactone)	<i>Stevia jaconensis</i> (Asteraceae)	AROM (55)
Peruvin (sesquiterpene lactone)	<i>Ambrosia artemisiifolia</i> , <i>A. tenuifolia</i> (Asteraceae)	AROM (65)
Psilostachyin (sesquiterpene lactone)	<i>Chrysanthemum</i> sp., <i>Ambrosia tenuifolia</i> (Asteraceae)	AROM (> 200) [dermatitic, molluscicidal]
Psilostachyin C (sesquiterpene lactone)	<i>Ambrosia artemisiifolia</i> (Asteraceae)	AROM (> 200) [molluscicidal]
SyI (germacranolide sesquiterpene lactone)	<i>Stevia jujensis</i> (Asteraceae)	AROM (> 200)
SyII (germacranolide sesquiterpene lactone)	Asteraceae	AROM (95)
Ursolic acid (ursane triterpene)	<i>Isodon excisus</i> , <i>Salvia triloba</i> (Lamiaceae)	AROM (31)
Ursolic acid 3-O-acetate (ursane triterpene)	<i>Isodon excisus</i> (Lamiaceae)	AROM (86)
Non-plant reference		11.1Jn
[Aminoglutethimide] (piperidinedione)	Synthetic	AROM [0.5] [anticonvulsant; for Cushing's syndrome, breast & prostate cancer]
[Flavanone] (flavanone)	Synthetic	AROM (14) (17 β HSOR)
[Hesperetin chalcone] (chalcone)	Synthetic	AROM (24)
[α -Naphthoflavone] (naphthoflavone)	Synthetic	AROM (0.5) [0.2]
Oestrogen metabolism – 17β-Hydroxysteroid oxidoreductase (17βHSOR)		11.1K
Phenolic		11.1Kp
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	Lamiaceae, ferns [leaf surface], <i>Apium graveolens</i> (Apiaceae), <i>Buddleja officinalis</i> (Loganiaceae) [flower]	17 β HSOR (0.9; 20; 45) (AR, AROM, cAMP PDE, CDK2, PKA, MLCK, RTK) [antibacterial, AI, diuretic, hypotensive, modulation signal for <i>Rhizobium</i>]
Biochanin A (= 5,7- Dihydroxy-4'- methoxyisoflavone; Pratensol) (isoflavone)	<i>Cicer arietum</i> , <i>Trifolium pratense</i> , <i>T.</i> spp., <i>Baptisia</i> spp., <i>Dalbergia</i> spp. (Fabaceae), <i>Virola cadudifolia</i> (Myristicaceae) [wood], <i>Cotoneaster pannosa</i> (Rosaceae) [fruit]	17 β HSOR (8; 14) (AROM, EGF-RTK, EST-R, MLCK) [hypolipidaemic, phytoestrogen]

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects
Chrysin (= 5,7-Dihydroxyflavone) (flavone)	<i>Daucus carota</i> (Apiaceae), <i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (poplar) (Salicaceae) [leaf bud], <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	17 β HSOR (13; 20) (AR, cAMP PDE, ECMOX, 17 β HSOR, ITD) [antibacterial, AI, anxiolytic, inhibits histamine release]
Coumestrol (coumestan isoflavone)	<i>Brassica oleracea</i> (Brassicaceae), <i>Spinacia oleracea</i> (Chenopodiaceae), <i>Medicago</i> spp. (alfalfa), <i>Pisum sativum</i> , <i>Trifolium pratense</i> (Fabaceae); induced phytoalexin in <i>Glycine max</i> , <i>Phaseolus lunatus</i> , <i>P. vulgaris</i> , <i>Vigna unguiculata</i> (Fabaceae)	17 β HSOR (0.2; 5; 11) ECDY-R, EST-R) [phytoestrogen]
2',4'-Dihydroxychalcone (chalcone)	Plant	17 β HSOR (35)
3,7-Dihydroxyflavone (flavone)	Plant	17 β HSOR (18; 20)
Flavone (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	17 β HSOR (41) (AROM, COX, EGF-RTK, EST-R, 5-LOX) [allergenic, antibacterial, AI, inhibits histamine release, PAI, phytoestrogen]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Phaseolus lunatus</i> , <i>Trifolium brachycalycinum</i> , <i>T. subterraneum</i> (clover) (Fabaceae); glucosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Sophora japonica</i> , <i>Ulex nanus</i> (Fabaceae)	17 β HSOR (1) EGF-RTK, EST-R, HISK, lipase, MLCK, peroxidase, PKA) [phytoestrogen; inhibits breast cancer cell proliferation, antifungal, oestrogenic]
4-Hydroxychalcone (chalcone)	<i>Dracaena cinnabari</i> (Agavaceae)	17 β HSOR (16)
[3-Hydroxyflavone] (flavone)	Synthetic; flavonol parent	17 β HSOR (20) (PKA)
7-Hydroxyflavone (flavone)	<i>Clerodendron phlomidis</i> (Verbenaceae) [flower, leaf]	17 β HSOR (0.9; 7; 24) (ADH, AROM) [antinociceptive]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koeleruteria henryi</i> (Sapindaceae)	17 β HSOR (8; 20) (COX-1, CYP, LOX) [blocks COX-2 & iNOS induction; AI, antibacterial, mutagenic, radical scavenger]
Naringenin (= 5,7,4'-Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia</i> spp. (Asteraceae), <i>Citrus paradisi</i> , <i>C. sinensis</i> (Rutaceae) [grapefruit juice]	17 β HSOR (10; 15; 33) (AR, AROM, cAMP PDE, EST-R, TPO) [antibacterial, antifungal, phytoestrogen]
Naringenin chalcone (chalcone)	<i>Dianthus caryophyllus</i> (carnation) (Asteraceae)	17 β HSOR (3)

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread (Asteraceae, Passiflorae, Rhamnaceae, Solanaceae), <i>Artemisia capillari</i> (Asteraceae), <i>Hypericum brasiliense</i> (Guttiferae) [leaf, flower], <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae)	17 β HSOR (5; 9) (AR, CDPK, ECMOX, MLCK, PKA, PKC, RTK, RTK) [antibacterial, antiviral, AI]
[Zearalenone (= Mycotoxin F2; Toxin F2)] (phenolic)	<i>Gibberella zeae</i> (fungus) on <i>Zea mays</i> (maize) (Poaceae)	17 β HSOR (2; 4) (EST-R) [oestrogenic, \uparrow prolactin secretion]
Terpene		11.1Kt
Abietic acid (abietane diterpene)	<i>Pinus</i> spp. (Pinaceae) [resin]	17 β HSOR (10; 20) (5-LOX)
18 β -Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [rhizome, root]	17 β HSOR (30) (ALDO-R, CBG, CORT-R, EST-R, 11 β HSDH, SBG) [elevated cortisol, hypermineralocorticoidism]
Non-plant reference		11.1Kn
[Diethylstilbestrol (= DES; 3,4-Bis(<i>p</i> -hydroxyphenyl)-3-hexene)] (stilbene phenolic)	Synthetic	17 β HSOR (20) (EST-R) [synthetic oestrogen; formerly in oestrogen therapy, cancer risk concerns]
[Flavanone] (flavanone)	Synthetic	17 β HSOR (50) (AROM)
Progesterone receptor (PROG-R)		11.1L
[Progesterone (= Progestin)] (steroid)	Animal <i>ex</i> corpus luteum; remains elevated after fertilization; Adolph Butenandt (Germany, Nobel Prize, Chemistry, 1939, sex hormones, acceptance forbidden by Nazis)	PROG-R [1 nM] (σ -R) [promotes implantation & embryo development]
[RU486 (= Mifepristone)] (polycyclic aromatic, tertiary amine)	Synthetic	PROG-R antagonist [early abortion]
Peripheral benzodiazepine receptor (PBZ-R) & steroidogenesis		11.1M
Cholesterol (sterol)	<i>Aloe vera</i> (Aloeaceae), <i>Helianthus annuus</i> (Asteraceae), <i>Vicia faba</i> (Fabaceae), <i>Phoenix dactylifera</i> (date palm) (Palmae), Rhodophyceae (marine red algae); animal membrane component	Transport into mitochondria depends on mitochondrial 18kDa PBZ-R protein; cholesteryl esters carried by LDLs (\uparrow LDL associated with atherosclerosis)

(continued)

Table 11.1 (Continued)

Compound (class)	Plant (family) part	Protein target (other targets) / in vivo effects/
Egb 761 (= Egb) (diterpenoid extract)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf] standardized extract	Contains Ginkgolide A & related ginkgolides [reduces expression of adrenocortical mitochondrial PBZ-R & thence corticosteroid synthesis; antistress, neuroprotective]
Ginkgolide A (diterpenoid)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	[Reduces expression of adrenocortical mitochondrial PBZ-R & thence corticosteroid synthesis; AI, anti-asthmatic, antistress, insect antifeedant, bitter, neuroprotective]
Ginkgolide B (diterpenoid)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [root bark, leaf]	[Reduces expression of adrenocortical mitochondrial PBZ-R & thence corticosteroid synthesis; AI, anti-asthmatic]

Table 11.2 Cytosolic non-steroid hormone receptor agonists and antagonists

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Aryl hydrocarbon receptor (ARH-R)		11.2A
Alkaloid		11.2Aa
Tryptanthrine (= Couroupitine A) (quinazoline)	<i>Strobilanthes cusia</i> (Acanthaceae), <i>Isatis tinctoria</i> (woad) (Brassicaceae), <i>Couroupita guaianensis</i> (Lecithidaceae), <i>Polygonum tinctorum</i> (Polygonaceae); woad yielded the blue dye and body paint of the ancient Britons such as Boadicea	ARH-R agonist (COX-2) [↓ iNOS expression; inhibits NO & PGE2 production]
Phenolic		11.2Ap
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	Lamiaceae, ferns [leaf surface], <i>Apium graveolens</i> (Apiaceae), <i>Buddleja officinalis</i> (Loganiaceae) [flower]	ARH-R (AD-R, cAMP PDE, cGMP PDE, AR, CDK2, PK, RTK) [antibacterial, AI, apoptotic, diuretic, hypotensive; cell cycle inhibition (at 20–40)]
Flavone (= 2-Phenyl-1,4- benzopyrone) (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	ARH-R (AD-R, COX, 5-LOX (ECMOX) [AI, apoptotic, PAI, inhibits basophil histamine release; cell cycle inhibition (at 20–50)]
Galangin (= 3,5,7- Trihydroxyflavone) (flavonol)	<i>Escallonia</i> spp. (Saxifrageaceae) [leaf], Betulaceae, Lamiaceae, Salicaceae [bud], ferns [leaf], <i>Alpinia officinarum</i> (Zingiberaceae)	ARH-R (blocks activation) [apoptotic] (AROM, CDPK, COX, MLCK, Na ⁺ , K ⁺ -ATPase, PKA) [antibacterial]

(continued)

Table 11.2 (Continued)

Compound (class)	Plant (family) / part /	Target (other targets) / in vivo effects/
Non-plant reference		11.2An
[α -Naphthoflavone] (naphthoflavone)	Synthetic	ARH-R (AD-R ligand) [apoptotic, cell cycle inhibition (at 20–50)]
[TCDD (= 2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin)] (chlorodibenzodioxin)	Synthetic; important environmental toxic, carcinogenic & teratogenic contaminant from combustion and industrial synthesis of chlorophenyl compounds	ARH-R [apoptotic, cell cycle inhibition (at 1–10 nM)]
Peroxisome Proliferator-Activated Receptor (PPA-R)		11.2B
Other		11.2Bo
Arachidonic acid (unsaturated FA)	<i>Brassica oleracea</i> (Brassicaceae), <i>Mnium</i> spp. (moss) (Mniaceae), <i>Scolopendrium vulgare</i> (fern) (Aspleniaceae); <i>Phytophthora infestans</i> elicitor in potato	PPA-R agonist (at 100) (SLOX, 5-LOX)
[Docosahexaenoic acid (= <i>cis</i> -4,7,10,13,16,19-C22:5)] (unsaturated FA)	After ingestion of α -Linolenic acid precursor from <i>Linum usitatissimum</i> (Linaceae) [seed oil, linseed oil]; fish oil	PPA-R agonist (at 100) [anti- hyperlipoproteinaemic]
[Eicosapentaenoic acid (= <i>cis</i> -5,8,11,14,17-C20:5)] (unsaturated FA)	After ingestion of α -Linolenic acid precursor from <i>Linum usitatissimum</i> (Linaceae) [seed oil, linseed oil]; <i>Phytophthora infestans</i> elicitor in potato; fish oil	PPA-R agonist (at 100) [anti- hyperlipoproteinaemic]
Linoleic acid (= <i>cis</i> -9, <i>cis</i> -12-Octadecenoic acid; Linolic acid) (unsaturated FA)	Widespread; <i>Helianthus annuum</i> (Asteraceae), <i>Cucumis melo</i> (Cucurbitaceae), <i>Arachis hypogaea</i> , <i>Glycine max</i> (Fabaceae), <i>Linum usitatissimum</i> (Linaceae), <i>Gossypium hirsutum</i> (Malvaceae) [seed oil]	PPA-R agonist (at 100) (5-LOX)
Myristic acid (= C14:0; Tetradecanoic acid) (saturated FA)	<i>Cocos nucifera</i> (Arecaceae), <i>Iris florentina</i> (Iridaceae), <i>Gossypium hirsutum</i> (Malvaceae), <i>Myristica fragrans</i> (nutmeg), <i>Viola surinamensis</i> (Myristicaceae)	PPA-R agonist (at 100)
Non-plant reference		11.2Bn
[Clofibrate (= Amotril; Clofibrac acid ethylester)] (chlorophenol ether)	Synthetic	PPA-R agonist [anti- hyperlipoproteinaemic]
[Ciglitazone] (thiazolidine)	Synthetic	PPA-R γ agonist [antihyperglycaemic]
[WY14643] (pyrimidinyl carboxylic acid)	Synthetic	PPA-R α agonist (0.6) [AI]

(continued)

Table 11.2 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Retinoic acid Receptor (RA-R)		11.2C
Terpene		11.2Ct
α -Carotene (carotene); Richard Kuhn (Germany, Nobel Prize, 1938, Chemistry, carotenes & vitamins; forbidden to accept award by Nazis)	Widespread (green leaves); <i>Daucus carota</i> (carrot) (Apiaceae) [root], <i>Zea mays</i> (corn) (Poaceae) [seed], <i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [fruit], & various other fruits, roots & seeds	Post-ingestion precursor for RA-R agonist RA
β -Carotene (carotene)	Widespread (green leaves, fruit); <i>Daucus carota</i> (Apiaceae) [root], <i>Ipomoea batatas</i> (Convolvulaceae), <i>Rosa</i> spp. (Rosaceae), <i>Capsicum annuum</i> (Solanaceae) [fruit]	Best post-ingestion precursor for RA-R agonist RA
β -Carotene 5,6-epoxide (carotene)	Leaf, fruit & petal of various plants e.g. <i>Malus</i> spp. (apple peel) (Rosaceae), <i>Citrus sinensis</i> (orange peel) (Rutaceae)	Post-ingestion precursor for RA-R agonist RA
β -Carotene 5,8-epoxide (= Mutatochrome) (carotene)	Plant leaf; fruit, leaf, petal of various plants e.g. <i>Citrus</i> spp. (Rutaceae) [fruit rind], <i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [fruit]	Post-ingestion precursor for RA-R agonist RA
γ -Carotene (carotene)	<i>Daucus carota</i> (carrot) (Apiaceae) [root], <i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [fruit], & various other fruit, root, seed	Post-ingestion precursor for RA-R agonist RA
(3 <i>R</i>)-3-Hydroxy- β -carotene (= β -Cryptoxanthin) (carotene)	Petal, leaf, fruit, leaf, petal, seed of various plants e.g. <i>Citrus</i> spp. (Rutaceae) [fruit rind]	Post-ingestion precursor for RA-R agonist RA
Non-plant reference		11.2Cn
[Retinal (= Vitamin A) aldehyde] (carotene); isolation by Paul Karrer (Russia/Switzerland, Nobel Prize, Chemistry, 1937, carotenoids, vitamins); Heilbron (UK)	Post-ingestion from α -, β - & γ -carotene & other carotenoids from plant leaves & a wide variety of fruit, root & seed sources e.g. <i>Daucus carota</i> (carrot) (Apiaceae) [root]; Retinal covalently linked to opsins (\rightarrow light receptor Rhodopsins in vision); colour blind John Dalton (atomic theory, 1766–1844) bequeathed his eyes to science; 2 centuries on molecular biology confirmed the absence of the gene for the green photoreceptor opsin	Post-ingestion precursor for RA-R agonist RA; 11- <i>cis</i> -Retinal chromophore linked to protein opsin, in visual excitation isomerizes to all- <i>trans</i> -Retinal – George Wald (USA, retinal isomerization), Ragnar Granit (Finland/Sweden) & Haldan Hartline (USA) (Nobel Prize, Physiology/Medicine, 1967, vision)

(continued)

Table 11.2 (Continued)

Compound (class)	Plant (family) part	Target (other targets) in vivo effects
[Retinol (= Vitamin A)] (carotene); E.V. McCollum showed xerophthalmia in rats due to Vitamin A deficiency	Post-ingestion from α -, β - & γ -carotene & other carotenes; Sir Douglas Mawson nobly denied himself but gave dog liver to his fellow Antarctic explorers who died of Vitamin A poisoning	Post-ingestion precursor for RA-R agonist RA; deficiency \rightarrow night blindness (nyctalopia); severe deficiency \rightarrow xerophthalmia \rightarrow blindness; excess \rightarrow carotenemia
11- <i>cis</i> -Retinoic acid] (carotene)	Post-ingestion from α -, β - & γ -carotene & other carotenes & thence isomerization of all <i>trans</i> -Retinoic acid	RA-R (retinoid X R) ligand
All <i>trans</i> -Retinoic acid (= Retinoic acid)] (carotene)	Post-ingestion from α -, β - & γ -carotene & other carotenes	RA-R agonist [0.2 nM] (PM NADH OX) [antioestrogenic at oestrogen response element level]
11.2D		
Thyroid hormone receptor (THY-R)		
[Thyroid hormones – Thyroxine (= T ₄ ; 3,5,3',5'-Tetraiodothyronine) & Triiodothyronine (= T ₃ ; 3,5,3'-Triiodothyronine)] (iodinated phenolics)	Animals; <i>ex</i> thyroid; Grave's disease (thyrotoxicosis, excess thyroid hormone) – highly excitable Sir Cecil Spring-Rice (World War 1 British Ambassador to USA 1913–4 January 1918) & WW2 General George Marshall (thyroid removed 1936)	Inactive T ₄ converted to THY-R agonist T ₃ by Iodothyronine 5'-deiodinase (ITD); thyroxine synthesized by Edward Kendall (USA) (Nobel Prize, Physiology/Medicine, 1950, glucocorticoids, with T. Reichstein and & P. Hench)
11.2E		
Thyroid hormone metabolism		
D-Cathinone (= (<i>S</i>)-2-Amino-1-phenylpropanone) (phenylpropanoid)	<i>Catha edulis</i> (khat), <i>Maytenus krukovii</i> (Celastraceae) [leaf]	\uparrow T ₃ & T ₄ (β A-R agonist) [anorexic, CNS stimulant, euphoriant]
N-Formylnorephedrine (phenylpropanoid)	<i>Catha edulis</i> (khat) [leaf]	\uparrow T ₃ & T ₄ (β A-R agonist) [anorexic, CNS stimulant, euphoriant]
Glucosinolates (sulfosugars yielding specific isothiocyanates (RNCS) on hydrolysis)	Brassicaceae (Cruciferae) e.g. <i>Brassica oleraceae</i> (broccoli) [leaf]; the least favourite vegetable of George Bush I	Some R–N=C=S products (e.g. BenzylNCS & 3-(Methylsulfonyl)-propylNCS) are goitrogenic & \downarrow T ₃ & T ₄ [toxic]
Goitrin (= (–)-5-Vinyloxazolidine-2-thione) (oxazolidine)	Metabolite via myrosinase from Progoitrin from Brassicaceae (Cruciferae) e.g. <i>Brassica napus</i> (rape) [seed], <i>Brassica oleraceae</i> (Brussels sprouts)	\downarrow T ₃ & T ₄ (DBH) [goitrogenic]
Iodide (I ⁻) (halide anion)	Seaweed e.g. <i>Macrocystis pyrifera</i> (giant kelp, brown alga) (Phaeophyceae)	1.8 billion at risk of iodide deficiency disorders (IDD) due to insufficient intake; 750 million with goitre, 43 million with IDD-related brain damage, 5.7 million with cretinism

(continued)

Table 11.2 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Progoitrin (= (2R)-2-hydroxybut-3-enylglucosinolate) (glucosinolate)	<i>Brassica</i> spp. (Brassicaceae)	Breakdown yields goitrogenic Goitrin
Thyroid hormone metabolism – Thyroid peroxidase (TPO)		11.2F
Alkaloid		11.2Fa
[3,4-Dihydroxypyridine] (pyridine)	Rumen metabolite of Mimosine from <i>Leucaena leucocephala</i> , <i>L. glauca</i> , <i>L. spp.</i> (Fabaceae) [leaf, seed]	TPO [anti-thyroid, goitrogenic]
[3,4-Dihydroxypyridine-3-O-glucuronide] (pyridine)	Metabolite of Mimosine from <i>Leucaena leucocephala</i> , <i>L. glauca</i> , <i>L. spp.</i> (Fabaceae) [leaf, seed]	TPO [anti-thyroid, goitrogenic]
Mimosine (= 3-Hydroxy-4-oxo-1(4H)-pyridinealanine (pyridine))	<i>Leucaena leucocephala</i> , <i>L. glauca</i> , <i>L. spp.</i> , <i>Mimosa pudica</i> (sensitive plant) (Fabaceae) [leaf, seed]; mechanically stimulated <i>M. pudica</i> leaves close	Metabolized to 3,4-Dihydroxypyridine (inhibits TPO) in rumen [depilatory]
Phenolic		11.2Fp
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Lamiaceae, ferns [leaf surface]; <i>Apium graveolens</i> (Apiaceae), <i>Buddleja officinalis</i> (Loganiaceae) [flower], <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]; widespread as glycoside	TPO (BZ-R-like R, EST-R, PK, RTK) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
Biochanin A (= 5,7-Dihydroxy-4'-methoxyisoflavone; Pratenol) (isoflavone)	<i>Cicer arietum</i> , <i>Trifolium pratense</i> , <i>T. spp.</i> , <i>Baptisia</i> spp., <i>Dalbergia</i> spp. (Fabaceae), <i>Viola cadudifolia</i> (Myristicaceae) [wood], <i>Cotoneaster pannosa</i> (Rosaceae) [fruit]	TPO (competitive) (EGF-RTK, EST-R, MLCK, PKA) [anti-thyroid, oestrogenic, hypolipidaemic]
Daidzein (= 4',7-Dihydroxyisoflavone) (isoflavone)	<i>Glycine max</i> , <i>Trifolium repens</i> (clover), <i>Ulex europaeus</i> (gorse) (Fabaceae); as glycoside in <i>Baptisia</i> spp., <i>Glycine max</i> , <i>Pueraria</i> spp., <i>Trifolium pratense</i> (Fabaceae)	TPO (1–10) (suicide inactivates minus iodide) (DNAPOL, EST-R, GABAA-R, lipase, TOPII) [antifungal, anti-thyroid, phytoestrogen]
Fisetin (= 5-Deoxyquercetin; 3,7,3',4'-Tetrahydroxyflavone) (flavonol)	<i>Rhus cotinus</i> , <i>R. rhodanthema</i> (Anacardiaceae), <i>Acacia</i> spp. (Fabaceae) [heartwood], <i>Ailanthus altissima</i> (Simaroubaceae); as glycosides in <i>Rhus succedanea</i> (Anacardiaceae) [wood], <i>Dalbergia odorifera</i> [wood], <i>Trifolium subterraneum</i> (Fabaceae)	TPO (CDPK, ITDI, LOX, MLCK, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PKA, PKC, succinate DH) [allergenic, antibacterial, anti-thyroid, inhibits SM contraction & histamine release]

(continued)

Table 11.2 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7- Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Phaseolus lunatus</i> , <i>Trifolium brachycalycinum</i> , <i>T. subterraneum</i> (clover) (Fabaceae); glucosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Sophora japonica</i> , <i>Ulex nanus</i> (Fabaceae)	TPO (1–10) (suicide inactivates minus iodide) (AD-R, EGF-RTK, GABAA-R, HSK, lipase, MLCK, PKA, pp60 ^{v-src} TK (RSV), pp110 ^{gag-fcs} TK, TOPII) [antifungal, anti-thyroid, oestrogenic]
Glucosylorientin (flavone C-glycoside)	<i>Pennisetum americanum</i> (millet) (Poaceae)	TPO [anti-thyroid, goitrogenic]
Glucosylvitexin (flavone C-glycoside)	<i>Pennisetum americanum</i> (millet) (Poaceae)	TPO [anti-thyroid, goitrogenic]
Kaempferol (= 3,5,7,4'- Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koelreuteria henryi</i> (Sapindaceae)	TPO (CDPK, CYP, EGF-RTK, EST-R, MLCK, PKA, p56 ^{lck} TK)
Luteolin (= 5,7,3',4'- Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium graveolens</i> (Apiaceae); widespread as glycosides in Brassicaceae, Fabaceae, Lamiaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	TPO (ACE, AR, CDPK, ITDI, MLCK, NADH DH, Na ⁺ , K ⁺ - ATPase, NEP, PKA, PKC, succinate DH, TOPII, [antibacterial, AI, anti-thyroid, nodulation signal])
Myricetin (= 3,5,7,3',4',5'- Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplopappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	TPO (CDPK, F ₁ -ATPase, IKK, 5- LOX, MLCK, PKA, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, 5αR, succinate DH, TOPII) [antibacterial, anti-thyroid, antigonadotropic]
Naringenin (= 5,7,4'- Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia</i> spp. (Asteraceae), <i>Citrus paradisi</i> , <i>C. sinensis</i> (Rutaceae)	TPO (AR, cAMP PDE, EST-R) [antibacterial, antifungal, anti- thyroid, phytoestrogen]
Naringin (= 2,3- Dihydroapigenin 7-O- rhamnosyl-glucoside; 2,3-Dihydro-5,7,4'- Trihydroxyflavone 7-O- neohesperidoside) (flavanone O-glycoside)	<i>Adiantum</i> spp., <i>Ceterach officinarum</i> (fern) (Adiantaceae), <i>Citrus paradisi</i> (grapefruit) (Rutaceae), <i>Origanum vulgare</i> (oregano) (Lamiaceae)	TPO (PKA) [anti-thyroid, bitter, oviposition stimulant]
Propyl gallate (phenolic)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	TPO [0.9]
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Artemisia capillari</i> (Asteraceae), <i>Hypericum brasilense</i> (Guttiferae) [leaf, flower], <i>Oenothera biennis</i> (Onagraceae) <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	TPO (AR, cAMP PDE, F ₁ - ATPase, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, NEP, PK, RTK, PS – EF-1α, TOPII) [allergenic, antibacterial, AI, anti-thyroid, antiviral]

(continued)

Table 11.2 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Resorcinol (= 1,3-Dihydroxybenzene; Resorcin) (phenolic)	<i>Morus alba</i> (Moraceae), <i>Pinus rigida</i> (Pinaceae) [needle]	TPO
Vitexin (= Apigenin 8-C-glucoside) (flavone C-glycoside)	<i>Pennisetum americanum</i> (millet) (Poaceae), <i>Camellia sinensis</i> (Theaceae), <i>Vitex lucens</i> (Verbenaceae)	TPO [anti-thyroid, goitrogenic]
Non-plant reference		11.2Fn
[Methimazole (= 1-Methyl-2-mercaptoimidazole)] (imidazole)	Synthetic	TPO [antihyperthyroid]
[Propylthiouracil] (pyrimidine)	Synthetic	TPO [antihyperthyroid]
Thyroid hormone metabolism – Iodothyronine deiodinase (ITD)		11.2G
Phenolic		11.2Gp
Ellagic acid (= Benzoic acid; Lagistase) (phenolic acid lactone)	Widespread [leaf], Ellagitannin product; <i>Psidium guajava</i> (guava) (Myrtaceae), <i>Fragaria</i> spp. (strawberry) (Rosaceae)	ITD (MLCK, PKA, PKA, PKC, p60 ^{src} TK) [anti-mutagen, haemostatic]
Luteolin 7-O-glucoside (flavone O-glycoside)	Widespread; <i>Humulus japonicus</i> (Cannabaceae), <i>Salix</i> spp. (Salicaceae)	ITD [insect feeding attractant]
[2',4',6',3,4-Pentahydroxychalcone] (chalcone)	Semi-synthetic	ITD [8]
Phloretin (= 2',4,4',6'-Tetrahydroxy-dihydrochalcone) (dihydrochalcone)	<i>Malus domestica</i> (Rosaceae); as 2'-glucoside (Phloridzin) in <i>Kalmia latifolia</i> , <i>Pieris japonica</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>Malus</i> spp. (Rosaceae), <i>Symplocos</i> spp. (Symplocaceae)	ITD [0.8] (PKC, ox. phos.) [antibacterial, AI, feeding deterrent]
Rosmarinic acid (phenylpropanoid)	<i>Symphytum officinale</i> (Boraginaceae), <i>Melissa officinalis</i> , <i>Mentha piperita</i> , <i>Ocimum sanctum</i> , <i>Prunella vulgaris</i> , <i>Rosmarinus officinalis</i> , <i>Salvia officinale</i> , <i>Teucrium scorodonia</i> (Lamiaceae), <i>Anethum</i> spp., <i>Levisticum</i> spp., <i>Sanicula</i> spp., <i>Astrantia major</i> (Apiaceae)	ITD (COX-1, COX-2) [AI]
4,6,3',4'-Tetrahydroxyaurone (= Aureusidine) (aurone)	As glycoside in <i>Chirita micromusa</i> , <i>Petrocosmea kerrii</i> (Gesneriaceae), <i>Marchantia polymorpha</i> (Hepaticae), <i>Antirrhinum majus</i> (Scrophulariaceae)	ITD [yellow colour]
2',4',6',4'-Tetrahydroxychalcone (= Chalconaringenin) (chalcone)	As glycoside in <i>Dianthus</i> sp. (Caryophyllaceae), <i>Helichrysum</i> sp. (Asteraceae), <i>Paeonia</i> spp. (Paeoniaceae), <i>Salix purpurea</i> (willow) (Salicaceae) [bark]	ITD [yellow colour]

(continued)

Table 11.2 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
4',4,6-Trihydroxyaurone (aurone phenolic)	Aurones found in Asteraceae	ITD – Type I T4-5'D (0.5) (TRY)
4,6,4'-Trihydroxyaurone (aurone)	Aurones found in Asteraceae	ITD [yellow colour]
Other		11.2Go
Thiocyanate (= SCN ⁻)	Metabolite via myrosinase from Glucosinolates from Brassicaceae (Cruciferae) e.g. <i>Brassica napus</i> , <i>Brassica oleraceae</i> (Brussels sprouts)	ITD – inhibits T4 to T3 conversion [goitrogenic]
Thyroid hormone transport via Transthyretin (TRY)		11.2H
4',4,6-Trihydroxyaurone (aurone phenolic)	Aurones found in Asteraceae	TRY (competes) (ITD)
Vitamin D Receptor (VITD-R)		11.2I
Terpene		11.2It
7-Dehydrocholesterol (sterol)	<i>Nicotiana glauca</i> , <i>Solanum glaucophyllum</i> (Solanaceae) [leaf]	UV-mediated conversion to VITD- R agonist 1,25- Dihydroxyvitamin D ₃
1 α ,25-Dihydroxyvitamin D ₃ (ring-opened sterol)	<i>Pinus nigra</i> , <i>P. sylvestris</i> (Pinaceae) [pollen], <i>Nicotiana glauca</i> , <i>Lycopersicon esculentum</i> (tomato), <i>Solanum glaucophyllum</i> , <i>S. malacoxylon</i> (Solanaceae) [leaf]; animals	VITD-R agonist (PM NADH OX) [antirachitic, promotes intestinal Ca ²⁺ transport; antioestrogenic at oestrogen response element level]
24,25-Dihydroxyvitamin D ₃ (ring-opened sterol)	<i>Pinus nigra</i> , <i>P. sylvestris</i> (Pinaceae) [pollen]	Analogue of VITD-R agonist 1,25-Dihydroxyvitamin D ₃
1,25-Dihydroxyvitamin D ₃ glucoside (ring-opened sterol glycoside)	<i>Solanum malacoxylon</i> (Solanaceae) [leaf]	Deglycosylation yields VITD-R agonist 1,25-Dihydroxyvitamin D ₃ [excess calcinogenic → pathological Ca ²⁺ deposition]
Ergosterol (= Ergosterin; Provitamin D ₂) (sterol)	<i>Triticum aestivum</i> (Poaceae); likely precursor of Ergosterol-5,8- endoperoxide in <i>Ajuga remota</i> (Lamiaceae); <i>Saccharomyces cerevisiae</i> (yeast) & other fungi	UV irradiation yields Vitamin D ₂ [indicator of plant product fungal contamination]
25-Hydroxyvitamin D ₃ (ring-opened sterol)	<i>Pinus nigra</i> , <i>P. sylvestris</i> (Pinaceae) [pollen], <i>Nicotiana glauca</i> , <i>Lycopersicon esculentum</i> , <i>Solanum glaucophyllum</i> , <i>S. malacoxylon</i> (Solanaceae) [leaf]; animals	Hydroxylation yields VITD-R agonist 1,25-Dihydroxyvitamin D ₃ [antirachitic]
25-Hydroxyvitamin D ₃ glucoside (ring-opened sterol glycoside)	<i>Solanum malacoxylon</i> (Solanaceae) [leaf]	Deglycosylation & hydroxylation yields VITD-R agonist 1,25- Dihydroxyvitamin D ₃

(continued)

Table 11.2 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Vitamin D ₂ (= Calciferol) (ring-opened sterol); isolated by Adolph Windaus (Nobel Prize, Chemistry, 1928)	<i>Medicago sativa</i> (Fabaceae) [leaf], <i>Pinus nigra</i> , <i>P. sylvestris</i> (Pinaceae) [pollen]; lichen	Precursor of VITD-R agonist 1,25-Dihydroxyvitamin D ₃ [antirachitic]
Vitamin D ₃ (= Cholecalciferol) (ring-opened sterol); synthesis by Adolph Windaus (Germany, Nobel Prize, Chemistry, 1928, sterols & Vitamin D)	<i>Medicago sativa</i> (Fabaceae) [leaf], <i>Pinus nigra</i> , <i>P. sylvestris</i> (Pinaceae) [pollen], <i>Nicotiana glauca</i> , <i>Lycopersicon esculentum</i> (tomato), <i>Solanum glaucophyllum</i> , <i>S. malacoxylon</i> (Solanaceae) [leaf]; lichen; cod liver oil	Hydroxylation yields VITD-R agonist 1,25-Dihydroxyvitamin D ₃ [antirachitic]; Vitamin D deficiency causes rickets – shown by Elmer McCollum
Vitamin D ₃ glucoside (ring-opened sterol glycoside)	<i>Solanum malacoxylon</i> (Solanaceae) [leaf]	Deglycosylation & hydroxylation yields VITD-R agonist 1,25- Dihydroxyvitamin D ₃
Other nuclear receptor superfamily receptors		11.2J
Phenolic		11.2Jp
Dopamine (= 4-(2-Aminoethyl) benzene-1,2-diol; 3-Hydroxytyramine) (catecholamine phenolic)	<i>Carnegiae gigantea</i> (giant cactus), <i>Lophophora williamsii</i> (mescal button) (Cactaceae), <i>Cytisus scoparius</i> (broom) (Fabaceae), <i>Musa cavendishii</i> , <i>M. paradisiaca</i> (banana peel), <i>M. sapientum</i> (Musaceae), <i>Hermidium alipes</i> (Nyctaginaceae); animal NT	COUP-TF agonist (α- & β-A-R, D-R) [dopaminergic NT, increases cardiac output, reduced in Parkinsonism, sympathomimetic]
Hyperforin (phloroglucinol)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae); major herbal antidepressant	Steroid X R agonist (D2-R) [antidepressant inhibits prolactin release]

12 Polynucleotides, polysaccharides, phospholipids and membranes

12.1 Introduction

In addition to proteins such as enzymes and hormone receptors, potential targets for plant defensive compounds include polynucleotides (i.e. DNA and RNA), polysaccharides and oligosaccharides (notably oligosaccharides covalently linked to proteins associated with the external surface of target cells) and cell membranes (composed of phospholipid bilayers). The obvious problem here for plant defence involving such targets is that polynucleotides, oligosaccharides, polysaccharides and cell membrane phospholipids are crucial components of plant cells as well as of animal and microbial cells. Accordingly there is a need for plants producing ligands for such components to ensure that such defensive agents do not bind to targets in the plant itself.

As described earlier, plant self-protection from its own defensive compounds can be variously achieved by localization of the active agents in the cell wall, seed protein bodies and vacuoles and by storage of inactive forms (e.g. inactive glycosylated derivatives of the active aglycone). Further, deposition of active agents in “dead” protective material such as fruit hull, wood and bark ensures effective defence at the point of predator entry as well as protection of the plant from its own defensive compounds.

While many defensive compounds are already synthesized and ready to act, other protein and non-protein defensive compounds are made in response to pathogen invasion or wounding by herbivores. Thus, the bioactive complement of plant material can be markedly affected by the circumstances of the plant prior to “harvesting”. A variety of low molecular weight, non-protein antifungal “phytoalexins” are elaborated by plants in response to fungal attack. While a range of plant antifungal proteins (notably those present in seeds) are already synthesized, many defensive proteins are inducible by pathogen attack and are referred to as “pathogenesis-related proteins” (PR proteins, PRPs). The PRPs are grouped into several classes, namely: PR-1 antifungal proteins (15–17 kDa cysteine-rich proteins); PR-2 β -glucanases (Class I basic, vacuolar ~33 kDa β -glucanases and Class II and Class III extracellular acidic β -glucanases); PR-3 chitinases (~32 kDa Class I chitinases with cysteine-rich and hevein-like domains, 27–28 kDa Class II chitinases with a hevein-like domain, distinct 28–30 kDa Class III chitinases, Class IV chitinases related to the Class I enzymes and 41–43 kDa Class V chitinases); PR-5 chitin-binding proteins (CBPs) (Class I hevein-like proteins and Class II antifungal proteins lacking the hevein-like domain); and PR-5 defensive proteins (that are related to the sweet-tasting protein thaumatin and to the water stress-induced osmotin proteins).

In addition to the PRPs outlined above, plants elaborate a variety of other defensive proteins (of which some are constitutive and others also induced by wounding) including: protein inhibitors of α -amylase, chitinase, polygalacturonase and of other glycosidases (Chapter 13);

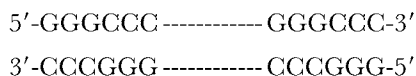
defensins (γ -thionins); cyclophilins; glycine/histidine-rich proteins; lectins (carbohydrate binding proteins); napins and napin-like proteins; plant non-specific lipid transfer proteins (LTPs); ribosome inactivating proteins (RIPs) (purine aminoglycosidases (PAGs) of type 1 [11–30 kDa single chain PAGs], type 2 [60 kDa heterodimers of a lectin B chain and PAG A chain] and type 3 tetramers [derived from dimerizing type 2 RIPs]) (Chapter 9); protease inhibitors (Chapter 13); and other proteins, for example, the abundant 7 kDa snak-in-1 from *Solanum tuberosum* (potato tuber) (Solanaceae) and a potent 30 kDa antifungal protein deriving from *Engelmannia pinnatifida* (Asteraceae) (and related to self-pollination restricting self-incompatibility glycoproteins). As outlined below, proteins from some of these defensive protein classes variously interact with polysaccharides and membranes and are accordingly listed in the appropriate tables below.

12.2 Polynucleotides

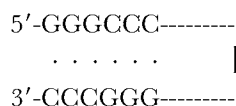
As described in Chapters 2 and 9, the typical information flow in living systems is from DNA (encoding structural genes as well as including regulatory and intron elements) to messenger RNA (mRNA) (by the process of transcription catalysed by RNA polymerases) and thence to translation of processed mRNA on ribosomes to yield pro-proteins that are subsequently localized by targeting, covalently modified (e.g. by proteolysis and glycosylation) and finally folded properly. This process of “gene expression” can be impaired by compounds that interfere with the protein machinery involved or by compounds interacting with DNA and RNA. As described in Chapter 9, DNA-binding compounds can variously inhibit the function of enzymes operating on DNA such as DNA polymerases (that replicate DNA), DNA helicases (that unwind DNA), topoisomerases (that relax supercoiled DNA by snipping and rejoining), DNA ligases (that join DNA segments) and RNA polymerases (that catalyse DNA template-dependent synthesis of a complementary mRNA).

The DNA target can be double-stranded (dsDNA), this double helix structure involving plectonemically intertwined complementary strands of opposite 5' → 3' polarity and specifically linked by hydrogen bonds between complementary bases (A–T, G–C). The double helix accordingly has a hydrophobic core of “stacked” aromatic, heterocyclic bases and a surface that is hydrophilic because of the backbone of deoxyribose elements joined by negatively charged phosphodiester linkages. The surface of dsDNA has two further features, namely the “major” and “minor” grooves formed by the plectonemically coiled strands. Some compounds with a hydrophobic, planar structure can insert or “intercalate” between the “stacked” bases of dsDNA and hence interfere with protein-DNA binding or the unwinding of DNA required for replication and transcription. However, polar parts of such DNA ligands can interact with the solvent (water) and the phosphodiester-linked deoxyribose backbone. Single-stranded DNA (ssDNA) and RNA may form double-stranded looped structures if there are complementary regions that can hybridize by hydrogen bonding and intercalators can accordingly potentially interact with these regions of single-stranded polynucleotide secondary structure.

Further potential polynucleotide–ligand interactions involve the negative surface charges (that can electrostatically interact with positively charged non-protein and protein ligands) and surface structural elements such as minor and major grooves and secondary structure loops. Thus, for example, polynucleotides can have palindromic complementary sequences, for example,



(noting that a palindrome reads the same forwards as backwards as in the quartet ABBA). Single strands of this kind can potentially form loops with the 5' and 3' ends of a strand hybridizing and the rest (shown as ----) forming a loop (the dots indicating complementary base pairing):



Palindromic double strands of this kind can potentially form cruciform structures through the individual single strands forming looped out structures.

A variety of plant substances with planar, polycyclic, aromatic structures can intercalate with DNA, examples being the quinoline alkaloid camptothecin and the furanocoumarin phenolic psoralen (Table 12.1). A variety of plant-derived anthraquinones and naphthoquinones bind to DNA and it is notable that the structurally related anthraquinones mitoxantrone and adriamycin are clinically employed as anticancer drugs (Table 12.1). DNA-binding compounds that interfere with DNA repair, DNA replication and gene expression are cytotoxic and have potential as anticancer agents (see Chapter 9).

12.3 Polysaccharides and oligosaccharides

The external surface of the plasma membrane of a typical eukaryote cell is decorated with glycosylated lipids (glycolipids) and glycosylated proteins (glycoproteins). Plants produce a variety of proteins (lectins) that specifically bind to particular monosaccharides or oligosaccharides on the surface of target cells. Many of the target glycoproteins are involved in cellular signalling and hence lectins, like so many other plant defensive compounds, can interfere with target organism signal transduction. Many lectins are mitogenic, initiating signalling pathways culminating in cell division (Table 12.2).

The lectins can be conveniently divided into the legume (Fabaceae family) and non-legume proteins. The legume lectins are exemplified by the homodimeric or homotetrameric, Ca^{2+} - and Mn^{2+} -binding and mitogenic protein concanavalin A (jackbean phytagglutinin) from *Canavalia ensiformis* that binds Man, Glc and Man- α 1-Me.

A further subset of lectins is comprised of those lectins associated with type 2 RIP lectin-PAG complexes (see Chapter 9). The lectin moiety targets the toxic lectin-PAG complex to the plasma membrane, thus permitting PAG entry and target cell death through ribosome inactivation and inhibition of protein synthesis (see Chapter 9).

Fungi that are pathogenic on plants have polysaccharide cell walls and insect herbivores have gastrointestinal coverings as well as external integuments involving the polysaccharide chitin (mostly unbranched chains of $\beta(1 \rightarrow 4)$ -2-acetamido-2-deoxy-D-glucose, that is, $\beta(1 \rightarrow 4)$ -*N*-acetyl-D-glucosamine). Plants produce defensive CBPs that are a subset of the large class of plant lectins and contain closely related chitin-binding domains (CBDs) homologous to that in the "parent" CBP hevein. A well-known non-legume lectin is wheatgerm agglutinin, a mitogenic homodimer that specifically binds chitin, $(\text{GlcNAc})_2$ and NeuNAc (sialic acid).

Plants also produce structurally related enzymes (chitinases) that catalyse the hydrolysis of chitin (Table 12.2) and hence damage chitin-based insect integuments. Class I chitinases are basic enzymes with an *N*-terminal hevein-related CBD and vacuole-targeting C-terminal signals whereas Class II enzymes are acidic proteins lacking these CBD and vacuole-targeting domains. Class IV chitinases are variously basic and acidic extracellular proteins with

a hevein-related CBD. Class III and V chitinases differ further from the other chitinases. A special case is the *Urtica dioica* (stinging nettle) (Urticaceae) CBP that contains two *N*-terminal hevein-like CBDs and derives from a chitinase precursor, the chitinase domain being cleaved post-translationally (Table 12.2).

A final group of defensive polysaccharide-binding enzymes are the β -1,3-glucanases that hydrolyse β -1,3-glucans in fungal cell walls and are in subset PR-2 of PRPs, the synthesis of which is induced by fungal infection (Table 12.2). Cleavage of fungal β -1,3-glucans by β -1,3-glucanases also yields some small oligosaccharides that can be biologically active in themselves as fungal “elicitors” that switch on plant antifungal defences.

12.4 Phospholipids and membranes

All prokaryote and eukaryote organisms are bounded by cell membranes that are basically phospholipid bilayers decorated with peripheral (loosely bound) and integral (tightly embedded) proteins. A variety of plant triterpenoid saponins (Table 12.3) and defensive antifungal proteins (Table 12.4) can directly interact with phospholipids and are accordingly likely to act by interfering with cell membrane structure, integrity and permeability.

Plant non-specific LTPs are *c.* 9 kDa disulfide-rich antifungal proteins that bind phospholipids and act by compromising target fungal cell membrane integrity. LTPs have a three-dimensional structure involving a spiral, cup-like arrangement of α -helices generating a central hydrophobic phospholipid-binding cavity. The LTPs in the oxidized state (i.e. with S–S linkages intact as would occur in the oxidizing extracellular environment) can promote phospholipid exchange between membranes (e.g. between artificial phospholipid bilayers and mitochondrial membranes *in vitro*). However, reduction of these S–S linkages (e.g. by thiols such as 2-mercaptoethanol) abolishes this lipid transfer activity. LTPs may be involved in transport of waxy protective molecules to the plant cell surface as well as having an antifungal protective function.

Napins and napin-like proteins are *c.* 14 kDa, disulfide-rich, heterodimeric antifungal proteins that are structurally similar to the LTPs and which may function by interacting with membrane phospholipids. Indeed, the napins can be synergistic with plant defensive thionin proteins in damaging pathogenic fungi. Some napins have protease inhibitory activity as do some LTPs (Chapter 13).

Thionins are small, disulfide-rich plant defensive proteins that variously interact with membranes. The α - and β -thionins can be structurally distinguished from the γ -thionins (plant defensins). While α -thionins can directly interact with phospholipid bilayers to increase membrane permeability, defensins (γ -thionins) may induce permeability changes by interacting with particular proteins on the cell membrane surface. Thaumatin and the related osmotins are further plant defensive proteins that are believed to interact with target pathogen cell membranes or membrane components to cause membrane permeability changes. However, some thaumatin can bind to β -1,3-glucan polysaccharides and some also have β -1,3-glucanase activity (Table 12.4).

Table 12.1 Polynucleotide-binding compounds

Hormone effect compound (class)	Plant (family) part	Target (other target inhibited) / in vivo effects
Alkaloid		12.1a
Aristolactam β -D-Glc (phenanthrene lactam glycoside)	<i>Goniothalamus griffithii</i> (Annonaceae)	DNA (intercalation, GC-rich specificity), RNA & DNA triple helices
Berberine (= Umbellatine) (protoberberine isoquinoline)	<i>Coelocline</i> sp. (Annonaceae), <i>Berberis vulgaris</i> , <i>B.</i> sp., <i>Hydrastis canadensis</i> , <i>Mahonia</i> , <i>Nandina</i> (Berberidaceae), <i>Archangelica</i> (Menispermaceae), <i>Argemone</i> , <i>Chelidonium</i> , <i>Corydalis</i> (Papaveraceae) spp., <i>Coptis japonica</i> , <i>C. sinensis</i> , <i>C.</i> spp., <i>Thalictrum</i> (Ranunculaceae), <i>Evodia</i> , <i>Toddalia</i> , <i>Zanthoxylum</i> (Rutaceae) spp.	DNA ligand (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, 5HT ₂ -R, mACh-R, nACh-R, MLCK, PKA, PKC) [antibacterial, antimalarial, antipyretic, bitter stomachic, cytotoxic]
[Berberrubine] (protoberberine isoquinoline)	Generated during herbal medicinal processing of <i>Coptis chinensis</i> (goldthread) (Ranunculaceae)	DNA (intercalation) (TOPII)
Camptothecin (= Camptothecine) (quinoline)	<i>Mappia foetida</i> (Icacinaceae), <i>Camptotheca acuminata</i> (Nyssaceae) [bark, fruit, wood]	DNA (intercalation) (TOPI) [DNA damage per blocking TOPI-mediated cleavage & religation; antitumour, antileukaemic, apoptotic, cytotoxic]
Cephaeline (emetine isoquinoline)	<i>Alangium lamarkii</i> (Alangiaceae), <i>Cephaelis ibecacuanha</i> (Rubiaceae) [root]	DNA [antiamebic, emetic, expectorant]
Cryptolepine (indoloquinoline)	<i>Cryptolepis sanguinolenta</i> , <i>C. triangularis</i> (Asclepiadaceae)	DNA (intercalation) (TOPII) [stabilizes DNA-TOPII complex & promotes TOPII-mediated DNA cutting; antimalarial, hypotensive]
Deoxytubulosine (β -carboline benzoquinolizidine alkaloid)	<i>Alangium lamarkii</i> (Alangiaceae)	DNA (TS) [cytotoxic]
Dictamnine (= Dictamine) (furoquinoline)	<i>Adiscanthus fusciflorus</i> , <i>Aegle marmelos</i> , <i>Afraegle paniculata</i> , <i>Dictamnus albus</i> , <i>D. dasycarpus</i> , <i>Esenbeckia</i> spp., <i>Flindersia</i> spp., <i>Geigeria</i> spp., <i>Glycosmis</i> spp., <i>Haplophyllum</i> spp., <i>Ruta graveolens</i> (rue), <i>Zanthoxylum</i> spp. (Rutaceae)	DNA monoadduct formation (photochemical cross-linking) (V-Ca ²⁺ CH) [vasorelaxant; phototoxic dermatitis, photo-induced genotoxicity]; contributes to rue phototoxic phyto dermatitis
Dicentrine (aporphine isoquinoline)	<i>Hordeum vulgare</i> (barley) (Poaceae)	DNA (unwinds) (TOPII)
Ellipticine (indole); structure determined (1959) by Robert Burns Woodward (USA, Nobel Prize, Chemistry, 1965)	<i>Aspidosperma williamsii</i> , <i>A. subincarnum</i> , <i>Bleekeria vitiensis</i> , <i>Ochrosia elliptica</i> (Apocynaceae)	DNA (intercalation) (AChE, DNAH, DNAS, RNAS, TOPII) [antitrypanosomal, antitumour]

(continued)

Table 12.1 (Continued)

Hormone effect/ compound (class)	Plant (family) part/	Target (other target inhibited) / in vivo effects/
Emetine (= Cephaeline methyl ether) (emetine isoquinoline)	<i>Hedera helix</i> (ivy) (Araliaceae), <i>Cephaelis ipecacuanha</i> (ipecac), <i>C. acuminata</i> (Rubiaceae)	DNA (PS) [antiemoebic, anticancer, antiviral, cytotoxic, emetic, expectorant]
γ -Fagarine (= 8-Methoxydictamine) (furoquinoline)	<i>Aegle marmelos</i> , <i>Dictamnus angustifolius</i> , <i>Flindersia</i> spp., <i>Fagara coco</i> , <i>F.</i> spp., <i>Haplophyllum</i> spp., <i>Zanthoxylum</i> spp. (Rutaceae)	DNA monoadduct formation (photoactivated cross-linking) [anti-arrhythmic, photomutagenic, phototoxic]
Fagaranine (benzophenanthridine isoquinoline)	<i>Zanthoxylum zanthoxyloides</i> (Rutaceae) [root]	DNA (intercalation, major groove) (RT, TOPI) [antibacterial, antitumour, antiviral]
Harmaline (= 3,4-Dihydroharmine; Harmidine) (indole, carboline)	<i>Banisteria caapi</i> , <i>Banisteriopsis caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae)	DNA ligand (α 2A-R, BZ-R, MAO-A, NMDA-Glu-R) [ataxic, excitatory, hallucinogenic, increases cGMP, tremorigenic]
Harman (= Aribine; Loturine; 1-Methyl- β -carboline; Passiflorin) (β -carboline, indole); cooked food, pyrolysate of Tryptophan	<i>Phaseolus vulgaris</i> (Fabaceae) [suspension culture], <i>Passiflora edulis</i> , <i>P. incarnata</i> (passion flower) (Passifloraceae), <i>Sickingia rubra</i> (Rubiaceae), <i>Symplocos racemosa</i> (Symplocaceae), <i>Tribulus terrestris</i> (puncture vine), <i>Zygophyllum fabago</i> (Zygophyllaceae); smoke of tobacco, <i>Nicotiana tabacum</i> (Solanaceae)	DNA ligand (α 1A-R, BZ-R, \uparrow CAT-REL, 5HT2-R, L-type Ca^{2+} CH MAO-A, MAO-B, I2-R) [anti-depressant, co-mutagenic, convulsant, cytotoxic, genotoxic, motor depressant, toxic]
Harmine (= Banisterine; Leucoharmine; Telepathine; Yageine) (β -carboline, indole)	<i>Passiflora incarnata</i> (passion flower) (Passifloraceae), <i>Banisteria caapi</i> (Malpighiaceae), <i>Peganum harmala</i> , <i>Tribulus terrestris</i> (Zygophyllaceae)	DNA ligand (MAO) [CNS stimulant, hallucinogenic; Second World War Nazi Gestapo use as "truth drug"]
Harmol (β -carboline, indole)	<i>Hippophae rhamnoides</i> (Elaeagnaceae), <i>Passiflora incarnata</i> (passion flower) (Passifloraceae)	DNA ligand
Matadine (indoloquinoline, pyridinoindole)	<i>Strychnos gossweileri</i> (Loganiaceae)	DNA (intercalation) (TOPII) [stabilizes DNA-TOPII \rightarrow DNA cutting; antimalarial]
Melinonine F (indole, β -carboline)	<i>Strychnos usambarensis</i> (Loganiaceae)	DNA (intercalation) [1]
Neocryptolepine (indoloquinoline)	<i>Cryptolepis sanguinolenta</i> (Asclepiadaceae)	DNA (intercalation) (esp. GC-rich sequences) (TOPII) [stabilizes DNA-TOPII \rightarrow DNA cutting; antimalarial]
Normelinonine F (indole, β -carboline)	<i>Strychnos usambarensis</i> (Loganiaceae)	DNA (intercalation) [1]
Palmatine (= Calystigine) (benzophenanthridine isoquinoline)	<i>Jateorrhiza palmata</i> (Menispermaceae), <i>Berberis</i> spp., <i>Mahonia</i> spp. (Berberidaceae), Papaveraceae	DNA ligand (α 1A-R, α 2A-R, AChE, ATPase, BChE, ChAT diamine oxidase, 5HT2-R, mACh-R, nACh-R, PK, TOPI) [AI, antibacterial]

(continued)

Table 12.1 (Continued)

Hormone effect compound (class)	Plant (family) part	Target (other target inhibited) / in vivo effects
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregriana</i> , <i>Chelidonium majus</i> , <i>Sanguinaria canadensis</i> (Papaveraceae), <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	DNA (intercalation) (α 1A-R, α 2A-R, AChE, ATPase, BChE, CDPK, ChAT, diamine oxidase, 5HT2-R, mACh-R, nACh-R, MLCK, PKA, PKC) [AI, antibacterial, cytotoxic]
Serpentine (indoloquinoline)	<i>Catharanthus roseus</i> , <i>Rauwolfia serpentina</i> , <i>R. tetraphylla</i> (Apocynaceae)	DNA (intercalation) (nAChR, TOPII) [stabilizes DNA-TOPII \rightarrow DNA cutting; antihypertensive, antimalarial, antitumour]
Skimmianine (= 7,8- Dimethoxydictamine; β -Fagarine) (furoquinoline)	<i>Skimmia arborescens</i> , <i>S. japonica</i> , <i>Ruta</i> <i>graveolens</i> ; <i>Dictamnus</i> , <i>Esenbeckia</i> , <i>Fagara</i> , <i>Glycosmis</i> , <i>Haplophyllum</i> , <i>Murraya</i> , <i>Zanthoxylum</i> spp. (Rutaceae)	DNA monoadduct formation (photoactivated cross-linking) [anti-convulsant, photomutagenic, phototoxic]
Strychnopentamine (bis-indole)	<i>Strychnos usambarensis</i> (Loganiaceae) [root]	DNA (intercalation) (RNAs) [antiplasmodial, cytotoxic]
Tubulosine (indole)	<i>Cephaelis ipecacuanha</i> , <i>Pogonopus</i> <i>tubulosus</i> , <i>Psychotria granadensis</i> (Rubiaceae)	[amoebicidal, antitumour, cytotoxic, very toxic]
Usambarensine (indole)	<i>Strychnos usambarensis</i> (Loganiaceae) [root]	DNA (intercalation) (mAChR, nAChR, RNA synthesis) [anti-amoebic, anticancer, antiplasmodial, apoptotic, poison, apoptotic, toxic]
Phenolic		12.1p
Alizarinprimeveraside (anthraquinone glycoside)	<i>Rubia tinctorum</i> (Rubiaceae); R. tinctorum herbal medicine used for kidney & bladder stones	Metabolized to genotoxic & carcinogenic 1-hydroxy- anthraquinone
Aloe-emodin (= 1,8- Dihydroxy-3- (hydroxymethyl)-9,10- anthracenedione; Rhubarberone) (anthraquinone)	<i>Oroxylum indicum</i> (Bignoniaceae), <i>Cassia</i> <i>senna</i> (Fabaceae), <i>Aloe vera</i> , <i>A.</i> spp., <i>Asphodelus microcarpus</i> , <i>Xanthorrhoea</i> <i>australis</i> (Liliaceae), <i>Rheum</i> spp. (Polygonaceae), <i>Tectona grandis</i> [teak wood] (Verbenaceae)	DNA (eEF-2, TOPII)
Angelicin (= Isopsoralen) (furanocoumarin)	<i>Angelica archangelica</i> [root], <i>Heracleum</i> <i>laciniatum</i> , <i>H.</i> spp., <i>Selinum vaginatum</i> (Apiaceae), <i>Psoralea coryfolia</i> (Fabaceae), <i>Castanopsis indica</i> (Fagaceae), <i>Ficus nitida</i> (Moraceae)	DNA (intercalation) (photosensitive yielding monoadduct) [photosensitizing, spasmolytic]
α -Asarone (= <i>trans</i> - Asarone; <i>trans</i> -1,4,5- Trimethoxyphenylprop- 1-ene) (phenylpropene)	<i>Daucus carota</i> (Apiaceae), <i>Acorus</i> <i>calamus</i> (oil) (Araceae), <i>Asarum</i> <i>europaeum</i> (Aristolochiaceae), <i>Piper angustifolium</i> (Piperaceae)	Forms covalent DNA adduct [genotoxic, spasmolytic, sterilant]
β -Asarone (= <i>trans</i> - Asarone; <i>trans</i> -1,4,5- Trimethoxyphenylprop- 1-ene) (phenylpropene)	<i>Daucus carota</i> (Apiaceae), <i>Acorus</i> <i>calamus</i> (oil) (Araceae), <i>Asarum</i> <i>europaeum</i> (Aristolochiaceae), <i>Piper angustifolium</i> (Piperaceae)	Forms covalent DNA adduct [carcinogenic, genotoxic, spasmolytic]

(continued)

Table 12.1 (Continued)

Hormone effect/ compound (class)	Plant (family) part/	Target (other target inhibited) / in vivo effects/
Chrysazin (= Dantron; Danthron; 1,8- Dihydroxy-9,10- anthracenedione) (anthraquinone)	<i>Rheum palmatum</i> (Polygonaceae) [root], <i>Cinchona ledgeriana</i> (Rubiaceae), <i>Xyris semifuscata</i> (Xyridaceae) [leaf, stem]	DNA (TOPII) (CDPK, MLCK, PKA, PKC, TOPII) [cathartic, genotoxic, immunosuppressive, mutagenic, purgative]
Elemicin (phenylpropene)	<i>Daucus carota</i> (carrot) (Apiaceae), <i>Aniba</i> sp. (Annonaceae), <i>Canarium</i> <i>commune</i> , <i>C. indicum</i> (Burseraceae), <i>Croton nepetaefolius</i> (Euphorbiaceae), <i>Dalbergia spruceata</i> , <i>Monopteryx uauca</i> (Fabaceae), <i>Cymbopogon procerus</i> (Poaceae), <i>Melaleuca bracteata</i> (Myrtaceae), <i>Boronia pinnata</i> (Rutaceae)	Forms covalent DNA adduct [genotoxic, PAI]
Ellagic acid (= Benzoic acid; Lagistase) (phenolic acid lactone)	Widespread; hydrolysis product of ellagitannins e.g. Sanguin H-6; <i>Psidium guajava</i> (guava) (Myrtaceae), <i>Fragaria</i> spp. (strawberry) (Rosaceae)	DNA (intercalation) (TOPI, TOPII) [anticarcinogen, haemostatic]
Emodin (= Archin; Frangula emodin; Frangula acid; Rheum emodin; 1,3,8- Trihydroxy-6-methyl- 9,10-anthracenedione) (anthraquinone)	<i>Senna obtusifolia</i> (Fabaceae), <i>Psorospermum</i> <i>glaberrimum</i> (Guttiferaceae), <i>Myrsine</i> <i>africana</i> (Myrsinaceae), <i>Rumex</i> spp., <i>Rheum</i> spp. (Polygonaceae), <i>Ventilago calyculata</i> , <i>Rhamnus frangula</i> (Rhamnaceae), lichen; glycosides in <i>Rheum moorcroftianum</i> , <i>Polygonum</i> <i>cuspidatum</i> (Polygonaceae), <i>Rhamnus cathartica</i> , <i>R. frangula</i> , <i>R. purshiana</i> (Rhamnaceae)	DNA (CDC2, CKI, CKII, CDPK, MLCK, PKA, PKC, p60 ^{src} TK, RTK p56 ^{lck} , TOPII) [cathartic, cytotoxic, genotoxic, mutagenic]
Estragole (= <i>p</i> - Allylanisole; <i>p</i> - Methoxyphenylprop-2- ene) (phenylpropene)	<i>Foeniculum vulgare</i> (fennel) (Apiaceae), <i>Tagetes florida</i> (Asteraceae), <i>Croton</i> sp. (Euphorbiaceae), <i>Agastache</i> spp.; (Lamiaceae), <i>Pinus</i> spp. (Pinaceae)	Forms covalent DNA adduct [genotoxic]
1-Hydroxy- anthraquinone (anthraquinone)	<i>Damnacanthus indicus</i> , <i>Morinda officinalis</i> , <i>Rubia tinctorum</i> (Rubiaceae); <i>R. tinctorum</i> herbal medicine used for kidney & bladder stones	Genotoxic (causing DNA damage) [carcinogenic, genotoxic]
8-Isoamlylenoxypsoralen (= Imperatorin) (furanocoumarin)	<i>Angelica</i> sp., <i>Heracleum</i> , <i>Pastinaca</i> spp. (Apiaceae), <i>Aegle marmelos</i> , <i>Citrus meyeri</i> (Rutaceae) [seed], <i>Fragaria</i> spp. (Rosaceae)	DNA (intercalation) (photosensitive yielding biadduct cross-links) [dermatitic, mutagenic, phototoxic]
Lucidin (anthraquinone)	<i>Morinda citrifolia</i> , <i>Rubia tinctorum</i> (Rubiaceae); <i>R. tinctorum</i> herbal medicine used for kidney & bladder stones	DNA damage [genotoxic & carcinogenic]
Lucidinprimeveraside (anthraquinone glycoside)	<i>Rubia tinctorum</i> (Rubiaceae); <i>R. tinctorum</i> herbal medicine used for kidney & bladder stones	Metabolized to genotoxic & carcinogenic Lucidin

(continued)

Table 12.1 (Continued)

Hormone /effect/ compound (class)	Plant (family) / part/	Target (other target inhibited) / in vivo effects/
5-Methoxypsoralen (= Bergapten; Bergapten; Heraclin; Majudin) (furanocoumarin)	<i>Ficus carica</i> [fig leaf] (Moraceae), <i>Citrus bergamia</i> [oil of bergamot], <i>Fagaria</i> spp. [oil, fruit], <i>Ruta graveolens</i> (Rutaceae), <i>Lycopersicon esculentum</i> [tomato leaf] (Solanaceae), <i>Ammi</i> sp., <i>Levisticum</i> sp., <i>Angelica</i> sp., <i>Petroselinum</i> sp., <i>Pimpinella</i> sp., <i>Seseli</i> sp. (Apiaceae)	DNA (intercalation) (photosensitive yielding biadduct cross-links) [dermatitic, mutagenic, phototoxic, PUVA therapy for leucoderma & psoriasis]
8-Methoxypsoralen (= Ammoidin, Methoxsalen; Xanthotoxin) (furanocoumarin)	<i>Ammi majus</i> [seed], <i>Levisticum</i> sp., <i>Angelica archangelica</i> [seed], <i>A. officinalis</i> [root], <i>Apium graveolens</i> [fungus infection-induced phytoalexin], <i>Heracleum sphondylium</i> [root, aerial], <i>Pastinaca sativa</i> (Apiaceae), <i>Fagaria</i> spp. [oil, fruit], <i>Ruta graveolens</i> (Rutaceae)	DNA (intercalation) (photosensitive yielding biadduct cross-links) [dermatitic, mutagenic, phototoxic, PUVA therapy for leucoderma & psoriasis]
Methyleugenol (= 4,4-Dimethoxyphenylprop-2-ene) (phenylpropene)	<i>Ocimum basilicum</i> (basil) (Lamiaceae), <i>Myristica fragrans</i> (nutmeg) (Myristicaceae) [oil], <i>Pimenta racemosa</i> (Myrtaceae)	Forms covalent DNA adduct [genotoxic]; basil-rich pesto sauce risk?
2-Methyl-1,4-naphthoquinone (naphthoquinone)	<i>Juglans regia</i> (walnut) (Juglandaceae)	DNA (intercalation)
Myristicin (= 5-Allyl-1-methoxy-2,3-(methylenedioxy)-benzene) (phenylpropene)	<i>Apium graveolens</i> , <i>Daucus carota</i> , <i>Levisticum scoticum</i> , <i>Pastinaca sativa</i> , <i>Petroselinum crispum</i> (Apiaceae), <i>Cinnamomum glanduliferum</i> (Lauraceae), <i>Orthodon</i> spp. (Lamiaceae), <i>Myristica fragrans</i> (Myristicaceae) [nutmeg oil]	Weak DNA covalent adduct formation (MAO) [PAI, psychotropic]
Plumbagin (= 5-Hydroxy-2-methyl-1,4-naphthoquinone) (naphthoquinone)	<i>Dionaea muscipula</i> , <i>Drosera rotundifolia</i> , <i>D.</i> spp. (Droseraceae), <i>Aristea</i> spp., <i>Sisyrinchium</i> spp., <i>Sparaxis</i> spp. (Iridaceae) [root], <i>Diospyros</i> spp. (Ebenaceae) [bark], <i>Pera ferruginea</i> (Euphorbiaceae) [bark], <i>Plumbago europaea</i> (Plumbaginaceae) [root]	DNA (intercalation) (DNA, MLCK, PKA, TOPI, TOPII) [anticancer, molluscicidal]
Psoralen (= Ficusin) (furanocoumarin)	<i>Coronilla glauca</i> , <i>Psoralea</i> spp. (Fabaceae) [seed], <i>Ficus carica</i> (Moraceae), <i>Phebalium argenteum</i> [oil], <i>Xanthoxylum flavum</i> [wood] (Rutaceae)	DNA (intercalation) (photosensitive yielding biadduct cross-links) [antimycobacterial, antiviral, photosensitizing]
Psorospermin (xanthone)	<i>Psorospermum</i> spp. (Guttiferae) [root]	DNA (intercalation) (TOPII) [antileukaemic, antitumour]
Rubiadin (anthraquinone)	<i>Rubia tinctorum</i> (Rubiaceae); R. tinctorum herbal medicine used for kidney & bladder stones	DNA damage [genotoxic & carcinogenic]
Rubiadinprimeveraside (anthraquinone glycoside)	<i>Rubia cordifolia</i> , <i>tinctorum</i> (Rubiaceae); R. tinctorum herbal medicine used for kidney & bladder stones	Metabolized to genotoxic & carcinogenic Rubiadin

(continued)

Table 12.1 (Continued)

Hormone /effect/ compound (class)	Plant (family) / part/	Target (other target inhibited) / in vivo effects/
Safrole (= Allylcatechol methylene ether; 3',4'- Methylenedioxy phenylprop2-ene; Shikimol) (phenylpropene)	<i>Cinnamomum</i> sp., <i>Ocotea</i> sp., <i>Sassafras albidum</i> (oil) (Lauraceae), <i>Areca catechu</i> (betel nut) (Palmaceae); species of genera <i>Aniba</i> (Annonaceae), <i>Nemuaron</i> (Atherospermataceae), <i>Juniperus</i> (Cupressaceae), <i>Illicium</i> (Illiciaceae), <i>Ocimum</i> (Lamiaceae), <i>Magnolia</i> (Myoporaceae), (Magnoliaceae), <i>Eremophila Myristica</i> (Myristicaceae)	Forms covalent DNA adduct [anticonvulsant, hepatocarcinogen, PAI]; chewing betel quid yields c. 0.4 mM Safrole in saliva & oral carcino- genesis risk (high nocturnal melatonin protects)
Swertifrancheside (= 1,5,8-Trihydroxy-3- methoxy-7-(5',7',3'',4''- tetrahydroxy-6'-C-β-D- glucopyranosyl-4'-oxy- 8'-flavyl)-xanthone) (flavone-xanthone C-glycoside)	<i>Swertia franchetiana</i> (Gentianaceae)	DNA (RT)
4,5',8- Trimethylpsoralen (= TMP; Trioxsale; Trioxalen) (furanocoumarin)	<i>Apium graveolens</i> (celery) (Apiaceae) [fungal infection-induced phytoalexin]	DNA (intercalation) (photosensitive yielding cross- links) [dermatitic]
Terpene		12.1t
Hymenoxon (seco-pseudoguaianolide sesquiterpene lactone)	<i>Helenium hoopesii</i> , <i>Hymenoxys odorata</i> (Asteraceae)	DNA (bifunctional alkylating agent) [toxic]
Jatrophone (jatrophone diterpene)	<i>Jatropha elliptica</i> , <i>J. gossypifolia</i> (Euphorbiaceae)	DNA (Glu-R)
Parthenin (= Parthenicin) (pseudoguaianolide sesquiterpene lactone)	<i>Ambrosia psilostachya</i> , <i>Iva nevadensis</i> , <i>Parthenium hysterophorus</i> (Asteraceae)	Causes chromosomal chromatid break induction [antifeedant, dermatitic, genotoxic]
Tingenone (friedllane triterpene)	<i>Crossopetalum uragoga</i> , <i>Maytenus</i> spp., <i>Schaefferia cuneifolia</i> (Celastraceae)	DNA (DNAS, RNAS, PS)
Other		12.1o
Cycasin (= Methylazoxy-methanol- β-D-glucoside; CH ₃ - N ⁺ (O ⁻) = N-CH ₂ -O- glucose)	<i>Cycas revoluta</i> , <i>C.</i> spp. (cycad sago palm) (Cycadaceae)	Yields genotoxic Methylazoxymethanol
GAP 31 (polypeptide)	<i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (a RIP) [anti-HIV-1 (0.3 nM), antitumour]
[GAP 31 V5-K42] (polypeptide)	Synthetic peptide based on GAP 31 (RIP) from <i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (RI) [anti-HIV-1 (21-35)]
[[C[GAP 31 V5- K42]] ₂] (disulfide-linked dimer) (polypeptide)	Synthetic peptide based on GAP 31 (RIP) from <i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (RI) [anti-HIV-1 (19-36)]

(continued)

Table 12.1 (Continued)

Hormone effect/ compound (class)	Plant (family) part	Target (other target inhibited) / in vivo effects/
[GAP 31 K10-K42] (polypeptide)	Synthetic peptide based on GAP 31 (RIP) from <i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (RI; potent protein precipitant) [anti-HIV-1 (22–36)]
[GAP 31 K10-N33] (polypeptide)	Synthetic peptide based on GAP 31 (RIP) from <i>Gelonium multiflorum</i> (Euphorbiaceae) [seed]	DNA & RNA binding (weak (RI) [anti-HIV-1 (700)]
Methylazoxymethanol (azoxyalkane)	From deglycosylation of Cycasin from <i>Cycas</i> species (cycad sago palm) (Cycadaceae)	DNA reaction & breakage [carcinogenic, DNA- damaging, genotoxic, mutagenic, toxic, teratogenic]
Mimosine (= Leucaenol) (pyridinone amino acid)	<i>Leucaena leucocephala</i> (jumbie bean), <i>Mimosa pudica</i> (sensitive plant) (Fabaceae) [leaf, seed] (leaves close on touch)	DNA – binding & breakage by Mimosine-(Fe(II) (FR formation) [depilatory, goitrogenic, teratogenic]
9-Octadecynoic acid (acetylene)	<i>Schoefia californica</i> (Olacaceae)	DNA (weak)
Ptaquiloside (= Pterosin B glucoside) (norsesquiterpene glycoside)	<i>Pteridium aquilinum</i> (bracken fern) (Dennstaedtiaceae); young sprouts (“fiddleheads”) eaten in New Brunswick & elsewhere in maritime Canada & USA – toxic if insufficiently cooked	DNA alkylation & breakage; yields aglycone Pterosin B [carcinogenic, toxic]
Pterosin B (norsesquiterpene)	<i>Pteridium aquilinum</i> (bracken fern) (Dennstaedtiaceae); young sprouts (“fiddleheads”) unwisely eaten in maritime Canada	DNA alkylation & breakage [carcinogenic, toxic]
Non-plant reference		12.1n
[Ascidiemin] (pentacyclic alkaloid)	<i>Cystodytes dellechiaiei</i> (ascidian)	DNA intercalator (TOPII) [stabilizes DNA–TOPII complex & promotes TOPII- mediated DNA cutting; cytotoxic]
[Actinomycin D] (cyclic peptide)	<i>Streptomyces chrysomallus</i> (fungus) (Actinomycete)	DNA (intercalation), DNAS, RNAS (TOPII) [antineoplastic]
[Actinomycin C1] (cyclic peptide)	<i>Streptomyces chrysomallus</i> (fungus) (Actinomycete)	DNA (intercalation), DNAS, RNAS (DNAH) [antineoplastic]
[Amsacrine (= 4’-(9- Acridinylamino)methan- sulfon- <i>m</i> -anisidine; <i>N</i> - [4-(9-Acridinylamino)- 3-methoxyphenyl]- methanesulfonamide; <i>m</i> -AMSA)] (arylsulfonamide aminoacridine)	Synthetic	DNA (intercalation), DNAS, RNAS (TOPII) [antineoplastic, antiviral, cytostatic, cytotoxic, immunosuppressive]
[Coralyne] (protoberberine alkaloid)	Synthetic	DNA (TOPI) [antileukaemic, cytotoxic]

(continued)

Table 12.1 (Continued)

Hormone /effect/ compound (class)	Plant (family) /part/	Target (other target inhibited) /in vivo effects/
[Daunomycin (= Daunorubicin; Daunomycinone daunosamine)] (anthracycline)	<i>Streptomyces peucetius</i> (fungus) (Actinomycete) cf. Doxorubicin	DNA (major groove intercalation) (DNAH, DNAS, RNAS, TOPII) [antineoplastic, cytotoxic]
[Doxorubicin (= Adriamycin; Adriamycinone daunosamine)] (anthracycline)	<i>Streptomyces peucetius</i> (fungus) (Actinomycete) cf. Daunomycin; major clinical anticancer drug	DNA (intercalation) (PK, TOPII) [antineoplastic, cytotoxic]
[Ethidium bromide (= 2,7-Diamino-10-ethyl- 9-phenyl-phenanthridinium bromide)] (phenanthridinium)	Synthetic; used for visualization in UV of electrophoretically separated DNA fragments in molecular biology	DNA (intercalation) (DNAH, DNAS, RNAS, RT)
[Ethoxidine] (benzophenanthridine isoquinoline)	Synthetic derivative of Fagaronine	DNA intercalator (major groove, A-T sequences) (TOPI) [cytotoxic]
[Heliquinomycin] (glycosylated rubromycin)	<i>Streptomyces</i> sp. (fungus) (Actinomycete)	DNA (DNAH, DNAS, RNAS, TOPI, TOPII)
[9-Hydroxyellipticine] (indole)	Semi-synthetic from Ellipticine	DNA (intercalation, major groove, GC-rich preference)
[4'-Hydroxymethyl- 4,5',8-trimethylpsoralen = HMT] (furanocoumarin)	Semi-synthetic cf. 4,5',8- Trimethylpsoralen	DNA (intercalation), RNA (intercalation) (photosensitive yielding cross-links)
[Mitoxantrone] (anthraquinone)	Synthetic anthraquinone (cf. Emodin); major clinical anticancer drug	DNA (intercalation), DNAS, RNAS (MLCK, PKA, PKC) [antineoplastic]
[Netropsin] (guanidinoacetamido pyrrole)	<i>Streptomyces netropsis</i> (fungus) (Actinomycete)	DNA (non-intercalative)
[Nogalamycin] (glycosylated anthraquinone)	<i>Streptomyces nogalater</i> (fungus) (Actinomycete)	DNA (intercalation), RNAS (DNAH)
Norharman (indole)	Animal	DNA ligand (BZ-R, MAO)
[Quinacrine = Mepacrine] (aminoacridine)	Synthetic	DNA & triple-stranded RNA (intercalation) [anthelmintic, antimalarial, teniacide]

Table 12.2 Lectins and polysaccharide hydrolases

Compound class	Plant (family) /part/	Target (other target inhibited) /in vivo effects/
Lectins		12.2
Legume (Fabaceae) lectins		12.2A
<i>Abrus</i> Agglutinin (134kDa α_4 homotetramer)	<i>Abrus precatorius</i> (abrin, jequirity bean) (Fabaceae) [seed]	Gal, GalNAc

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) [part]	Target (other target inhibited) / in vivo effects/
<i>Abrus</i> Abrins (toxic lectins) (~60 kDa; S-S-linked ~30 kDa subunits)	<i>Abrus precatorius</i> , <i>A. pulchellus</i> (abrin, jequirity bean) (Fabaceae) [seed]	Gal [apoptotic]
<i>Amphicarpea</i> lectin (135 kDa; tetrameric glycoprotein)	<i>Amphicarpea bracteata</i> (hog peanut) (Fabaceae) [seed]	Gal, GalNAc [25]; adenine [0.8]
<i>Arachis</i> lectin (agglutinin) (120 kDa; homotetramer; Ca ²⁺ , Mn ²⁺)	<i>Arachis hypogaea</i> (peanut) (Fabaceae) [seed]	Gal, Glc, Man, β-Gal(1 → 3)GalNAc
<i>Bandeiraea</i> lectin BS-I (114 kDa; homotetramer)	<i>Bandeiraea</i> (<i>Griffonia simplicifolia</i>) (Fabaceae) [seed]	Gal, α-GalNAc
<i>Bandeiraea</i> lectin BS-I-A ₄ (114 kDa; homotetramer)	<i>Bandeiraea</i> (<i>Griffonia simplicifolia</i>) (Fabaceae) [seed]	GalNAc
<i>Bandeiraea</i> lectin BS-I-B ₄ (114 kDa; homotetramer)	<i>Bandeiraea</i> (<i>Griffonia simplicifolia</i>) (Fabaceae) [seed]	Gal
<i>Bandeiraea</i> lectin BS-II (113 kDa; homotetramer)	<i>Bandeiraea</i> (<i>Griffonia simplicifolia</i>) (Fabaceae) [seed]	GlcNAc
<i>Bauhinia</i> lectin (195 kDa; tetramer; glycoprotein; 29 kDa aglycone)	<i>Bauhinia purpurea</i> (orchid tree, camel's foot tree) (Fabaceae) [seed]	β-Gal(1 → 3)GalNAc [mitogenic]
<i>Boweringia</i> lectin (50 kDa; α ₂ β-S-S-β tetramer; Ca ²⁺ , Mn ²⁺)	<i>Boweringia milbraedii</i> (Fabaceae) [seed]	Man, Glc
<i>Caragana</i> lectin (60 kDa homodimer; 120 kDa homotetramer)	<i>Caragana arborescens</i> (Siberian pea tree) (Fabaceae) [seed]	GalNAc, Man, Glc
<i>Cicer</i> lectin (44 kDa homodimer)	<i>Cicer arietinum</i> (chick pea) (Fabaceae) [seed]	Fetuin
<i>Codium</i> lectin (60 kDa homotetramer)	<i>Codium fragile</i> (marine alga)	GalNAc
<i>Canavalia ensiformis</i> Concanavalin A (jackbean phytagglutinin) (108 kDa homotetramer; 54 kDa homodimer; Ca ²⁺ , Mn ²⁺)	<i>Canavalia ensiformis</i> (jack bean) (Fabaceae) [seed]	Man, Glc, Man-α-1-Me
<i>Canavalia gladiata</i> lectin (multimer)	<i>Canavalia gladiata</i> (Japanese jack bean) (Fabaceae) [seed]	Man, Glc
<i>Cratylia</i> lectin (50 kDa α ₃ ; 100 kDa α ₄ ; Ca ²⁺ , Mn ²⁺)	<i>Cratylia floribunda</i> (Fabaceae) [seed]	Man, Glc
<i>Crotalaria</i> lectin (multimer)	<i>Crotalaria juncea</i> (sunn hemp) (Fabaceae)	Gal, GalNAc
<i>Cytisus scoparius</i> lectin (54 kDa α ₂ ; 108 kDa α ₄ ; Ca ²⁺ , Mn ²⁺)	<i>Cytisus scoparius</i> (Scotch broom) (Fabaceae) [seed]	GalNAc, Gal
<i>Cytisus sessifolius</i> lectin (54 kDa; α ₂ homodimer; Ca ²⁺ , Mn ²⁺)	<i>Cytisus sessifolius</i> (broom) (Fabaceae) [seed]	Gal, lactose

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) / part/	Target (other target inhibited) / in vivo effects/
<i>Datura</i> lectin (86 kDa; $\alpha_2\beta_2$ heterotetramer)	<i>Datura stramonium</i> (jimson weed, thorn apple) (Solanaceae) [seed]	(GlcNAc) ₂
<i>Dioclea guianensis</i> lectin (51 kDa dimer; 102 kDa tetramer; Ca ²⁺ , Mn ²⁺)	<i>Dioclea guianensis</i> (Fabaceae) [seed]	Man, Glc
<i>Dioclea grandiflora</i> lectin (102 kDa; ($\alpha\beta\gamma$) ₁ tetramer & $\alpha = \beta - \gamma$; Ca ²⁺ , Mn ²⁺)	<i>Dioclea grandiflora</i> (Fabaceae) [seed]	Man, Glc
<i>Dolichos biflorus</i> (140 kDa homotetramer)	<i>Dolichos biflorus</i> (horse gram) (Fabaceae) [seed]	GalNAc, Gal
<i>Dolichos lab lab</i> lectin (140 kDa homotetramer)	<i>Dolichos lab lab</i> (field bean) (Fabaceae) [seed]	GalNAc, Gal
<i>Erythrina corallodendron</i> lectin (60 kDa homodimer)	<i>Erythrina corallodendron</i> (coral tree) (Fabaceae) [seed]	β -Gal(1 \rightarrow 4)GlcNAc, β -Gal(1 \rightarrow 4)Glc
<i>Erythrina cristagalli</i> lectin (57 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Erythrina cristagalli</i> (Fabaceae) [seed]	β -Gal(1 \rightarrow 4)GlcNAc
<i>Glycine</i> lectins (e.g. soya bean agglutinin, SBA) (110 kDa homotetramer)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	GalNAc, β -Gal(1 \rightarrow 4)GlcNAc oligosaccharide, adenine (at 1–10) [mitogenic]
<i>Griffonia</i> lectin (54 kDa; dimer; glycoprotein; Ca ²⁺ , Mn ²⁺)	<i>Griffonia simplicifolia</i> (Fabaceae) [seed]	GalNAc, Gal, GlcNAc, oligosaccharide
<i>Laburnum</i> seed lectin (Ca ²⁺ , Mn ²⁺)	<i>Laburnum alpinum</i> (Scotch laburnum) (Fabaceae) [seed]	Di- <i>N</i> -acetylchitobiose
<i>Lathyrus</i> spp. lectins (42 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Lathyrus</i> spp. (peas) (Fabaceae) [seed]	α -Man, Glc
<i>Lathyrus ochrus</i> lectins LOLI, LOLII (42 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Lathyrus ochrus</i> (yellow flowered pea) (Fabaceae) [seed]	α -Man, Glc, oligosaccharide
<i>Lathyrus odoratus</i> lectin (42 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Lathyrus odoratus</i> (sweet pea) (Fabaceae) [seed]	α -Man [mitogenic]
<i>Lathyrus sphaericus</i> lectin (55 kDa α_2 homodimer)	<i>Lathyrus sphaericus</i> (yellow vetchling) (Fabaceae) [seed]	α -Man [mitogenic]
<i>Lens</i> lectin (49 kDa; homodimer; glycoprotein; Ca ²⁺ , Mn ²⁺)	<i>Lens culinaris</i> (lentil) (Fabaceae) [seed]	α -Man, Glc [mitogenic]
<i>Lonchocarpus</i> lectin (multimer)	<i>Lonchocarpus capassa</i> (Fabaceae) [seed]	GalNAc, Gal
<i>Lotus</i> lectin (multimeric; Ca ²⁺ , Mn ²⁺)	<i>Lotus tetragonolobus</i> (<i>Tetragonolobus purpurea</i>) (winged pea) (Fabaceae) [seed]	1-Fucose [mitogenic]
<i>Maackia</i> lectin (130 kDa; $\alpha\beta$ heterodimer)	<i>Maackia amurensis</i> (Fabaceae) [seed]	Oligosaccharide, sialic acid [mitogenic]
<i>Medicago</i> lectins (multimers; Ca ²⁺ , Mn ²⁺)	<i>Medicago sativa</i> (alfalfa), <i>M.</i> spp. (Fabaceae) [seed]	Gal, GalNAc
<i>Onobrychis</i> lectin (53 kDa; homodimer)	<i>Onobrychis viciifolia</i> (sainfoin) (Fabaceae) [seed]	Man, Glc
<i>Phaseolus coccineus</i> lectin (112 kDa homotetramer)	<i>Phaseolus coccineus</i> (scarlet runner bean) (Fabaceae)	GalNAc

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) [part]	Target (other target inhibited) / in vivo effects/
<i>Phaseolus limensis</i> lectin (247 kDa multimer)	<i>Phaseolus limensis</i> (lima bean) (Fabaceae)	GalNAc
<i>Phaseolus lunatus</i> lectins (124 kDa homotetramers; glycoproteins; Ca ²⁺ , Mn ²⁺)	<i>Phaseolus lunatus</i> (lima bean) (Fabaceae)	GalNAc
<i>Phaseolus vulgaris</i> lectins (PHA-E, PHA-L, PHA-P, PHA-M) (tetramers)	<i>Phaseolus vulgaris</i> (red kidney bean) (Fabaceae)	Oligosaccharides; <i>P. vulgaris</i> leuko-agglutinin (PHA-L) binds adenine (at 1–10)
<i>Phaseolus vulgaris</i> lectin homologue Arcelin 5 α (monomeric)	<i>Phaseolus vulgaris</i> (red kidney bean) (Fabaceae)	No carbohydrate ligand identified
<i>Pisum</i> lectin (49 kDa; $\alpha_2\beta_2$ heterotetramer; Ca ²⁺ , Mn ²⁺)	<i>Pisum sativum</i> (garden pea) (Fabaceae)	Man
<i>Psophocarpus</i> lectin (35 kDa)	<i>Psophocarpus tetragonolobus</i> (winged bean) (Fabaceae) [seed]	Gal, GalNAc
<i>Robinia</i> lectin (multimer)	<i>Robinia pseudoacacia</i> (black locust) (Fabaceae) [seed]	Oligosaccharide
<i>Sophora</i> lectin (133 kDa homotetramer)	<i>Sophora japonica</i> (Japanese pagoda tree) (Fabaceae) [bark, seed]	Man, Glc, GalNAc
<i>Trifolium</i> lectin (multimer)	<i>Trifolium repens</i> (white clover) (Fabaceae) [seed]	2-Deoxyglucose
<i>Ulex</i> lectin UEA I (68 kDa)	<i>Ulex europaeus</i> (furze, gorse) (Fabaceae) [seed]	α -L-Fucose
<i>Ulex</i> lectin UEA II (68 kDa)	<i>Ulex europaeus</i> (furze, gorse) (Fabaceae) [seed]	(GlcNAc) ₂
<i>Vatairea</i> seed lectin (104 kDa; homotetramer; glycoprotein; Ca ²⁺ , Mn ²⁺)	<i>Vatairea macrocarpa</i> (Fabaceae)	Gal
<i>Vicia cracca</i> lectin ($\alpha\beta$ multimer)	<i>Vicia cracca</i> (common vetch) (Fabaceae) [seed]	Man, Glc, Gal, GalNAc [mitogenic]
<i>Vicia faba</i> lectin (50 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Vicia faba</i> (broad bean, fava bean) (Fabaceae) [seed]	Man, Glc [mitogenic]
<i>Vicia graminea</i> lectin (multimer)	<i>Vicia graminea</i> (Fabaceae) [seed]	Oligosaccharide
<i>Vicia sativa</i> lectin (40 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Vicia sativa</i> (Fabaceae) [seed]	Man, Glc [mitogenic]
<i>Vicia villosa</i> lectin (139 kDa tetramer)	<i>Vicia villosa</i> (hairy vetch) (Fabaceae) [seed]	GalNAc
<i>Vicia villosa</i> lectin A ₄ (134 kDa tetramer)	<i>Vicia villosa</i> (hairy vetch) (Fabaceae) [seed]	GalNAc
<i>Vicia villosa</i> lectin B ₄ (143 kDa tetramer)	<i>Vicia villosa</i> (hairy vetch) (Fabaceae) [seed]	GalNAc
<i>Vigna</i> lectin (160 kDa homotetramer)	<i>Vigna radiata</i> (mung bean) (Fabaceae) [seed]	Gal
<i>Wisteria</i> lectin (68 kDa homodimer)	<i>Wisteria floribunda</i> (Japanese wisteria) (Fabaceae) [seed]	GalNAc, oligosaccharide

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) part	Target (other target inhibited) / in vivo effects
Non-legume lectins		12.2B
[<i>Agaricus</i> lectin] (59 kDa)	<i>Agaricus bisporus</i> (mushroom) (fungus)	β -Gal(1 \rightarrow 3)GalNAc
<i>Allium porrum</i> lectin (18 kDa)	<i>Allium porrum</i> (leek) (Alliaceae)	Man
<i>Allium sativum</i> lectin (18 kDa)	<i>Allium sativum</i> (garlic) (Alliaceae)	Man
<i>Aloe</i> lectin (35 kDa; homotetramer)	<i>Aloe arborescens</i> (Asphodelaceae)	Man
<i>Arabidopsis</i> lectin-homologues (genes) (17–39 kDa)	<i>Arabidopsis thaliana</i> (mouse-ear cress) (Brassicaceae)	
<i>Artocarpus</i> lectin Jacalin (65 kDa; α (15 kDa), β (2 kDa) tetramer)	<i>Artocarpus heterophyllus</i> (jackfruit) (Moraceae) [seed]	α -Gal \rightarrow OMe [mitogenic]
<i>Artocarpus</i> lectin (jacalin type) (42 kDa; homotetramer)	<i>Artocarpus integrifolia</i> (jackfruit) (Moraceae) [seed]	α -Gal \rightarrow OMe [mitogenic]
<i>Arum</i> lectin (25 kDa)	<i>Arum maculatum</i> (Araceae) [tuber]	
<i>Calystegia</i> lectin (jacalin type) (16 kDa)	<i>Calystegia sepium</i> (hedge bindweed) (Convolvulaceae) [rhizome]	Maltose, Man [mitogenic]
<i>Cinnamomum</i> Cinnamomin (~60 kDa; A[30 kDa PAG toxin] S–S-linked to B [~30 kDa lectin])	<i>Cinnamomum camphora</i> (Lauraceae) [seed]	A: PAG (RNA, adenine nucleotides except 5'-ATP); B: lectin; A-B: PSI (IC ₅₀ 14 nM) [toxic (insect larvae)]
<i>Cinnamomum</i> Porrectin (64.5 kDa; A[31 kDa PAG toxin] S–S-linked to B [34 kDa glycoprotein lectin])	<i>Cinnamomum porrectum</i> (Lauraceae) [seed]	A: PAG (rat rRNA A4324 in R/S domain); B: lectin; PSI (RRL) [toxic; PSI]
<i>Citrus</i> lectin (29 kDa)	<i>Citrus paradisi</i> (grapefruit) (Rutaceae)	
<i>Convolvulus</i> lectin (16 kDa)	<i>Convolvulus arvensis</i> (field bindweed) (Convolvulaceae)	Man
<i>Crocus</i> lectins (agglutinins) (29 kDa)	<i>Crocus sativus</i> , <i>C. vernus</i> (Iridaceae)	Man
<i>Cucurbita</i> phloem lectin (24 kDa; $\alpha\beta$ heterodimer)	<i>Cucurbita maxima</i> (pumpkin, winter squash) (Cucurbitaceae)	
<i>Cymbidium</i> lectin (18 kDa)	<i>Cymbidium</i> sp. (Orchidaceae)	Man
<i>Epipactus</i> lectin (agglutinin) (18 kDa)	<i>Epipactus helleborine</i> (broadleaved helleborine) (Orchidaceae)	Man
<i>Euonymus</i> lectin (166 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Euonymus europaeus</i> (scotch elm, spindle tree) (Celastraceae) [seed]	α -Gal(1 \rightarrow 3)Gal [mitogenic]
<i>Galanthus</i> lectin (52 kDa; homotetramer)	<i>Galanthus nivalis</i> (snowdrop) (Liliaceae); Arpad Pusztai (UK) showed changed gastric mucosa in rats fed GM potato expressing <i>Galanthus</i> lectin	α -Man (non-reducing end), α -Man 1-Me

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) [part]	Target (other target inhibited) / in vivo effects/
<i>Helianthus</i> lectin (Jacalin-like) (15 kDa)	<i>Helianthus tuberosus</i> (Jerusalem artichoke) (Asteraceae)	[Jasmonate induced]
<i>Hippeastrum</i> lectin (agglutinin) (12 kDa)	<i>Hippeastrum</i> sp. (Amaryllidaceae)	
<i>Hordeum</i> Jacalin-like lectin (17 kDa; 4 hevein-like CBDs)	<i>Hordeum vulgare</i> (barley) (Poaceae) [leaf]	
<i>Lycopersicon</i> lectin (71 kDa)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	(GlcNAc) ₃
<i>Maclura</i> lectin (42 kDa; $\alpha\beta$ heterodimer)	<i>Maclura pomifera</i> (osage orange) (Moraceae)	α -Gal, α -GalNAc
<i>Momordica</i> lectin (120 kDa; $\alpha_2\beta_2$ heterotetramer)	<i>Momordica charantia</i> (bitter melon) (Cucurbitaceae)	Gal, GalNAc
<i>Narcissus</i> lectin (agglutinin) (26 kDa; homodimer)	<i>Narcissus pseudonarcissus</i> (daffodil) (Amaryllidaceae)	α -O-Mannoside
<i>Oryza</i> Jacalin-like lectin (gene) (15 kDa)	<i>Oryza sativa</i> (Poaceae)	Man (putative)
<i>Persea</i> lectin (multimer)	<i>Persea americana</i> (avocado) (Lauraceae)	
<i>Phoradendron californicum</i> lectin (~60 kDa; A [\sim 30 kDa PAG toxin] S-S-linked to B [\sim 30 kDa lectin])	<i>Phoradendron californicum</i> (Viscaceae) [plant]	PAG (rat liver 28S rRNA A4324)
<i>Ptilota</i> lectins (65 kDa, 170 kDa)	<i>Ptilota plumosa</i> (red marine alga) (Florideophyceae) (Rhodophyta)	α -Man
<i>Polygonatum</i> lectin (agglutinin) (17 kDa)	<i>Polygonatum multiflorum</i> (Solomon's seal) (Liliaceae) [leaf]	Man
<i>Polygonatum multiflorum</i> RIPs – monomer (PMRIPm) (~60 kDa; A (~30 kDa PAG toxin) S-S-linked to B (~30 kDa lectin]) & ~240 kDa tetramer (PMRIPt)	<i>Polygonatum multiflorum</i> (Liliaceae) [leaf]	A: PAG (rRNA) B: Gal/GalNAc-specific lectin [low toxicity for human, animal cells]
<i>Ricinus</i> lectin RCA ₆₀ (60 kDa dimer)	<i>Ricinus communis</i> (castor bean) (Euphorbiaceae)	GalNAc, β -Gal, β -Gal (1 \rightarrow 4)Glc
<i>Ricinus</i> lectin RCA ₁₂₀ (120 kDa tetramer)	<i>Ricinus communis</i> (castor bean) (Euphorbiaceae)	GalNAc, β -Gal
<i>Ricinus</i> Ricin (65 kDa; A [32 kDa PAG toxin] S-S-linked to B [34 kDa glycoprotein lectin; binds toxin (A) to PM])	<i>Ricinus communis</i> , <i>R. sanguineus</i> (Euphorbiaceae) [castor bean seed]; Bulgarian dissident Georgi Markov murdered in London by ricin-tipped umbrella (1978)	PAG (rat 28S rRNA A4324 in R/S domain; not <i>E. coli</i> ribosomes); ssDNA depurination & cleavage; PSI; galactose-specific [toxic; apoptotic, cytotoxic, PSI]
<i>Sambucus</i> lectin (140 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Sambucus nigra</i> (elder) (Caprifoliaceae)	α -NeuNAc(2 \rightarrow 6)gal, α -NeuNAc(2 \rightarrow 6)galNAc [mitogenic for neuraminidase-treated lymphocytes]
<i>Sambucus ebulus</i> Ebulins 1, r1 & r2 (56 kDa; A [26 kDa PAG] S-S-linked to B [30 kDa lectin])	<i>Sambucus ebulus</i> (Caprifoliaceae) [bark, leaf]	PAG (rRNA); PSI (RRL, rat brain & liver) [non-toxic (mice, NHC human epithelial cells)]

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) part	Target (other target inhibited) / in vivo effects
<i>Sambucus nigra</i> RIP-related lectin (35 kDa)	<i>Sambucus nigra</i> (European elder) (Caprifoliaceae) [fruit]	[Derives from truncation of RIP gene]
<i>Sambucus nigra</i> nigrins a & b (58 kDa; A [26 kDa PAG] S-S-linked to B [32 kDa lectin])	<i>Sambucus nigra</i> (European elder) (Caprifoliaceae) [leaf]	PAG (rRNA); PSI (mammalian; not plant or bacterial)
<i>Sambucus sieboldiana</i> Sieboldin-b (60 kDa; A [27 kDa PAG] S-S-linked to B [33 kDa lectin])	<i>Sambucus sieboldiana</i> (Caprifoliaceae) [bark]	PAG (rRNA); PSI (mammalian; not plant or bacterial) [not toxic]
<i>Saraca</i> lectin (protein)	<i>Saraca indica</i> (Caesalpaeniaceae) [seed]	Neu5Ac- α -Gal- β -GlcNAc [apoptotic, mitogenic]
<i>Solanum tuberosum</i> lectin (50 kDa monomer, 100 kDa homodimer)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	(GlcNAc) ₃
<i>Tulipa</i> lectins (agglutinins) (28 kDa)	<i>Tulipa</i> sp. (tulip) (Liliaceae)	Man
<i>Triticum</i> lectin (36 kDa homodimer)	<i>Triticum vulgare</i> (wheatgerm) (Poaceae)	(GlcNAc) ₂ , NeuNAc, Sialoglycopeptide [mitogenic]
<i>Viscum</i> lectin (115 kDa $\alpha_2\beta_2$ heterotetramer)	<i>Viscum album</i> (mistletoe) (Viscaceae)	β -Gal
<i>Viscum album</i> (mistletoe) lectins MLI, MLII & MLIII (~60 kDa; A [~30 kDa PAG] S-S-linked to B [~30 kDa lectins])	<i>Viscum album</i> (mistletoe) (Viscaceae)	PAG (rRNA); PSI [cytotoxic]
Chitin-binding proteins (CBPs)		12.2C
<i>Arabidopsis</i> hevein-like protein (gene) (hevein-like N-terminal CBD)	<i>Arabidopsis thaliana</i> (Brassicaceae)	Chitin (putative) [inducible by ethylene, viral infection & Salicylic acid; like <i>Solanum</i> Win1 & Win2 PR proteins]
<i>Amaranthus</i> CBP Ac-AMP2 (4 kDa, single hevein-like domain)	<i>Amaranthus caudatus</i> (Amaranthaceae)	Chitin [antifungal]
<i>Beta</i> CBP IWF4 (30 kDa; hevein-like N-terminal CBD)	<i>Beta vulgaris</i> (sugar beet) (Chenopodiaceae)	Chitin
<i>Citrus</i> CBP (5 kDa; hevein-like N-terminal CBD)	<i>Citrus sinensis</i> (Rutaceae) [phloem]	Chitin [Zn ²⁺ -binding; stress-induced phloem accumulation]
<i>Canavalia</i> concanavalin B (34 kDa protein)	<i>Canavalia ensiformis</i> (jackbean) (Fabaceae)	Chitinase-homologue
<i>Hevea</i> CBP hevein (5 kDa, 43 aa, 8 Cys, 4 S-S; 1 CBD)	<i>Hevea brasiliensis</i> (rubber tree) (Euphorbiaceae) [latex]; under Belgian King Leopold, rubber latex collection-associated atrocities (e.g. cutting off hands) killed over 10 million Congo Africans	Chitin [rubber latex allergy esp. spina bifida & health work exposure e.g. surgeons]; Congo atrocities exposed by Edmund Morel & Sir Roger Casement (Irish patriot, hanged 1916)

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) / part/	Target (other target inhibited) / in vivo effects/
<i>Hordeum</i> lectin Barwin (14 kDa; 6 Cys, 3 S-S)	<i>Hordeum vulgare</i> (barley) (Poaceae) [root, seed]	(GlcNAc) ₁ (weak); related to C-terminal domain of <i>Solanum</i> wound-induced Win1 & Win2 & Hevein pre-protein
<i>Hordeum</i> CBP lectin (20 kDa; 4 hevein-like CBDs)	<i>Hordeum vulgare</i> (barley) (Poaceae) [root, seed]	Chitin
<i>Lycopersicon</i> hevein-related PR protein P2 (no hevein-like N-terminal CBD) (protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	Hevein-related [pathogen induced; Hevein, Nicotiana PR-4 & <i>Solanum</i> Win C-terminal domains homologous]
<i>Nicotiana</i> acidic hevein-related PR-4 (no hevein-like N-terminal CBD)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	Hevein-related [pathogen induced; Hevein & PR-4 C-terminal domains homologous]
<i>Oryza</i> CBP (19 kDa; 4 CBDs)	<i>Oryza sativa</i> (Poaceae) [embryo, seed]	Chitin, GlcNAc
<i>Pharbitis</i> CBP Pn-AMP1, Pn-AMP2 (4 kDa, single hevein-like CBD)	<i>Pharbitis nil</i> (Convolvulaceae)	Chitin [antifungal] Pn-AMP1
<i>Phytolacca</i> CBP (32 kDa; dimer; hevein-like CBDs)	<i>Phytolacca americana</i> (pokeweed) (Phytolaccaceae)	Chitin, (GlcNAc) ₃
<i>Sambucus</i> CBP SN-HLPf (hevein-like N-terminal domain; Class V chitinase-like C-terminal domain)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [fruit]	Chitin
<i>Solanum</i> chimeric chitin-binding-hydroxyproline-rich glycoprotein (glycoprotein)	<i>Solanum tuberosum</i> (potato) (Solanaceae)	Chitin
<i>Solanum</i> wound-induced Win-1 & Win-2 (hevein-like N-terminal CBD)	<i>Solanum tuberosum</i> (potato) (Solanaceae)	Chitin (putative) [wounding induced; C-terminal domain related to <i>Hordeum</i> Barwin]
<i>Triticum</i> CBP – wheatgerm agglutinins (= WGA isolectins) (19 kDa, 4 hevein-like CBDs)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	Chitin [agglutinates RBCs]
<i>Triticum</i> Wheatwin (14 kDa)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	Homologue of Barwin; related to C-terminal domain of <i>Solanum</i> wound-induced Win1 & Win2 & Hevein pre-protein
<i>Urtica</i> CBP UDA (<i>Urtica dioica</i> agglutinin) (38 kDa; 2 hevein-like CBDs)	<i>Urtica dioica</i> (stinging nettle) (Urticaceae)	Chitin [agglutinin]
<i>Viscum</i> CBP (11 kDa; α-S-S-α; 1 CBD)	<i>Viscum album</i> (European mistletoe) (Viscaceae)	Chitin
<i>Viscum</i> CBP UDA, cbML1, cbML2 & cbML3 (11 kDa; α-S-S-α; 1 CBD)	<i>Viscum album</i> (European mistletoe) (Viscaceae)	Chitin

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) / part/	Target (other target inhibited) / in vivo effects/
Chitinases (Classes I–V)		12.2D
<i>Beta</i> proline-rich chitinase (protein)	<i>Beta vulgaris</i> (sugar beet) (Chenopodiaceae)	Chitin
<i>Capsicum</i> chitinase (Class I) (~30 kDa protein)	<i>Capsicum annuum</i> (bell pepper) (Solanaceae) leaf]	Chitin [PRP; induced by fungal infection]
<i>Carica</i> chitinase (Class II) (lysozyme) (basic protein)	<i>Carica papaya</i> (papaya) (Caricaceae) [latex]	Chitin
<i>Castanea</i> chitinase (Class I) (32 kDa proteins; hevein-like N-terminal CBD)	<i>Castanea</i> sp. (chestnut) (Fagaceae) [seed]	Chitin [allergenic]
<i>Castanea</i> chitinase (Class II) (32 kDa proteins)	<i>Castanea</i> sp. (chestnut) (Fagaceae) [seed]	Chitin
<i>Cucumis</i> chitinase (Class I) (30 kDa protein; hevein-like N-terminal CBD)	<i>Cucumis sativa</i> (Cucumber) (Cucurbitaceae)	Chitin
<i>Ficus</i> chitinase (Class I) (45 kDa; acidic protein; hevein-like N-terminal CBD)	<i>Ficus benjamina</i> (fig) (Moraceae)	Chitin [allergen]
<i>Glycine</i> chitinase (Class I) (32 kDa protein)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	Chitin
<i>Gossypium</i> chitinase (putative) (23 kDa precursor)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae)	Chitin
<i>Hevea</i> chitinase/lysozyme hevamines A & B (Class I) (30 kDa proteins; hevein-like N-terminal CBD)	<i>Hevea brasiliensis</i> (rubber tree) (Euphorbiaceae) [latex];	Chitin
<i>Hordeum</i> chitinase CHI-26 (Class I) (hevein-like N-terminal CBD)	<i>Hordeum vulgare</i> (Poaceae) [seed]	Chitin
<i>Lycopersicon</i> chitinase (Class II) (gene)(protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	Chitin
<i>Musa</i> chitinase (Class I) (32 & 34 kDa proteins; hevein-like N-terminal CBD)	<i>Musa</i> (banana) (Musaceae) [fruit]	Chitin [allergens]
<i>Nicotiana</i> chitinase CHN-B (Class I) (hevein-like N-terminal CBD)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	Chitin
<i>Nicotiana</i> chitinases (Class II) – PR-P & PR-Q (acidic PR proteins)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	Chitin
<i>Nicotiana</i> chitinases (Class V) (41, 42 kDa proteins)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	Chitin
<i>Oryza</i> chitinases CHT2, RCH10 (Class I) (basic; hevein-like N-terminal CBD)	<i>Oryza sativa</i> (Poaceae)	Chitin
<i>Oryza</i> chitinase IIb (Class II) (protein)	<i>Oryza sativa</i> (Poaceae) [shoot]	Chitin

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) / part	Target (other target inhibited) / in vivo effects
<i>Parthenocissus</i> chitinase/lysozyme (Class I) (30 kDa protein; hevein-like N-terminal CBD)	<i>Parthenocissus quinquefolia</i> (Vitaceae)	Chitin
<i>Persea</i> chitinase (Class I) (32 kDa proteins; hevein-like N-terminal CBD)	<i>Persea americana</i> (avocado) (Lauraceae) [fruit]	Chitin [allergenic]
<i>Persea</i> chitinase (Class II) (32 kDa proteins)	<i>Persea americana</i> (avocado) (Lauraceae) [fruit]	Chitin
<i>Petunia</i> chitinase (gene)	<i>Petunia</i> sp. (petunia) (Solanaceae)	Chitin
<i>Phaseolus</i> chitinase (Class I) (hevein-like N-terminal CBD)	<i>Phaseolus vulgaris</i> (Fabaceae)	Chitin
<i>Picea</i> chitinase (Class I) (hevein-like N-terminal CBD)	<i>Picea glauca</i> (white spruce) (Pinaceae)	Chitin
<i>Pinus strobus</i> chitinase (gene)	<i>Pinus strobus</i> (eastern white pine) (Pinaceae)	Chitinase (putative)
<i>Populus</i> acidic Win6 & Win8 chitinases (PR proteins)	<i>Populus</i> sp. (poplar)	Chitin [wound-induced PR proteins]
<i>Rehmannia</i> TLP/chitinase (21 kDa protein)	<i>Rehmannia glutinosa</i> (Scrophulariaceae)	Chitin [TLP, chitinase]
<i>Sambucus</i> putative chitinases (Class I) SNCHJET 15 & 19 (hevein-like N-terminal CBDs)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [leaf]	Chitin
<i>Sambucus</i> chitinase (Class II) PR-3 (PR protein)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [leaf]	Chitin [PR protein, ethylene- & pathogen-induced]
<i>Sambucus</i> chitinase (Class I–Class V) (hevein-like N-terminal CBD, distinct C-terminal domain, PR protein-related)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [fruit]	Chitin
<i>Sambucus</i> chitinase (Class V) (distinct C-terminal domain, PR protein-related)	<i>Sambucus nigra</i> (elderberry) (Caprifoliaceae) [fruit]	Chitin
<i>Solanum</i> chitinases ChtB & ChtC (Class I) (Cht glycoprotein; hevein-like N-terminal CBD)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	Chitin
<i>Solanum</i> chitinase (basic protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae)	Chitin
<i>Urtica</i> CBP (chitinase-like precursor) (38 kDa; 2 hevein-like CBDs)	<i>Urtica dioica</i> (stinging nettle) (Urticaceae)	Chitin (but chitinase domain cleaved off in processing)

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) part/	Target (other target inhibited) / in vivo effects/
<i>Zea</i> chitinase (Class I) (30 kDa protein; hevein-like N-terminal CBD)	<i>Zea mays</i> (corn) (Poaceae) [seed]	Chitin
β1,3-Glucanases (hydrolyse β1,3-glucan)		12.2E
<i>Arabidopsis thaliana</i> β1,3- glucanase (Brassicaceae) (50 kDa PR protein)	<i>Arabidopsis thaliana</i> (Brassicaceae); pathogen induced	β1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Brassica</i> β1,3-glucanase (38 kDa protein)	<i>Brassica campestris</i> (field mustard) (Brassicaceae)	β1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Capsicum</i> β1,3-glucanase (PR protein)	<i>Capsicum annuum</i> (pepper) (Solanaceae) [leaf]; induced by ethylene (<i>ex</i> Ethepon) & methyl jasmonate	β1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Glycine</i> β1,3-glucanase (38 kDa protein)	<i>Glycine max</i> (soya bean) (Fabaceae) [vacuolar]	β1,3-Glucan [antifungal – degrades fungal cell wall & releases oligosaccharide elicitor]
<i>Hevea brasiliensis</i> (rubber tree) (Euphorbiaceae) β1,3- glucanase (35 kDa PR protein)	<i>Hevea brasiliensis</i> (rubber tree) (Euphorbiaceae); pathogen induced	β1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Hordeum</i> TLP IFW19 β-1,3-glucanase (19 kDa proteins)	<i>Hordeum vulgare</i> (barley)	β-1,3-Glucan [PRPs; accumu- late in fungal-infected leaf]
<i>Hordeum</i> β1,3-glucanases (33–36 kDa proteins)	<i>Hordeum vulgare</i> (barley) (Poaceae) [leaf, seed]	β1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Lycopersicon</i> β1,3-glucanases (34, 40 kDa protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae); pathogen induced	β1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Lycopersicon</i> TLP AP24 β-1,3- glucanase (20 kDa protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	β-1,3-Glucan [PRP; antifungal]
<i>Lycopersicon</i> TLP NP24 β-1,3-glucanase (~20 kDa protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	β-1,3-Glucan [PRPs; antifungal; I increases during ripening]
<i>Musa</i> Ban-TLP/β-1,3- glucanase (22 kDa protein)	<i>Musa acuminata</i> (Musaceae) [fruit]	β-1,3-Glucan [TLP; induced by Methyljasmonate]
<i>Nicotiana plumbaginifolia</i> β1,3-glucanase (35 kDa protein)	<i>Nicotiana plumbaginifolia</i> (Solanaceae) [vacuolar]	β1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Nicotiana tabacum</i> β1,3- glucanase (30–36 kDa PR proteins)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae) [leaf]; induced by ethylene & salicylic acid	β1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Nicotiana</i> TLP SE22 β-1,3-glucanase (22 kDa pro-protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	β-1,3-Glucan ligand
<i>Nicotiana</i> TLP SE39b β-1,3-glucanase (26 kDa pro-protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	β-1,3-Glucan [expressed in stigma & style]
<i>Olea</i> β1,3-glucanase Ole e9 (46 kDa protein)	<i>Olea europaea</i> (Oleaceae)	β1,3-Glucan [antifungal – degrades fungal cell wall, major olive pollen allergen causing olive pollinosis]

(continued)

Table 12.2 (Continued)

Compound class	Plant (family) part	Target (other target inhibited) / in vivo effects/
<i>Phaseolus</i> β 1,3-glucanase (35 kDa PR protein)	<i>Phaseolus vulgaris</i> (kidney bean) (Fabaceae); induced by fungal elicitor	β 1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Pisum sativum</i> (garden pea) β 1,3-glucanase (Fabaceae) (35 kDa PR protein)	<i>Pisum sativum</i> (garden pea) (Fabaceae); fungal elicitor induced	β 1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Prunus</i> β 1,3-glucanase (38 kDa protein)	<i>Prunus persica</i> (peach) (Rosaceae)	β 1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Prunus</i> TLP CHTL β -1,3-glucanase (21–29 kDa protein)	<i>Prunus</i> sp. (cherry) (Rosaceae) [ripening fruit]	β -1,3-Glucan
<i>Salix</i> β 1,3-glucanase (protein)	<i>Salix gilgiana</i> (willow) (Salicaceae)	β 1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Solanum</i> β 1,3-glucanase (35, 37 kDa protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [leaf]; induced by wounding & infection	β 1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Triticum</i> β 1,3-glucanase (Poaceae) (48 kDa PR protein)	<i>Triticum aestivum</i> (wheat) (Poaceae); induction per pathogenesis & Al(III) toxicity	β 1,3-Glucan [antifungal – degrades fungal cell wall]
<i>Zea mays</i> (maize) (Poaceae) β 1,3-glucanase (34 kDa PR protein)	<i>Zea mays</i> (maize) (Poaceae); pathogen induced	β 1,3-Glucan [antifungal – degrades fungal cell wall]

Table 12.3 Non-protein plant compounds permeabilizing membranes

Compound class	Plant (family) part	Effect (other target inhibited) / in vivo effects/
Terpene		12.3t
Aescins (= Escins) (triterpene glycosides)	<i>Aesculus hippocastanum</i> (horse chestnut) (Hippocastanaceae)	Permeabilizes membranes (HYAL) [antifungal, AI, haemolytic]
Avenacin A-1 (triterpene glycoside saponin)	<i>Avena sativa</i> (oats) (Poaceae)	Permeabilizes membranes (cholesterol reorganized into pores) [antifungal, haemolytic]
Avenacins A-2, B-1, B-2 (triterpene glycoside saponins)	<i>Avena sativa</i> (oats) (Poaceae); pre-formed antimicrobial saponins examples of “phytoanticipins”	Permeabilize membranes (cholesterol association) [antifungal, haemolytic]
Cevine (= Cevadine) (steroidal alkaloid); structure (1954) by R.B. Woodward (USA, Nobel Prize, Chemistry, 1965)	<i>Schoenocaulon officinale</i> (Liliaceae) [seed]	Haemolytic; derives from hydrolysis of Cevadine

(continued)

Table 12.3 (Continued)

Compound class	Plant (family) part	Target (other target inhibited) / in vivo effects
Cholesterol (sterol); Konrad Bloch (Germany/USA, Nobel Prize, Physiology/Medicine, 1964, cholesterol biosynthesis); John Cornforth (Australia, Nobel Prize, Chemistry, 1975; isoprenoid biosynthesis, stereochemistry); George Popják (cholesterol biosynthesis)	<i>Aloe vera</i> (Aloeaceae), <i>Helianthus annuus</i> (Asteraceae), <i>Vicia faba</i> (Fabaceae), <i>Phoenix dactylifera</i> (date palm) (Palmae), Rhodophyceae (marine red algae); animal membrane component; hyperlipidaemia & in many heart attack victims; LDL carries cholesteryl esters; ↑ LDL → ↑ cholesterol-rich arterial atheromas → atherosclerosis → blockage, clots → stroke & myocardial infarction (heart attack)	Modifies membrane fluidity; synthesis (1951) by Robert Woodward (USA, Nobel Prize, Chemistry, 1965); Michael Brown & Joseph Goldstein (USA, Nobel Prize, Physiology/Medicine, 1985, hypercholesterolaemia present cholesterol & LDL receptor); Fyodor Lynen (Germany, Nobel Prize, Physiology/Medicine, 1964, FA synthesis & oxidation, isoprenoid biosynthesis)
Cyclamin (triterpene glycoside saponin)	<i>Cyclamen europaeum</i> , <i>C. mirabile</i> (Primulaceae)	Permeabilizes membranes [antibiotic, antifungal, cytotoxic, haemolytic]
Digitonin (steroid glycoside)	<i>Acacia nilotica</i> (Fabaceae), <i>Digitalis purpurea</i> (foxglove) (Scrophulariaceae)	Permeabilizes membranes e.g. mitochondrial “digitonin particles”; cholesterol interaction [antifungal, detergent, haemolytic]
Gracillin (steroid glycoside)	<i>Ex</i> precursor Protogracillin in <i>Dioscorea</i> spp. (Mexican yam) (Dioscoreaceae) [anti-rheumatic, anti-arthritic plant], <i>Costus speciosus</i> (Zingiberaceae)	Permeabilizes membranes [haemolytic]; hydrolysis yields important steroid synthesis precursor Diosgenin
α-Hederin (triterpene glycoside saponin)	<i>Hedera helix</i> (ivy) (Araliaceae)	Permeabilizes membranes [antifungal, cytotoxic, haemolytic]
Helianthosides 1, 2 & 3 (triterpene glycoside saponins)	<i>Helianthus annuus</i> (sunflower) (Asteraceae) [flower]	Permeabilize membranes [bitter, haemolytic]
Sarsaparillin (= Parillin) (triterpene glycoside saponin)	<i>Smilax aristolochiaefolia</i> (sarsaparilla) (Liliaceae) [root]	Permeabilizes membranes [bitter, haemolytic]
Theasaponin (triterpene glycoside saponin)	<i>Camellia sinensis</i> (tea) (Theaceae) [seed]	Permeabilizes membranes [antifungal, haemolytic]
Tomatine (triterpene glycoside saponin)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [leaf]	Permeabilizes membranes (cholesterol interaction) [antifungal, haemolytic]
Other		12.3o
Ajoene (= (<i>E</i>)-4,5,9-Trithiadodeca-1,6,11-triene-9-oxide) (aliphatic disulphide)	From rearrangement of Allicin from <i>Allium sativum</i> (garlic) (Liliaceae) [bulb]	Alters membrane (PAI per inhibition of granule release & fibrinogen binding)

(continued)

Table 12.3 (Continued)

Compound class	Plant (family) part	Target (other target inhibited) / in vivo effects
Long chain fatty acids (aliphatic carboxylic acids); Feodor Lynen (Germany, Nobel Prize, Physiology/Medicine, 1964, fatty acid (FA) synthesis & oxidation)	Universal; from saponification of fatty acid esters (e.g. mono-, di- & triglycerides) to yield “soap”; 2 million bars of soap part of unsuccessful Second World War offer for 1 million Hungarian Jews (Joel Brand, 1944)	Amphipathic detergents [permeabilize cell membranes] revolutionized public health & hygiene; use of soap still a major Third World public health issue (washing hands with soap to decrease infection e.g. conjunctivitis, GI disease)
Non-plant reference [Filipins (Filipins II, III & IV; mixture, Filipin I)] (polyhydroxy macrocyclic lactones)	<i>Streptomyces filipinensis</i> (fungus)	12.3n Permeabilize membranes (bind cholesterol, form pores) [antibiotic, haemolytic]

Table 12.4 Plant proteins directly or indirectly perturbing membranes

Compound class	Plant (family) part	Target & activities (other target inhibited) / in vivo effects
Defensin (γ-thionin) (DEF)		12.4A
<i>Aesculus</i> Ab-AMP1 (5 kDa, 8 Cys, 4 S-S)	<i>Aesculus hippocastanum</i> (Hippocastanaceae) [seed]	PM (indirect) [antifungal]
<i>Arabidopsis</i> DEF (5 kDa, 8 Cys, 4 S-S)	<i>Arabidopsis thaliana</i> (Brassicaceae) [seed]	PM (indirect) [antifungal]
<i>Beta</i> AX1, AX2 (5 kDa, 8 Cys, 4 S-S)	<i>Beta vulgaris</i> (beet) (Chenopodiaceae) [seed]	PM (indirect) [antifungal]
<i>Cassia</i> 5459 Da & 5144 Da DEFs (5 kDa, 8 Cys, 4 S-S)	<i>Cassia fistula</i> (Fabaceae) [seed]	[Presumed antifungal]
<i>Clitoria</i> DEF (5 kDa, 8 Cys, 4 S-S)	<i>Clitoria ternatea</i> (Fabaceae) [seed]	PM (indirect) [antifungal]
<i>Dahlia</i> Dm-AMP1 (5 kDa, 8 Cys, 4 S-S)	<i>Dahlia merckii</i> (Asteraceae) [seed]	PM (indirect) [antifungal; permeabilizes fungal PM]
<i>Hardenbergia</i> HvAMP1 (5 kDa, 8 Cys, 4 S-S)	<i>Hardenbergia violacea</i> (Fabaceae)	PM (indirect) (PS)
<i>Heuchera</i> Hs-AFP1 (5 kDa, 8 Cys, 4 S-S)	<i>Heuchera sanguinea</i> (Saxifragaceae) [seed]	PM (indirect) [antifungal]
<i>Hordeum</i> γ 1-H (= γ 1-Hordothionin), $\bar{\omega}$ -H (= $\bar{\omega}$ -Hordothionin) (5 kDa, 8 Cys, 4 S-S)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	PM (indirect) [antifungal]
<i>Nicotiana</i> FST (5 kDa, 8 Cys, 4 S-S)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae) [seed]	PM (indirect) [antifungal]
<i>Petunia inflata</i> PPT (5 kDa, 8 Cys, 4 S-S)	<i>Petunia inflata</i> (Solanaceae) [flower pistil]	PM (indirect) [antifungal]
<i>Petunia hybrida</i> Pet 4 (5 kDa, 8 Cys, 4 S-S)	<i>Petunia hybrida</i> (Solanaceae) [flower petal]	Presumed PM [antifungal]
<i>Petunia hybrida</i> Pet 5 (5200 Da) (5 kDa, 10 Cys, 5 S-S)	<i>Petunia hybrida</i> (Solanaceae) [flower petal]	PM (indirect) [antifungal]

(continued)

Table 12.4 (Continued)

Compound class	Plant (family) / part/	Target & activities (other target inhibited) / in vivo effects/
<i>Pisum</i> p1230, p139 (5 kDa, 8 Cys, 4 S-S)	<i>Pisum sativum</i> (garden pea) (Fabaceae) [pod]	Presumed PM target [antifungal]
<i>Raphanus</i> Rs-AFP1, Rs-AFP2 (5 kDa, 8 Cys, 4 S-S)	<i>Raphanus sativus</i> (radish) (Brassicaceae) [seed]	PM (indirect) [antifungal; permeabilizes fungal PM]
<i>Sinapis alba</i> (yellow mustard) (Brassicaceae) [seed] M1, M2A, M2B (6 kDa, 8 Cys, 4 S-S)	<i>Sinapis alba</i> (yellow mustard) (Brassicaceae) [seed]	PM (indirect) [antifungal]
<i>Solanum</i> p322, Pth-1, DL1 & DL2 defensins (5 kDa, 8 Cys, 4 S-S)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	PM (indirect) [antifungal, model membrane interactions by Pth-1 & DL2]
<i>Sorghum</i> SI α 1, SI α 2, SI α 3 (5 kDa, 8 Cys, 4 S-S)	<i>Sorghum bicolor</i> (sorghum) (Poaceae)	PM (indirect) [antifungal]
<i>Triticum turgidum</i> γ 1- & γ 2-P (= γ 1- & γ 2-Purothionin) (5 kDa, 8 Cys, 4 S-S)	<i>Triticum turgidum</i> (Poaceae) [seed]	PM (indirect) [antifungal]
<i>Vicia faba</i> Fabatin (5 kDa, 8 Cys, 4 S-S)	<i>Vicia faba</i> (broad bean) (Fabaceae) [seed]	PM (indirect) [antifungal]
<i>Vigna unguiculata</i> pSAS10 (10 kDa, 8 Cys, 4 S-S)	<i>Vigna unguiculata</i> (Fabaceae) [seed]	PM (indirect) [antifungal]
Lipid transfer proteins (LTPs)		12.4B
<i>Arabidopsis</i> LTP (~9 kDa protein)	<i>Arabidopsis thaliana</i> (Brassicaceae) [seed]	PL [antifungal, phospholipid transfer]
<i>Brassica</i> LTP (~9 kDa protein)	<i>Brassica oleraceae</i> (broccoli) (Brassicaceae)	PL [antifungal, phospholipid transfer]
<i>Capsicum</i> LTPs I & II (~10 kDa proteins)	<i>Capsicum annuum</i> (bell pepper) (Solanaceae) [leaf]	PM [PRP; induced by fungal infection]
<i>Cassia</i> 9378 Da LTP (9 kDa protein)	<i>Cassia fistula</i> (Fabaceae) [seed]	LTP homologue
<i>Daucus</i> LTP (~9 kDa protein)	<i>Daucus carota</i> (carrot) (Apiaceae)	PL [antifungal, phospholipid transfer]
<i>Eleusine</i> double-headed TRY- α AI inhibitor I-2 (~9 LTP homologue)	<i>Eleusine coracana</i> (ragi, finger millet) (Poaceae) [seed]	LTP homologue (α AI, TRY)
<i>Gerbera</i> LTP (~9 kDa protein)	<i>Gerbera hybrida</i> (Asteraceae)	PL [antifungal, phospholipid transfer]
<i>Hordeum</i> LTP PAPI (LTP1) (~9 kDa protein)	<i>Hordeum vulgare</i> (barley) (Poaceae)	PL [antifungal, phospholipid transfer]
<i>Hordeum</i> LTP LTP2 (~9 kDa protein)	<i>Hordeum vulgare</i> (barley) (Poaceae)	PL [antifungal, phospholipid transfer; model membrane interactions \rightarrow leakage & aggregation]
<i>Nicotiana</i> LTP (~9 kDa protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	PL [antifungal, phospholipid transfer]
<i>Oryza</i> LTP (~9 kDa)	<i>Oryza sativa</i> (rice) (Poaceae)	PL [antifungal, phospholipid transfer]
<i>Petunia</i> LTPs Pet1, Pet2, Pet3 (~9 kDa protein)	<i>Petunia hybrida</i> (petunia) (Solanaceae) [flower]	LTP homologues
<i>Phaseolus</i> 9 kDa LTP PI (~9 kDa protein)	<i>Phaseolus angularis</i> (adzuki bean) (Fabaceae) [seed]	LTP homologue (TRY) [also 10 kDa glycosylated forms of LTP]

(continued)

Table 12.4 (Continued)

Compound class	Plant (family) part	Target & activities (other target inhibited) / in vivo effects/
<i>Pinus</i> LTP (PBP) (~9 kDa protein)	<i>Pinus pinea</i> (Pinaceae) [seed]	LTP homologue
<i>Raphanus</i> LTP (~9 kDa protein)	<i>Raphanus sativus</i> (radish) (Brassicaceae) [seed]	PL [antifungal, phospholipid transfer]
<i>Ricinus</i> LTP (~9 kDa protein)	<i>Ricinus communis</i> (castor bean) (Fabaceae)	PL [antifungal, phospholipid transfer]
<i>Spinacia</i> LTP (~9 kDa protein)	<i>Spinacia oleracea</i> (spinach) (Chenopodiaceae)	PL [antifungal, phospholipid transfer]
<i>Triticum</i> LTPs (WBP 1A, 1B, 2 & 3) (~9 kDa proteins)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	LTP homologues
<i>Zea</i> LTP (~9 kDa protein)	<i>Zea mays</i> (maize) (Poaceae) [seed]	PL [antifungal, phospholipid transfer]
Napins & Napin-like proteins (NLPs)		12.4C
<i>Brassica campestris</i> napin (14 kDa; small (S) & Large (L) chains)	<i>Brassica campestris</i> (field mustard) (Brassicaceae) [seed]	PM [antifungal]
<i>Brassica</i> C1, C2, C3, C4, C5, C6, C7 <i>et al.</i> (14–15 kDa; S–S-linked 4 kDa S & 10 kDa L chains)	<i>Brassica napus</i> (kohlrabi) (Brassicaceae) [seed]	PM [antifungal]
<i>Brassica</i> TIBN (14 kDa; S & L chains)	<i>Brassica napus</i> (kohlrabi) (Brassicaceae) [seed]	PM (TRY) [antifungal]
<i>Brassica</i> 2S proteins – napin 1, napin 2, napin 1A, napin 1B, embryo napin, BNIII, napA, napB (14 kDa; S & L chains)	<i>Brassica napus</i> (rape) (Brassicaceae) [seed]	PM [antifungal]
<i>Brassica</i> BN (16 kDa; S & L chains)	<i>Brassica nigra</i> (Brassicaceae) [seed]	PM (CHY, SUB, TRY) [antifungal]
<i>Cucurbita</i> napin (14 kDa; S & L chains)	<i>Cucurbita maxima</i> (pumpkin) (Cucurbitaceae) [seed]	PM [antifungal]
<i>Glycine</i> 2S napin (14 kDa; S & L chains)	<i>Glycine max</i> (soya bean) (Fabaceae) [seed]	PM [antifungal]
<i>Momordica</i> NLP (14 kDa; S & L chains)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	PM [antifungal]
<i>Raphanus</i> napin (14 kDa; S & L chains)	<i>Raphanus sativus</i> (radish) (Brassicaceae) [seed]	PM [antifungal]
<i>Ricinus</i> NLP (14 kDa; S & L chains)	<i>Ricinus communis</i> (castor bean) (Euphorbiaceae) [seed]	PM [antifungal]
<i>Sinapis</i> TISA-1, TISA-2 (16 kDa; S & L chains)	<i>Sinapis arvensis</i> (charlock) (Brassicaceae) [seed]	PM (CHY, SUB) [antifungal]
Osmotin-like proteins (OLPs) (Thaumatococcus-like)		12.4D
<i>Arabidopsis</i> OLPs (27 kDa pro-protein)	<i>Arabidopsis thaliana</i> (mouse-ear cress) (Brassicaceae)	PM [PRP, antifungal]
<i>Atriplex</i> OLPs (24 kDa pro-proteins)	<i>Atriplex mummularia</i> (Chenopodiaceae) (halophyte plant)	PM
<i>Benincasa</i> OLP (27 kDa pro-protein)	<i>Benincasa hispida</i> (Cucurbitaceae)	PM

(continued)

Table 12.4 (Continued)

Compound class	Plant (family) / part/	Target & activities (other target inhibited) / in vivo effects/
<i>Capsicum</i> TLP/OLP (26 kDa pro-protein)	<i>Capsicum annuum</i> (bell pepper) (Solanaceae)	PM [antifungal, PRP]
<i>Fragaria</i> OLP (24 kDa pro-protein)	<i>Fragaria ananassa</i> (strawberry) (Rosaceae)	PM
<i>Lycopersicon</i> OLP (27 kDa pro-protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	PM [PRP, antifungal]
<i>Nicotiana sylvestris</i> OLPs (28 kDa pro-proteins)	<i>Nicotiana sylvestris</i> (wood tobacco) (Solanaceae)	PM [ethylene induced]
<i>Nicotiana tabacum</i> Osmotin & OLPs (28 kDa pro-proteins)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	PM (PR5 PRPs)
<i>Oryza</i> OLP (26 kDa pro-protein)	<i>Oryza sativa</i> (rice) (Poaceae)	PM
<i>Petunia</i> Osmotin (26 kDa pro-protein]	<i>Petunia hybrida</i> (petunia) (Solanaceae)	PM [osmotic stress induced]
<i>Solanum tuberosum</i> OLP (27 kDa pro-protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae)	PM [PRP, antifungal; induced by abscisic acid, salicylic acid, salt, wounding & fungal pathogen infection]
<i>Solanum commersonii</i> OLPs (27 kDa pro-proteins)	<i>Solanum commersonii</i> (nightshade) (Solanaceae)	PM
<i>Solanum dulcamara</i> OLP (27 kDa pro-protein)	<i>Solanum dulcamara</i> (nightshade) (Solanaceae)	PM [cryoprotective]
<i>Spartina</i> OLP (14 kDa)	<i>Spartina anglica</i> (Poaceae)	PM [salt induced]
<i>Vitis</i> OLP (24 kDa pro-protein)	<i>Vitis vinifera</i> (grape) (Vitaceae)	PM
Thaumatococin-like proteins (TLPs) (Osmotin-like)		12.4E
<i>Arabidopsis</i> TLP (26 kDa pro-protein)	<i>Arabidopsis thaliana</i> (mouse-ear cress) (Brassicaceae)	PM
<i>Avena</i> TLP 4 (18 kDa pro-protein)	<i>Avena sativa</i> (oats) (Poaceae)	PM [PRP]
<i>Beta</i> TLP (23 kDa protein)	<i>Beta vulgaris</i> (sugar beet) (Chenopodiaceae)	PM
<i>Capsicum</i> TLP/OLP (26 kDa pro-protein)	<i>Capsicum annuum</i> (bell pepper) (Solanaceae)	PM [antifungal, PRP]
<i>Castanea</i> TLP (26 kDa pro-protein)	<i>Castanea sativa</i> (chestnut) (Fagaceae)	PM [antifungal]
<i>Cicer</i> TLP PR-5a (19 kDa pro-protein)	<i>Cicer arietinum</i> (chickpea) (Fabaceae)	PM [PRP]
<i>Daucus</i> TLP (23 kDa protein)	<i>Daucus carota</i> (carrot) (Apiaceae)	PM [drought-inducible]
<i>Hordeum</i> TLPs (15–19 kDa proteins)	<i>Hordeum vulgare</i> (barley) (Poaceae)	PM [PRPs; accumulate in fungal-infected leaf]
<i>Hordeum</i> TLPs, IFW19 (19 kDa proteins)	<i>Hordeum vulgare</i> (barley) (Poaceae)	PM – IFW19 is a β -1,3-Glucanase & a β -1,3-Glucan ligand [PRPs; accumulate in fungal-infected leaf]
<i>Hordeum</i> IFW16 (16 kDa protein)	<i>Hordeum vulgare</i> (barley) (Poaceae)	PM – β -1,3-Glucan ligand [PRP; accumulates in fungal-infected leaf]
<i>Hordeum</i> IFW15 (15 kDa protein)	<i>Hordeum vulgare</i> (barley) (Poaceae)	PM – β -1,3-Glucan ligand [PRP; accumulates in fungal-infected leaf; antifungal]

(continued)

Table 12.4 (Continued)

Compound class	Plant (family) part	Target & activities (other target inhibited) / in vivo effects
<i>Hordeum</i> HvPR5b (protein)	<i>Hordeum vulgare</i> (barley) [seed] (Poaceae)	β -1,3-Glucan ligand (weak) [PRP, TLP]
<i>Hordeum</i> HvPR5c (protein)	<i>Hordeum vulgare</i> (barley) [seed] (Poaceae)	β -1,3-Glucan ligand [PRP, TLP]
<i>Lycopersicon</i> TLP AP24 (20 kDa protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	PM is a β -1,3-glucanase [PRP; antifungal]
<i>Lycopersicon</i> TLP NP24 I & II (~20 kDa proteins)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	PM – NP24 is a β -1,3-glucanase [PRPs; antifungal; I increases during ripening]
<i>Malus</i> TLP Mdt1l (26 kDa pro-protein)	<i>Malus domestica</i> (apple) (Rosaceae) [fruit]	PM
<i>Musa</i> Ban-TLP (22 kDa protein)	<i>Musa acuminata</i> (Musaceae) [fruit]	PM is a β -1,3-Glucanase [TLP; induced by Methyljasmonate]
<i>Nicotiana</i> TLP SE22 (22 kDa pro-protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	PM is a β -1,3-Glucanase & a β -1,3-Glucan ligand
<i>Nicotiana</i> TLP SE39b (26 kDa pro-protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	PM is a β -1,3-Glucanase & a β -1,3-Glucan ligand [expressed in stigma & style]
<i>Nicotiana</i> TLP E22 (= PRP R major) (25 kDa pro-protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	PM [PRP]
<i>Nicotiana</i> TLP E2 (= PRP R minor) (25 kDa pro-protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	PM [PRP]
<i>Nicotiana</i> TLP PR-5d (23 kDa pro-protein)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	PM [PRP; antifungal]
<i>Oryza</i> TLP (18 kDa pro-protein)	<i>Oryza sativa</i> (rice) (Poaceae)	PM [PRP; pathogen induced]
<i>Phaseolus</i> TLP (20 kDa protein)	<i>Phaseolus vulgaris</i> (French bean) (Fabaceae)	PM [antifungal]
<i>Pisum</i> TLPs IFW16-1 & IFW16-2 (16 kDa proteins)	<i>Pisum sativum</i> (pea) (Fabaceae)	PM- β -1,3-Glucan ligands
<i>Prunus</i> TLP (26 kDa pro-protein)	<i>Prunus avium</i> (cherry) (Rosaceae) [ripening fruit]	PM [fruit ripening-related]
<i>Prunus</i> TLP CHTL (21–29 kDa protein)	<i>Prunus</i> sp. (cherry) (Rosaceae) [ripening fruit]	PM is a β -1,3-Glucanase & a β -1,3-Glucan ligand
<i>Pseudotsuga</i> TLP (25 kDa pro-protein)	<i>Pseudotsuga menziesii</i> (Douglas fir) (Pinaceae)	PM
<i>Pyrus</i> TLP (25 pro-protein; glycoprotein)	<i>Pyrus pyrifolia</i> (Japanese pear) (Rosaceae)	PM [PRP]
<i>Rehmannia</i> TLP/chitinase (21 kDa protein)	<i>Rehmannia glutinosa</i> (Scrophulariaceae)	TLP (Chitin) [is a chitinase]
<i>Sambucus</i> TLPs (24 kDa pro-proteins)	<i>Sambucus nigra</i> (European elder) (Adoxaceae)	PM
<i>Secale</i> TLP 4 (18 kDa protein)	<i>Secale cereale</i> (rye) (Poaceae)	PM
<i>Thaumatococcus</i> Thaumatin I (21 kDa, 16 Cys, 8 S–S, 23 kDa protein; α -helix-rich domain & 2 β strand-rich domains)	<i>Thaumatococcus danielli</i> (Marantaceae) [fruit]	Sweet protein (100,000 \times > Sucrose); among primates only Old World monkeys, gibbons, apes and man respond to this tastant

(continued)

Table 12.4 (Continued)

Compound class	Plant (family) part	Target & activities (other target inhibited) in vivo effects
<i>Thaumatococcus</i> Thaumatin II (20 kDa protein)	<i>Thaumatococcus daniellii</i> (Marantaceae) [fruit]	Sweet protein
<i>Triticum</i> TLP PWIR2, TLPs (18 kDa pro-proteins)	<i>Triticum aestivum</i> (wheat) (Poaceae)	PM [PRPs]
<i>Vitis</i> TLP VVTL1 (24 kDa protein)	<i>Vitis vinifera</i> (grape) (Vitaceae) [fruit]	PM [elevated in fruit at time of minimal ability of powdery mildew to infect]
<i>Zea</i> TRY/ α A inhibitor – TLP (22 kDa, 16 Cys, 8 S–S protein)	<i>Zea mays</i> (corn, maize) (Poaceae) [seed]	TLP (α A, TRY) bifunctional inhibitor (α A)
<i>Zea</i> Zeamatin – TLP & permatin (19–22 kDa protein)	<i>Zea mays</i> (corn, maize) (Poaceae) [seed]	PM – β -1,3-Glucan ligand (α A, TRY) [antifungal; membrane permeabilizing]
<i>Zea</i> Zeamatin-like protein (19–22 kDa protein)	<i>Zea mays</i> (corn, maize) (Poaceae) [seed]	PM – (α A, TRY) [antifungal]
Thionins		12.4F
<i>Avena</i> α - & β -Avenathionins (5 kDa proteins)	<i>Avena sativa</i> (oats) (Poaceae) [seed]	PM [permeabilize PM; antifungal]
<i>Capsicum</i> thionin (~5 kDa protein)	<i>Capsicum annuum</i> (bell pepper) (Solanaceae) leaf]	PM [PRP; induced by fungal infection; antifungal]
<i>Crambe</i> thionins Crambins 1 & 2 (5 kDa proteins)	<i>Crambe abyssinica</i> (Brassicaceae) [seed]	PM [hydrophobic]
<i>Crambe</i> non-seed crambins (5 kDa proteins)	<i>Crambe abyssinica</i> (Brassicaceae) [various tissues]	PM [hydrophobic]
<i>Dendrophthora</i> Denclatoxin (5 kDa protein)	<i>Dendrophthora clavata</i> (mistletoe) (Viscaceae); parasitic plant	PM [toxic]
<i>Hordeum</i> α -Hordothionin & β -Hordothionin (5 kDa protein)	<i>Hordeum vulgare</i> (barley) [seed] (Poaceae)	PM (PS) [permeabilize PM; antifungal]
<i>Hordeum</i> thionin BCP-2 (5 kDa protein)	<i>Hordeum vulgare</i> (barley) [leaf] (Poaceae)	PM (PS) [antifungal; binds chitin & β -1,3-1,6-glucan]
<i>Hordeum</i> leaf thionins DB4, DC4 & DG3 (5 kDa proteins)	<i>Hordeum vulgare</i> (barley) [leaf] (Poaceae)	PM (PS) [permeabilize PM; antifungal]
<i>Phoradendron</i> Ligatoxin (5 kDa protein)	<i>Phoradendron liga</i> (mistletoe) (Viscaceae); parasitic plant	PM [toxic]
<i>Phoradendron</i> Phoratoxins A & B (5 kDa protein)	<i>Phoradendron tomentosum</i> (mistletoe) (Viscaceae); parasitic plant	PM [Phoratoxin B depolarizes PM; toxic]
<i>Pyricularia</i> toxin (thionin) (5 kDa protein)	<i>Pyricularia pubera</i> (Santalaceae); parasitic plant	PM [permeabilizes & depolarizes PM; binds to unilamellar vesicles; haemolytic; antifungal]
<i>Triticum</i> α -1, α -2 & β -Purothionins (5 kDa proteins)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	PM – α -1 binds to unilamellar vesicles [permeabilize PM; model membrane interactions \rightarrow leakage & aggregation antifungal]
<i>Viscum</i> Viscotoxins A1, A2, A3, B & 1-PS (5 kDa proteins)	<i>Viscum album</i> (mistletoe) (Viscaceae) [seed]; parasitic plant	PM [permeabilize PM; antifungal, cytotoxic]

13 Inhibitors of digestion and metabolism

13.1 Introduction

Apart from photosynthesis, vacuolar metabolite storage and cell wall construction, plant metabolism is strategically and in detail much like the aerobic metabolism of other eukaryotes, that is, based on conservation of free energy through coupling formation of ATP to the oxidation of carbohydrate and other energy sources such as organic acids, long chain fatty acids and protein. As we have seen in the preceding chapters, plant chemical defences are overwhelmingly directed at the “signal transduction” regulatory elements of herbivores and plant pathogens, exploiting differences between the signalling biochemistry of such organisms and the plants they consume.

Where plants target common biochemical systems, there is elaborate protection of the plant from self-inflicted damage. Thus, cyanogenic glycosides are innocuous to the plant producer but after ingestion and digestion by herbivores yield cyanide (CN^-), a potent inhibitor of cytochrome oxidase and hence of the mitochondrial respiratory chain and aerobic metabolism. A further powerful strategy has been to impair herbivore and pathogen digestion of ingested plant-derived polysaccharides and proteins catalysed by glycosidases (glycohydrolases) and proteases (proteinases), respectively. Such inhibition impairs growth of herbivores (e.g. insect larvae) through nutrient deficiency and acts as a feeding deterrent.

Most of the plant defensive inhibitors encountered so far are low molecular weight secondary metabolites that, unlike proteins, can readily get across the plasma membrane of the target cells. However, since digestion by organisms with a gastrointestinal (GI) tract is extracellular, inhibition of such processes can be effected by protein inhibitors. This has a tremendous advantage of permitting the rapid evolution possible with protein inhibitors. Thus, a single point mutation may yield a more effective protease inhibitor (PI) protein in one plant generation whereas evolution of pathways yielding novel secondary metabolite inhibitors may take eons.

13.2 Glycohydrolases

Starch (from plants) and glycogen (from animals) are polymers of glucose in which the glucose residues are linked by α -1,4-glycosidic bonds (except for branch points at which α -1,6-glycosidic bonds are present). Salivary and pancreatic α -amylases hydrolyse α -1,4-glycosidic bonds of starch provided that the bonds are no closer than two residues to a chain terminus or a branch point, that is, these amylases cut at all bonds except at the outermost bonds and those bonds at branch points. The major products are the disaccharide maltose and the trisaccharide maltotriose together with longer linear polymers up to $(\text{glucose})_9$ and 1,6-branch products (5–9 glucose residues) known as α -dextrins.

A variety of glycohydrolases hydrolyse dietary oligosaccharides including the oligosaccharide products of α -amylase action on starch and glycogen. α -Glucosidase is an α -1,4-glycosidase located in the intestinal brush border membrane and successively removes glucose residues from linear oligosaccharides. Isomaltase (α -dextrinase) located in the intestinal brush border is an α -1,4- and α -1,6-glycosidase, hydrolysing both α -1,4- and α -1,6-glycosidic linkages. Other brush border glycosidases include: β -galactosidase (lactase) that hydrolyses the disaccharide lactose (β -galactose(1 \rightarrow 4)- α -glucose) to galactose and glucose; sucrase (β -fructofuranosidase) that hydrolyses sucrose (α -glucose(1 \rightarrow 2)- β -fructose) to yield glucose and fructose; and trehalase that hydrolyses the disaccharide trehalose (α -glucose(1 \rightarrow 1)- α -glucose) to glucose.

Cellulose (a β -1,4-glucan polymer), inulin (a polyfructosan), agar (a complex of variously sulphated hexose polymers involving β -1,4 and β -1,3 linkages) and cell wall β -1,3-glucans are indigestible polysaccharides. However, such an indigestible “fibre” is beneficial for bowel health. Reduced ability to digest oligosaccharides can have negative effects such as abdominal distention, cramps, pain, diarrhoea and flatulence. Thus, “lactose intolerance” arises from deficiency in the ability to digest lactose (e.g. from milk). Abdominal discomfort and flatulence can arise from consumption of legume seeds rich in indigestible oligosaccharides such as raffinose (α -Gal-(1 \rightarrow 6)- α -Glc-(1 \rightarrow 2)- β -Fru), stachyose (α -Gal-(1 \rightarrow 6)- α -Gal-(1 \rightarrow 6)- α -Glc-(1 \rightarrow 2)- β -Fru) and verbascone (α -Gal-(1 \rightarrow 6)- α -Gal-(1 \rightarrow 6)- α -Gal-(1 \rightarrow 6)- α -Glc-(1 \rightarrow 2)- β -Fru), these oligosaccharides being catabolized by intestinal anaerobic bacteria (see Chapter 9).

Compounds that inhibit oligosaccharide digestion not only impair herbivore nutrition but can also act as antifeedants. A variety of plant-derived secondary metabolites inhibit glycosidases (Table 13.1). Numerous plant protein glycosidase inhibitors have been isolated and some of these have dual functions as both α -amylase and trypsin inhibitors (Table 13.2).

Various glycosidases are involved in the modification, biosynthetic processing and trafficking of glycoproteins. Castanospermin and swainsonine, plant inhibitors of such glycosidases, interfere with glycoprotein biosynthesis and are consequently very toxic (Table 13.1).

13.3 Proteases

The proteases catalyse the hydrolysis of the peptide bonds in proteins. Proteases are grouped into the aspartic proteases, the cysteine proteases, the metalloproteases and the serine proteases because of the critical involvement of aspartic acid, cysteine, divalent metal ion or serine, respectively, in the catalytic mechanism. Proteases are involved extracellularly in the digestion of ingested proteins; in “protease cascades” in blood clotting; in extracellular matrix protein digestion in inflammatory responses and in angiogenesis required for tissue remodelling (and also pathologically for tumour growth). Proteases also have a wide range of intracellular functions including processing of newly synthesized proteins, protein turnover (notably involving ubiquitination and proteasome-mediated proteolysis), protein degradation during the cell cycle and apoptosis (programmed cell death).

The effective irreversibility of proteolysis means that proteases must be tightly controlled to prevent inappropriate proteolysis and autolysis. Thus, digestive proteases such as chymotrypsin, pepsin and trypsin exist as inactive zymogens (proenzymes) (chymotrypsinogen, pepsinogen and trypsinogen, respectively, in this example) before being secreted into the GI tract and subsequent activation. The caspases catalysing proteolysis in apoptosis (programmed cell death) are activated by “cascades” involving successive proteolytic activation of protease proenzymes. Successive proteolytic activation of proteases is involved in the

proteolytic “cascade” leading to blood clotting. Intracellular proteolysis is controlled through compartmentation of proteases within organelles called lysosomes (in which endocytosed proteins are degraded) and the control of cytosolic proteolysis through the proteasome machinery. Cytosolic proteins are marked for destruction by covalent linkage to the ubiquitous protein ubiquitin and are then degraded by the proteolytic proteasome complex. This elaborate process of cytosolic proteolysis enables strict control over key processes such as cell division in which stage-specific cyclin proteins are newly synthesized (for mitosis) and then destroyed.

Animal proteases, particularly those involved in blood clotting, can be also regulated by endogenous protease inhibitory proteins that act as inhibitory substrate analogues. These inhibitor proteins bind at the active site through key inhibitory sequences in which the key residues about the peptide bond contribute to inhibition and are denoted (N-terminal side)–P2–P1–(peptide bond to be hydrolysed)–P1′–P2′–(C-terminal side) or simply P2–P1–P1′–P2′. A large number of plant PI proteins also act as peptide substrate mimetics.

The major kinds of proteases and their plant-derived inhibitors are briefly described below.

(a) *Aspartic proteases*

Aspartic proteases are so-called because of the involvement of aspartic acid residues in the catalytic mechanism. The key features of some medically significant aspartic proteases are sketched below. Pepsin A, pepsin B, gastricsin and chymosin are secreted as inactive zymogens by the gastric mucosa and are subsequently activated at the low stomach pH which initiates a conformational change affecting autoinhibitory N-terminal prosegments and leading to their removal. Oesophagitis derives from excessive exposure of the oesophagus to gastric juice containing these enzymes. Cathepsin D is an aspartic protease that is overexpressed in breast cancer cells. A transmembrane aspartic protease (β -secretase) cuts an amyloid precursor protein to form the β -amyloid that forms amyloid deposits in Alzheimer’s disease. The aspartic protease renin cleaves angiotensinogen to form angiotensin I which is then cleaved by angiotensin converting enzyme (ACE) (a metalloprotease) to yield the vasoconstrictive hormone angiotensin II. The aspartic protease haemoglobinase of the malaria-causing organism *Plasmodium falciparum* is critical for parasite nutrition and is accordingly a potential drug target. The HIV-1 protease that is critical for HIV-1 replication is a major target for some clinically employed anti-HIV-1 drugs (Table 13.3). A variety of plant-derived substances inhibit HIV-1 protease (Table 13.3).

(b) *Cysteine proteases*

Cysteine proteases are so called because of a critical cysteine involved (together with an adjacent histidine) in the catalytic mechanism. Cysteine proteases include papain-related proteases, calpain-related proteases and the caspases. Papain-like cysteine proteases include the plant enzymes actinidin, aleurain, bromelain, caricain, chymopapain, ficin and papain and the lysosomal cathepsins B, C, H, K, L and S. Cathepsin C is multimeric (MW ~200,000), but the other papain-related proteases are monomeric with MWs of about 20,000–35,000. While cathepsin C is a dipeptidyl aminopeptidase, the other enzymes are endopeptidases. Cathepsin B is an endopeptidase and a dipeptidyl carboxypeptidase. Cathepsin H is an endopeptidase and an aminopeptidase. In higher animals, cathepsin B generates peptides from antigens for presentation to T cells by the major histocompatibility

complexes (MHCs) on antigen presenting cells (APCs) in the immune response. Lysosomal cysteine proteases are involved in protein degradation in lysosomes.

Ca^{2+} -activated neutral cysteine proteases include the heterodimeric μ - and *m*-calpains which are composed of homologous 80 kDa catalytic subunits and identical 30 kDa Ca^{2+} -binding regulatory subunits. Calpain activation requires a signal-induced elevation of cytosolic Ca^{2+} concentration and the activated calpains are inhibited by the calpain inhibitor protein calpastatin. Calpains are involved in Ca^{2+} -mediated signalling pathways, apoptosis (programmed cell death), cell cycle control (through cyclin destruction), neurodegenerative disease (e.g. Alzheimer's disease), muscular dystrophy, susceptibility to gastric cancer and in type 2 diabetes.

Caspases are involved in intracellular proteolytic protease activation "cascades" leading to apoptosis that are initiated by ligands such as tumour necrosis factor (TNF) and Fas ligand. These proteins bind to PM receptors with cytosolic "death domains" that activate the caspase cascades leading to cell death. Caspases are cysteine proteases that cleave peptide bonds on the carboxyl side of aspartate (hence c-asp-ases).

Animal lysosomal cathepsins are safely compartmented in lysosomes and are variously inhibited by the protein cystatins that also inhibit the related plant cysteine protease papain. The stefins A, B and D are Type 1 animal cystatins, these 11 kDa proteins having a structure involving an α -helix linked to five antiparallel β -strands. The Type 2 animal cystatins (notably egg white cystatin that is structurally similar to the Type 1 cystatins) include the 12 kDa cystatins C, D and S. The kininogens that are the protein precursors for pro-inflammatory kinins such as bradykinin, have cystatin-like domains and inhibit cysteine proteases such as papain and cathepsins B, H and L. The kininogens are single chain glycoproteins and include high MW kininogen (HK), low MW kininogen (LK) and T-kininogen (TK). After microbial invasion and wounding, kininogens are cleaved by the protease kallikrein to yield disulfide-linked heavy and light chains with loss of the vasodilatory, pro-inflammatory kinin part.

The plant cysteine proteases are necessarily initially inactive, are activated by N-terminal processing and indeed can be inhibited by the N-terminal inhibitory fragments of such processing. Plant phytocystatins are endogenous cysteine protease inhibitory proteins that are structurally similar to animal cystatins. The plant cysteine PIs inhibit insect digestive cysteine proteases and are also involved in control of seed germination through inhibition of cysteine proteases involved in seed storage protein degradation.

(c) *Metalloproteases*

Metalloproteases have a Zn^{2+} ion at the active site. The matrix metalloproteases (MMPs or matrixins) are involved in the degradation of the extracellular matrix and catalyse the hydrolysis of collagen, elastin, fibronectin, laminin, proteoglycans and glycoproteins found in the extracellular matrix. The MMPS include collagenases (MMP-1, MMP-8, MMP-13 and MMP-18), gelatinases A and B (MMP-2 and MMP-9, respectively), stromelysins 1, 2 and 3 (MMP-3, MMP-10 and MMP-11, respectively), matrilysin (MMP-7), metalloelastase (MMP-12), MMP-19 and membrane-type MMPs MT1-MMP, MT2-MMP, MT3-MMP and MT4-MMP (MMP-14, MMP-15, MMP-16 and MMP-17, respectively). As with other proteases, these enzymes are synthesized and secreted as inactive zymogens or proenzymes that are subsequently proteolytically activated. The MMPs have a major role in breaking down the extracellular matrix and permitting angiogenesis (the formation of new blood vessels). These enzymes are thus important in embryogenesis, endometrial cycling, organ

morphogenesis, tissue remodelling in development and wound healing. The activities of the MMPs are regulated by expression and degradation and also by protein tissue inhibitors of MMPs (TIMPs). MMPs also have a major role in tumour growth and inflammation and accordingly are potential targets for anticancer drugs and anti-inflammatory drugs. Certain plant carbohydrate-binding proteins (or lectins) can bind to externally oriented PM glycoproteins and activate signalling pathways that either induce or suppress synthesis of particular MMPs by leucocytes (Table 13.4).

The metalloprotease ACE catalyses the conversion of angiotensin I to the vasoconstrictive hormone angiotensin II. ACE inhibitors are widely used as anti-hypertensive drugs and a variety of plant-derived peptides are ACE inhibitors (Table 13.4).

The metalloprotease carboxypeptidase catalyses the removal of C-terminal residues and is structurally related to the PM-located epidermal growth factor (EGF) receptor tyrosine kinase (see Chapter 8). Several plant carboxypeptidase inhibitor proteins have been characterized and the potato carboxypeptidase inhibitor (PCI) is also an EGF receptor antagonist (Table 13.4).

(d) Serine proteases

Serine proteases are so called because their catalytic mechanism involves an active site serine. This key residue is transiently acylated by the N-terminal part of the cleaved peptide, the mechanism also involving an aspartate and a histidine at the active site. The serine protease family includes trypsin, chymotrypsin, chymase, elastase, cathepsin G, granzymes A, B, D and F, proteases A–D, tryptase, kallikrein, urokinase type plasminogen activator (uPA), the blood clotting factors V, VII, VIII, IX, X, XI, XII and XIII, thrombin (also involved in blood clotting) and the clot-removing protease plasmin (that is also involved in MMP activation). The serine proteases variously have important functions in angiogenic processes, blood clotting and blood clot removal, cellular proteolysis, protein processing, GI digestion, inflammation and tissue remodelling.

Trypsin cleaves a peptide bond on the C-terminal side of a basic residue such as arginine (Arg) or lysine (Lys) whereas chymotrypsin cleaves on the C-terminal side of the hydrophobic residues phenylalanine (Phe), tryptophan (Trp) or tyrosine (Tyr). Elastase cleaves on the C-terminal side of small amino acids such as alanine (Ala) and glycine (Gly). A large number of serine PI proteins have been isolated from plants (Table 13.4) and the substrate specificity of the target proteases corresponds with the inhibitory amino acid sequences (P2–P1–P1′–P2′) of the PI proteins. Thus, the “double-headed” trypsin- and chymotrypsin-inhibitory Bowman–Birk PI protein 1 (BBI-1) from soybean (*Glycine* BBI-1, Table 13.5G) has a P1–P1′ sequence of Lys–Ser at the trypsin inhibitory domain I site and a P1–P1′ sequence of Leu–Ser at the chymotrypsin inhibitory domain II site.

The plant-derived serine PI proteins fall into various classes including (approximate molecular masses in parentheses): monocot Bowman–Birk PIs (7–15 kDa), dicot Bowman–Birk PIs (typically 8 kDa), a cyclotide (cyclic protein) Bowman–Birk-related PI (2 kDa), Brassicaceae PIs (7–10 kDa), defensin PIs (6 kDa), Kunitz PIs (15–25 kDa), lipid transfer protein (LTP) PIs (10 kDa), napin PIs (14–16 kDa), potato inhibitor I family PIs (7–11 kDa), potato inhibitor II family PIs (6–12 kDa), squash family PIs (3 kDa), Ragi/barley bifunctional α -amylase inhibitor PIs (13–15 kDa), high MW plant serpins (45 kDa) and other PIs (Table 13.4).

Some of these PIs are among the most potent naturally occurring enzyme inhibitors or protein ligands. Thus the squash family serine PIs have protease K_i values of the order of

10 picomolar (10pM). With the exception of the Kunitz inhibitors, these PI proteins are very compact, disulfide-rich proteins and correspondingly very stable to protein denaturing conditions such as low pH and elevated temperature. The squash family PIs from *Momordica cochinchinensis* (Vietnamese squash) are unusual in being cyclic peptides (cyclotides) and a PI protein from *Helianthus annuum* (sunflower seeds) is also a cyclotide (Table 13.4).

13.4 Glycolysis and tricarboxylic acid cycle

Photosynthesis aside, basic energy metabolism in plant cells involving glycolysis and the tricarboxylic acid cycle is essentially the same as in plant-consuming eukaryotes. As we saw in Chapter 2, glycolysis is a cytosolic process in which the hexose sugar glucose (C₆) is converted to two molecules of the α -keto acid pyruvate (C₃). This exergonic (free energy releasing) process is “coupled” to the formation of ATP, the energy currency of cells. The net ATP yield from glycolytic conversion of glucose through to pyruvate is two ATP per glucose and a further two NADH (reduced nicotinamide adenine dinucleotide) per glucose are also generated in this process. However, the subsequent aerobic oxidation of pyruvate in mitochondria yields a much greater yield of ATP as outlined below.

In aerobic conditions, pyruvate (C₃) is oxidized in mitochondria to yield (other byproducts in parentheses) acetyl-coenzyme A (C₂, acetyl-CoA) (+ NADH, CO₂) [via pyruvate dehydrogenase]. The subsequent reactions of the TCA cycle also occur in the mitochondrial matrix. Acetyl-CoA (C₂-CoA) plus oxaloacetate (C₄, dicarboxylic acid) yields citrate (C₆, tricarboxylic acid) [via citrate synthase] which is subsequently transformed through successive intermediates of the TCA cycle. This process can be simply summarized in terms of its organic acid products as follows (other by-products in parentheses): citrate (C₆, tricarboxylic acid) \rightarrow *cis*-aconitate (C₆) \rightarrow isocitrate (C₆, tricarboxylic acid) [via aconitase] \rightarrow α -ketoglutarate (C₅, dicarboxylic acid) (+ NADH, CO₂) [via isocitrate dehydrogenase] \rightarrow succinyl-CoA (C₄-CoA) (+ NADH, CO₂) [via α -ketoglutarate dehydrogenase] \rightarrow succinate (C₄, dicarboxylic acid) (+ GTP) [via succinic thiokinase] \rightarrow fumarate (C₄, dicarboxylic acid) (+ FADH₂) [via succinate dehydrogenase] \rightarrow malate (C₄, dicarboxylic acid) [via fumarase] \rightarrow oxaloacetate (C₄, dicarboxylic acid) (+ NADH) [via malate dehydrogenase] \rightarrow continuation of the cycle.

The GTP formed as described above yields ATP [via nucleoside diphosphokinase]. The reduced coenzymes (4 NADH and FADH₂) feed electrons into the mitochondrial electron transport chain (ETC) to yield 14 ATP per pyruvate oxidized (12 ATP/4 NADH and 2 ATP/FADH₂) through the process of oxidative phosphorylation as described in Section 13.5. This total yield of ATP corresponds to a total of 32 ATP per glucose oxidized plus a further 6 ATP from mitochondrial oxidation of NADH generated in glycolysis, that is, 38 ATP per glucose oxidized.

13.5 Mitochondrial electron transport and oxidative phosphorylation

The mitochondrial ETC is composed of complex I (NADH-coenzyme Q reductase) and complex II (FADH₂ utilizing succinate-coenzyme Q reductase) [that both generate reduced coenzyme Q (CoQH₂)] and then, successively, complex III (CoQH₂-cytochrome *c* reductase) [that generates reduced cytochrome *c*] and complex IV (cytochrome oxidase) [that catalyses the final transfer of electrons to oxygen (O₂)]. The exergonic oxidation of NADH and FADH₂ via the ETC is coupled to the endergonic formation of ATP in the process called

oxidative phosphorylation. Oxidation of NADH yields 3 ATP and the oxidation of FADH₂ yields 2 ATP.

The synthesis of ATP in oxidative phosphorylation is catalysed by the F₀-F₁ ATPase (ATP synthase) complex associated with the mitochondrial inner membrane. The F₁ complex is knob-like, oriented towards the interior of the matrix and composed of many subunits ($\alpha_3\beta_3\gamma\delta\epsilon$) of which the β subunits catalyse ATP synthesis. The F₁ complex rotates around the F₀ complex (one a, two b and a dozen c subunits) which is buried in the mitochondrial membrane. The flow of electrons from reduced coenzymes (NADH and FADH₂) through the ETC results in electrogenic extrusion of protons across the mitochondrial membrane, this generating a large transmembrane potential difference (inside negative with respect to the outside). Protons (H⁺) return to the matrix via the F₀ complex in a process that results in the rotation of the F₁ complex and conformational changes of the β subunits to yield three successive states in which, respectively, ADP and phosphate bind; ATP is formed and is bound very tightly; and a state in which ATP is released from the active site.

Various plant-derived and other compounds interfere with oxidative phosphorylation at various levels. Thus, electron transport inhibitors interfere with the primary electron flow to the terminal electron acceptor oxygen (O₂), good examples being plant-derived rotenone and Annonaceae acetogenins (which block complex I NADH-coenzyme Q reductase) and plant cyanogenic glycoside-derived cyanide (CN⁻) (that inhibits the terminal complex IV cytochrome oxidase). Annonaceae acetogenins have cytotoxic and anticancer properties (Table 13.6). Uncouplers are H⁺-specific “ionophores” (or “protonophores”) that increase the permeability of the mitochondrial inner membrane to protons (H⁺ ions) and hence abolish the H⁺ (or electrical charge) gradient that “drives” oxidative phosphorylation. Uncouplers are typically very weak acids (such as phenolics) that are also lipophilic (i.e. soluble in the membrane lipid bilayer). Some plant-derived phenolics are uncouplers (noting that glycosylation of such compounds would decrease lipophilicity and potentially protect the plant from uncoupling its own mitochondria). Ionophores that increase the membrane permeability for other key ions (e.g. for K⁺) can also uncouple by abolishing the transmembrane potential difference that is interconvertible with the H⁺ gradient that drives ATP synthesis. Finally, “energy-transfer inhibitors” inhibit the ATP synthase that actually uses the H⁺ gradient to make ATP. Some plant-derived phenolics are inhibitors of the ATP synthase (Table 13.6).

13.6 Gluconeogenesis

A key metabolic process in man involves maintenance of a blood glucose concentration of about 4 mM to satisfy the glucose-dependent functioning of the brain. This process involves various organs and tissues and is exquisitely regulated by hormones, notably glucagon (in fasting) and insulin (after eating). In periods of fasting, gluconeogenesis (i.e. synthesis of glucose from amino acids and lactate) helps increase blood glucose in the absence of ingestion of glucose or glucose precursors (see Chapter 2). The protein-derived amino acids alanine (C₃) and aspartate (C₄) yield pyruvate (C₃, α -keto carboxylic acid) and oxaloacetate (C₄, α -keto dicarboxylic acid), respectively, [via pyridoxalphosphate-dependent transamination catalysed by alanine- α -ketoglutarate aminotransferase and aspartate- α -ketoglutarate aminotransferase, respectively]. Pyruvate (C₃) is also generated from the anaerobic glycolysis endproduct lactate (C₃) [via NAD⁺-dependent lactate dehydrogenase]. In the mitochondrion pyruvate (C₃) is converted to oxaloacetate (C₄) [via ATP- and biotin-dependent pyruvate carboxylase] which is thence converted to phosphoenolpyruvate (PEP, C₃)

[via cytosolic GTP-dependent PEP carboxykinase (PEPCK)]. The reversion of the glycolytic pathway from PEP ultimately yields glucose-6-phosphate (C_6) and thence glucose (C_6) in the blood [via glucose-6-phosphate phosphohydrolase]. It should be noted that pyruvate carboxylase (mitochondrial), PEPCK (cytosolic), phosphofructokinase (PFK) (cytosolic) and fructose 1,6-bisphosphatase (FBPase) (cytosolic) are critically feedback- and feed-forward-regulated by particular metabolites to achieve this gluconeogenic carbon flow back to glucose.

Fatty acid and acetate (the product of fatty acid oxidation) cannot be converted back to carbohydrate in animals through gluconeogenesis. However, this is possible in plants, notably in plant seeds during germination. Plant seeds are often rich in triacylglycerides which yield fatty acids and thence acetyl-CoA (C_2) through fatty acid oxidation (β -oxidation). The glyoxylate cycle occurs in the specialized plant organelles called glyoxysomes as follows: isocitrate (C_6 , tricarboxylic acid) \rightarrow succinate (C_4 , dicarboxylic acid) + glyoxylate (C_2 , aldehyde-carboxylic acid) [via isocitrate lyase]; glyoxylate (C_2) + acetyl-CoA (C_2 -CoA) \rightarrow malate (C_4 , dicarboxylic acid) [via malate synthase]. Both succinate (C_4) and malate (C_4) generate oxaloacetate (C_4) that can enter the gluconeogenesis pathway by GTP-dependent conversion to PEP (C_3) [via PEPCK]. This enables fatty acids to be converted into carbohydrate by this anabolic pathway to provide readily transportable energy for seedling growth.

Gluconeogenesis (occurring principally in the mammalian liver) is switched on by the successive events of fasting, decrease in blood glucose, consequential pancreatic secretion of the peptide hormone glucagon, elevation of the “hunger signal” cAMP, decrease in the “plenty signal” fructose 2,6-bisphosphate (F26BP) and activation or inhibition of key enzymes. Gluconeogenesis is also promoted by cortisol-mediated and cAMP-mediated expression of PEPCK. It is consequently subject to indirect interference by plant compounds that interfere with G protein-linked signalling (Chapter 5), cyclic AMP metabolism (such as cAMP phosphodiesterase inhibitors or adenylyl cyclase ligands) (Chapter 7), cAMP-dependent protein kinase (PKA) (see Chapter 8) and glucocorticoid hormone action (Chapter 11).

13.7 Solute translocation

Necessary solutes (such as glucose) have to be taken up by cells and unwanted compounds have to be removed from cells (e.g. CO_2 , urea and xenobiotics). Such translocation can be passive (not requiring an energy source) or active (requiring coupling to an exergonic reaction such as the hydrolysis of ATP). Active or passive membrane-associated transporter proteins mediate such translocations. As detailed in Table 13.7, a variety of plant-derived compounds interfere with such translocators. Thus, plant-derived atractyloside inhibits the transmembrane potential-driven ATP/ADP translocator that transports ADP into mitochondria for phosphorylation and simultaneously ejects the triphosphorylated entity ATP. Other plant-derived components variously inhibit the cystic fibrosis transmembrane conductance regulator (CFTR) (responsible for ATP-dependent chloride efflux and resultant water removal), the passive glucose transporter (mobilized to the plasma membrane by insulin signalling) and the Na^+ -dependent coupled translocation of glucose into intestinal cells driven by the Na^+ gradient set up via the Na^+ , K^+ -ATPase (see Chapter 4).

A large number of plant compounds interact with the ATP-dependent, multidrug resistance transporter (MDR transporter or P glycoprotein transporter). This belongs to the ATP-binding cassette family of solute transporters (ABC transporters) and functions to remove unwanted chemicals of xenobiotic origin (notably compounds from plants).

The MDR transporter is of importance in drug resistance in antiprotozoal and anticancer chemotherapy and hence compounds that inhibit this transporter are potentially very useful as adjuncts to chemotherapy to overcome such drug resistance (Table 13.7). This chapter also deals with numerous plant-derived compounds that inhibit various other enzymes (Table 13.8).

Table 13.1 Inhibition of glycosidases by plant non-protein compounds

<i>Compound (details)</i>	<i>Plant source (family) plant part </i>	<i>Biochemical target inhibited (other targets) in vivo effects </i>
Alkaloids		13.1a
Alexine (polyhydroxy pyrrolizidine)	<i>Alexa leiopetala</i> (Fabaceae)	Glucan 1,4- α -glucosidase; trehalase; thioglucosidase
1,7a- <i>diepi</i> -Alexine (polyhydroxy pyrrolizidine)	<i>Castanospermum australe</i> (Fabaceae) [seed]	Glucan 1,4- α -glucosidase
7,7a- <i>diepi</i> -Alexine (polyhydroxy pyrrolizidine)	<i>Castanospermum australe</i> (Fabaceae) [seed]	Glucan 1,4- α -glucosidase; trehalase
3,7a- <i>diepi</i> -Alexine (polyhydroxy pyrrolizidine)	<i>Castanospermum australe</i> (Fabaceae) [seed]	Glucan 1,4- α -glucosidase
7a- <i>epi</i> -Alexine (= Australine) (polyhydroxy pyrrolizidine)	<i>Castanospermum australe</i> (Fabaceae) [seed]	Glucan 1,4- α -glucosidase; amyloglucosidase (α - glucosidase); glycoprotein processing glucosidase I; [glycoprotein processing impairment]
Broussonetines A–H, K–T, U & V (pyrrolidine alkaloids)	<i>Broussonetia kazinoki</i> (Moraceae)	Glycosidase
β -1-C-Butyl- deoxygalactonojirimycin (piperidine)	<i>Adenophora</i> spp. (Campanulaceae) [root]	α -Galactosidase
Calystegine A3 (trihydroxy nortropane)	<i>Physalis alkekengi</i> (Solanaceae); <i>Calystegia sepium</i> (Convolvulaceae) [root]; edible fruit & vegetables (Convolvulaceae, Moraceae, Solanaceae)	β -Glycosidase; α -glycosidase; β -xylosidase; β -glucosidase
Calystegine B1 (tetrahydroxy nortropane)	<i>Physalis alkekengi</i> (Solanaceae), <i>Calystegia sepium</i> (Convolvulaceae) [root]; edible fruit & vegetables (Convolvulaceae, Moraceae, Solanaceae)	β -Glucosidase; β -galactosidase; β -xylosidase
Calystegine B2 (tetrahydroxy nortropane)	<i>Physalis alkekengi</i> (Solanaceae), <i>Ipomoea carnea</i> , <i>Calystegia sepium</i> (Convolvulaceae) [root]; edible fruit & vegetables (Convolvulaceae, Moraceae, Solanaceae)	β -Glucosidase; α -glycosidase; α -galactosidase; β -xylosidase [lysosomal storage disease]
Calystegine B4 (tetrahydroxy nortropane)	<i>Scopolia japonica</i> (Solanaceae)	β -Glucosidase; trehalase
Calystegine C1 (tetrahydroxy nortropane)	<i>Ipomoea carnea</i> (Convolvulaceae) [aerial]; edible fruit & vegetables (Convolvulaceae, Moraceae, Solanaceae)	β -Glucosidase; β -galactosidase; β -xylosidase

(continued)

Table 13.1 (Continued)

Compound (details)	Plant source (family) / plant part/	Biochemical target inhibited (other targets) / in vivo effects/
Castanospermine (= 1,6,7,8-Tetrahydroxy-octahydroindolizine) (tetrahydroxy indolizine)	<i>Castanospermum australe</i> (Fabaceae) [seed]	Glucan 1,4- α -glucosidase (an exo-1,4- α -glucosidase); β -glucosidase; trehalase; thioglucosidase; glycoprotein processing glucosidases I & II; [glycoprotein processing impairment; toxic]
6- <i>epi</i> -Castanospermine (tetrahydroxy indolizidine)	<i>Castanospermum australe</i> (Fabaceae) [seed]	Amyloglucosidase (an exo-1,4- α -glucosidase); β -glucosidase (weak)
6,7- <i>diepi</i> -Castanospermine (tetrahydroxy indolizidine)	<i>Castanospermum australe</i> (Fabaceae) [seed]	Amyloglucosidase (an exo-1,4- α -glucosidase); β -glucosidase
(+)-Casuarine (pentahydroxy pyrrolizine)	<i>Casuarina equisetifolia</i> (Casuarinaceae) [bark]	Glucosidase I
5-Deoxyadenophorine (piperidine)	<i>Adenophora</i> spp. (Campanulaceae) [root]	α -Galactosidase
6-Deoxy-DMDP (pyrrolidine)	<i>Angylocalyx pynaertii</i> (Fabaceae) [seed]	β -Mannosidase
6-DeoxyhomoDMDP (piperidine)	<i>Hyacinthus orientalis</i> (Hyacinthaceae) [bulb]	α -Glucosidase; maltase
Deoxymannojirimycin (DMJ) (polyhydroxy piperidine)	<i>Angylocalyx pynaertii</i> , <i>A.</i> spp., <i>Lonchocarpus sericeus</i> , <i>L. costaricensis</i> (Fabaceae) [seed]; <i>Hyacinthus orientalis</i> (Hyacinthaceae) [bulb]; <i>Omphalea</i> spp. (Euphorbiaceae)	Mannosidase I
1-Deoxynojirimycin (polyhydroxy piperidine)	<i>Hyacinthus orientalis</i> (Hyacinthaceae) [bulb]; <i>Morus</i> spp. (Moraceae)	Sucrase & isomaltase; α -glucosidase; β -glucosidase
1,5-Dideoxy-1,5-imino-D-mannitol (polyhydroxy piperidine)	<i>Omphalea</i> spp. (Euphorbiaceae)	α -Glycosidases
(2 <i>R</i> ,5 <i>R</i>)-Dihydroxymethyl-(3 <i>R</i> ,4 <i>R</i>)-dihydroxypyrrolidine (DMDP) (polyhydroxy pyrrolidine)	<i>Derris elliptica</i> [leaf], <i>Lonchocarpus sericeus</i> [seed] (Fabaceae), <i>Hyacinthus orientalis</i> (Hyacinthaceae) [bulb] <i>Omphalea</i> spp. (Euphorbiaceae)	α -Glycosidases; α - & β -glucosidases; thioglucosidase; viral glycoprotein processing glucosidase I [insect antifeedant & larvicide]
3- <i>epi</i> -Fagomine (polyhydroxy piperidine)	<i>Xanthocercis zambesiaca</i> (Fabaceae)	Isomaltase; β -glucosidase
Fagomine (polyhydroxy piperidine)	<i>Angylocalyx pynaertii</i> , <i>Xanthocercis zambesiaca</i> (Fabaceae); <i>Fagopyrum esculentum</i> (Polygonaceae) [seed]	Isomaltase; α -glucosidase; β -glucosidase
7- <i>O</i> - β -D-Glc-5-deoxy-adenophorine (glycosylated piperidine)	<i>Adenophora</i> spp. (Campanulaceae) [root]	α -Glucosidases; α -galactosidase
7- <i>O</i> - β -D-Glc- α -homonojirimycin (glycosylated piperidine)	<i>Lobelia sessilifolia</i> (Campanulaceae) [whole]	α -Glucosidase; trehalase
Harmaline (3,4-dihydroharmine) (indole)	<i>Banisteria caapi</i> , <i>Banisteriopsis caapi</i> (Malpighiaceae), <i>Passiflora incarnata</i> (Passifloraceae), <i>Peganum harmala</i> (Zygophyllaceae)	Invertase (sucrose hydrolase) (weak)

(continued)

Table 13.1 (Continued)

Compound (details)	Plant source (family) / plant part/	Biochemical target inhibited (other targets) / in vivo effects/
HomoDMDP (see DMPD) (pyrrolidine)	<i>Hyacinthus orientalis</i> , <i>Hyacinthoides non-scripta</i> (Hyacinthaceae) [bulb]	β -Glucosidase [2]; β -galactosidase [2]; lactase; trehalase [2]
HomoDMDP-7- <i>O</i> - β -D-Xyl (pyrrolidine)	<i>Hyacinthoides non-scripta</i> (Hyacinthaceae) [bulb]	β -Glucosidase [60 nM], lactase [70 nM], β -galactosidase
α -Homonojirimycin (piperidine)	<i>Omphalea</i> spp. (Euphorbiaceae)	α -Glycosidases
α -4- <i>epi</i> -Homonojirimycin (piperidine)	<i>Aglaonema treublilii</i> (Araceae)	Glycosidase
2,5-Imino-2,5,6-trideoxy-d-gulo-heptitol (imino sugar)	<i>Hyacinthus orientalis</i> (Hyacinthaceae) [bulb]	α -L-Fucosidase
Lentiginosine (dihydroxy indolizidine)	<i>Astragalus lentiginosus</i> (Fabaceae) [leaf]	Amyloglucosidase (α -glucosidase)
<i>N</i> -Methylcalystegine B2 (tetrahydroxy nortropane)	<i>Lycium chinense</i> (Solanaceae) [root]	α -Galactosidase; α -galactosidase [model for lysosomal storage disorder Fabry's disease]
<i>N</i> -Methylcalystegine C1 (tetrahydroxy nortropane)	<i>Lycium chinense</i> (Solanaceae) [root]	β -Glucosidase
Swainsonine (polyhydroxy indolizidine)	<i>Swainsona canescens</i> , <i>S. luteola</i> , <i>S. galagifolia</i> , <i>Astragalus</i> spp., <i>Oxytropis</i> spp. (Fabaceae)	Golgi α -D-mannosidase II; lysosomal mannosidase; glycoprotein <i>N</i> -linked oligosaccharide processing [toxic, neurotoxic effects mimic hereditary lysosomal storage disease mannosidosis]
Trihydroxypipelic acid (trihydroxylated piperidine)	<i>Baphia racemosa</i> (Papilionaceae) [seed]	β -D-Glucuronidase; α -L-iduronidase
Uniflorine A (= 1,2,6,7,8-Pentahydroxyindolizidine) (indolizidine)	<i>Eugenia multiflora</i> (Myrtaceae) [leaf]; antidiabetic plant	Glucosidase
Uniflorine B (= 1,2,5,7,8-Pentahydroxyindolizidine) (indolizidine)	<i>Eugenia multiflora</i> (Myrtaceae) [leaf]; antidiabetic plant	Glucosidase
Phenolics		13.1p
Baicalein (= 5,6,7-Trihydroxy flavone) (polyhydroxy flavone)	<i>Scutellaria baicalensis</i> , <i>S.</i> spp. (Lamiaceae) [root, leaf], <i>Plantago major</i> (Plantaginaceae)	Sucrase (α -glycosidase)
Desmanthin-1 (= 2''- <i>O</i> -Galloylmyricitrin; 2''- <i>O</i> -Galloylmyricetin-3- <i>O</i> -rhamnoside) (flavonol glycoside gallic acid ester)	<i>Myrcia multiflora</i> (Myrtaceae) [leaf]	Maltase (α -glycosidase) (240), sucrase (α -glycosidase) (260) (AR)
Diacylcyanidin (anthocyanidin)	<i>Pharbitis</i> sp. (morning glory) (Convolvulaceae)	α -Glucosidase
Diacylpelargonidin (anthocyanidin)	<i>Pharbitis</i> sp. (morning glory) (Convolvulaceae)	α -Glucosidase
3- <i>O</i> -Digalloyl-1,2,6-trigalloyl-D-glucose (gallotannin)	<i>Spirogyra varians</i> (freshwater green alga)	α -Glucosidase (0.3) (NADH DH, succinate DH)

(continued)

Table 13.1 (Continued)

Compound (details)	Plant source (family) / plant part/	Biochemical target inhibited (other targets) / in vivo effects/
Guaijaverin (= Quercetin-3- <i>O</i> -1-arabinoside) (flavonol <i>O</i> -glycoside)	<i>Hypericum brasiliense</i> (Guttiferaceae) [leaf, flower], <i>Myrcia multiflora</i> (Myrtaceae) [leaf]	Maltase (α -glycosidase) (290), sucrase (α -glycosidase) (100) (AR)
Isoscutellarein-8- <i>O</i> - glucuronide (flavone glycoside)	<i>Scutellaria baicalensis</i> (Lamiaceae) [leaf]	Sialidase
Methyl gallate (= 3,4,5- trihydroxybenzoic acid methyl ester) (phenolic ester)	<i>Rheum officinale</i> (Polygonaceae), <i>Paeonia suffruticosa</i> (Boraginaceae)	Sucrase (α -glycosidase)
Myrciacitrin I (flavanone glucoside)	<i>Myrcia multiflora</i> (Myrtaceae) [leaf]	Maltase (α -glycosidase) (600), sucrase (α -glycosidase) (700) (AR)
Myrciaphenone B (acetophenone glycoside)	<i>Myrcia multiflora</i> (Myrtaceae) [leaf]	Maltase (α -glycosidase) (440), sucrase (α -glycosidase) (310) (AR)
Myricitrin (= 5,7,3',4',5'- Pentahydroxyflavone-3- <i>O</i> - rhamnoside; Myricetin-3- <i>O</i> - rhamnoside) (flavone glycoside)	<i>Catha edulis</i> (khat) (Celastraceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Myrcia multiflora</i> (Myrtaceae) [leaf]	Maltase (α -glycosidase) (420), sucrase (α -glycosidase) (490) (AR)
Pentagalloyl- β -D-glucose (gallotannin)	<i>Acer</i> (Aceraceae), <i>Cotinus</i> , <i>Rhus</i> , <i>Schinus</i> (Anacardiaceae), <i>Terminalia</i> (Combretaceae), <i>Quercus</i> (Fagaceae), <i>Geranium</i> (Geraniaceae), <i>Nuphar</i> (Nymphaeaceae), <i>Epilobium</i> , <i>Fuchsia</i> (Onagraceae), <i>Paeollia</i> , <i>Paeonia lactiflora</i> (Paeoniaceae), <i>Rosa</i> (Rosaceae), <i>Camellia</i> (Theaceae)	α -Glucosidase (2) (ETC – NADH DH, H ⁺ , K ⁺ -ATPase, Na ⁺ , K ⁺ -ATPase)
1,2,3,6-Tetra- <i>O</i> -galloyl-D- glucose (gallotannin)	<i>Quercus pedunculata</i> (Fagaceae)	α -Glucosidase (3) (NADH DH, succinate DH)
1,2,6-Tri- <i>O</i> -galloyl-D-glucose (gallotannin)	<i>Terminalia catappa</i> (Combretaceae), <i>Mallotus japonica</i> (Euphorbiaceae)	α -Glucosidase (7) (NADH DH, succinate DH)
Terpenes		13.1t
Aescins (= Escins) (triterpene glycosides)	<i>Aesculus hippocastanum</i> (horse chestnut) (Hippocastanaceae)	HYAL (150) (permeabilize membranes) [antifungal, AI, haemolytic]
Escinol (triterpene)	<i>Aesculus hippocastanum</i> (horse chestnut) (Hippocastanaceae)	HYAL (hyaluronidase) (1650)
Hederagenin (triterpene sapogenin)	<i>Hedera helix</i> (ivy) (Araliaceae) [leaf]	HYAL (280)
Oleanolic acid (oleanane triterpene)	<i>Luffa cylindrica</i> (sponge gourd); (Cucurbitaceae), <i>Lavandula</i> , <i>Rosmarinus</i> , <i>Salvia</i> , <i>Thymus</i> (Lamiaceae), <i>Syzygium aromaticum</i> (Myrtaceae); 3- <i>O</i> -glucuronide in <i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae)	HYAL (300) (C3-convertase, DNAL, DNAP, ELA, HYAL, PK, TOPI, TOPII) [anti- angiogenic, AI]

(continued)

Table 13.1 (Continued)

Compound (details)	Plant source (family) plant part	Biochemical target inhibited (other targets) in vivo effects
3,11 β ,5 α ,23,24-Pentahydroxy-30-norolean-12,20(29)-dien-28-oic acid (triterpene)	<i>Paeonia emodi</i> (Paeoniaceae)	β -Glucuronidase
Scoparic acid A (labdane-type diterpene acid)	<i>Scoparia dulcis</i> (Scrophulariaceae)	β -Glucuronidase
Other		13.1o
D-Glucaro-1,4-lactone (sugar)	Widespread (e.g. edible vegetables & fruit)	Intestinal & liver microsomal β -glucuronidase
Glucarate (sugar)	Widespread (e.g. edible vegetables & fruit)	[Yields D-glucaro-1,4-lactone which inhibits intestinal & liver microsomal β -glucuronidase]
δ -Gluconolactam (sugar)	Widespread	β -Glucosidase
Kotalanol (tetrahydrothiophene)	<i>Salacia oblonga</i> (Celastraceae) [root]	Rat intestinal maltase & sucrase (α -glycosidase)
Salacinol (tetrahydrothiophene)	<i>Salacia oblonga</i> (Celastraceae) [root]	Rat intestinal maltase & sucrase (α -glycosidase)

Table 13.2 Plant α -amylase inhibitor (α AI) proteins

Protein (properties)	Plant source (family) plant part	Target inhibited (other targets) in vivo effects
<i>Amaranthus</i> α AI AAI (32 aa; 4 kDa; 6 Cys; knottin- like protein)	<i>Amaranthus</i> <i>hypochondriacus</i> (amaranth) (Amaranthaceae) [seed]	α A (insect)
<i>Avena</i> α AI 10 kDa; LTP-like protein)	<i>Avena sativa</i> (oats) (Poaceae) [seed]	α A (weak)
<i>Coix</i> α AI-endochitinase (2 \times 26,400 Da S-S-linked dimeric protein)	<i>Coix lachryma-jobi</i> (Job's tears) (Poaceae) [seed]	α A (animal, fungal, bacterial) [α AI \rightarrow insect antifeedant; endochitinase \rightarrow antifungal per chitin-binding & cell wall digestion]
<i>Eleusine</i> α AI I-2 (95 aa; 10 kDa; LTP- homologous protein)	<i>Eleusine coracana</i> (ragi, Indian finger millet) (Poaceae) [seed]	α A
<i>Eleusine</i> TRY- α AI = RBI (Ragi bifunctional I) = RATI (Ragi α A and Trypsin I) (122 aa; 13 kDa protein; 10 Cys; 5 S-S; protein)	<i>Eleusine coracana</i> (ragi, Indian finger millet) (Poaceae) [seed]	α A (insect), TRY [anti-insect]
<i>Hordeum</i> PAPI (Probable α A & protease I) = LTP-1 (10 kDa)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	<i>Eleusine</i> α AI I-2 homologue [antifungal, anti-insect]
<i>Hordeum</i> BMAI-1 (Barley monomeric α AI-1) (146 aa; 16 kDa glycoprotein)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	α A (insect) [anti-insect]

(continued)

Table 13.2 (Continued)

Protein (properties)	Plant source (family) plant part	Target inhibited (other targets) in vivo effects
<i>Hordeum</i> BDAI-1 (Barley dimeric α AI-1) (122 aa; 13 kDa monomer; dimeric protein)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	α A (insect) [anti-insect]
<i>Hordeum</i> CM α A-TRY I proteins a–e (Barley chloroform-methanol soluble proteins a–e) = BTAI (Barley tetrameric α AI – CMA–e subunits) (16 kDa monomers; tetrameric glycoproteins)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	α A (insect) (CMA), TRY (CMc, CMe) [anti-insect]
<i>Hordeum</i> BASI (Barley α A & SUB I) (20 kDa Kunitz-related protein)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	Bifunctional I – α A (insect), SUB [antifungal, anti-insect]
<i>Lablab</i> AILP (36 kDa lectin-like protein)	<i>Lablab purpureus</i> (Fabaceae)	α A (fungal) [related to lectin, arcelin & α A inhibitor proteins]
<i>Oryza</i> PAPI-B (Probable α A & protease I-B) (10 kDa protein)	<i>Oryza sativa</i> (rice) (Poaceae) [seed]	<i>Eleusine</i> α AI I-2 homologue [antifungal, anti-insect]
<i>Oryza</i> RASI (Rice α A & SUB I) (20 kDa Kunitz-related protein)	<i>Oryza sativa</i> (rice) (Poaceae) [seed]	Bifunctional I – α A (insect), SUB [antifungal, anti-insect]
<i>Oryza</i> RA proteins (Rice α A/TRY I family allergenic proteins) – e.g. RA1, RA14 (14–16 kDa proteins)	<i>Oryza sativa</i> (rice) (Poaceae) [seed]; rice Bengali staple; Amartya Sen “entitlement” famine analysis (India/UK, Nobel Prize, Economics, 1998)	α A [allergenic, antifungal, anti-insect]; man-made (rice price/income) Bengal 1769–1770 famine killed 10 million (see Adam Smith & Thomas Macaulay) & Bengal 1943–44 famine killed 4 million people (see Amartya Sen, Paul Greenough & Satyajit Ray)
<i>Phaseolus</i> α AI (PHA-I) (α AI, arcelin & phytohaemagglutinin homology family) (29 kDa α glycoprotein subunit–15 kDa β glycoprotein subunit)	<i>Phaseolus coccineus</i> , <i>P. costaricensis</i> , <i>P. lunatus</i> , <i>P. polyanthus</i> , <i>P. vulgaris</i> (common bean) (Fabaceae) [seed]	α A [anti-insect]
<i>Secale</i> α AI 1, 2 & 3 (cereal TRY/ α AI family) (13 kDa proteins)	<i>Secale cereale</i> (rye) (Poaceae) [seed]	α A (insect) (1–3), α A (human) (1 & 3) [allergenic, anti-insect]
<i>Secale</i> RAI-3 (Rye α AI-3) (cereal TRY/ α AI family) (13 kDa protein)	<i>Secale cereale</i> (rye) (Poaceae) [seed]	α A (insect, human) [allergenic, anti-insect]
<i>Secale</i> c1 (cereal trypsin/ α AI family) (13 kDa protein)	<i>Secale cereale</i> (rye) (Poaceae) [seed]	Homologous to cereal trypsin/ α AI family proteins; inactive as α AI [allergenic, anti-insect]
<i>Sorghum</i> defensin (γ -thionin) α AI 1 (SI α -1, SI α -2, SI α -3) (5 kDa; 8 Cys; 4 S–S proteins)	<i>Sorghum bicolor</i> (sorghum) (Poaceae) [seed]	α A [antifungal, anti-insect]
<i>Sorghum</i> α AI 1 & 2 (SI α 4, SI α 5) (13 kDa; 8 Cys; 4 S–S proteins)	<i>Sorghum bicolor</i> (sorghum) (Poaceae) [seed]	α A [allergenic, anti-insect]
<i>Triticum</i> PAPI (Probable α A & protease I) (10 kDa LTP-like protein)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	<i>Eleusine</i> α AI I-2, <i>Hordeum</i> PAPI & LTP homologue [antifungal, anti-insect] [allergenic]

(continued)

Table 13.2 (Continued)

<i>Protein (properties)</i>	<i>Plant source (family) / plant part</i>	<i>Target inhibited (other targets) / in vivo effects</i>
<i>Triticum</i> 0.19AI; 0.28AI (= CIII; Wheat monomeric α AI-1 (WMAI-1)); 0.39AI (14kDa; 10 Cys; 5 S-S proteins)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	α A [allergenic, anti-insect]
<i>Triticum</i> 0.53AI; Wheat dimeric α AI-3 (WDAI-3); CM2 (2 \times 14kDa subunit S-S-linked homodimer; 9 Cys; 5 S-S proteins)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	α A (homologous to 0.53AI-type proteins [allergenic, anti-insect])
<i>Triticum</i> WASI (Wheat α A/subtilisin inhibitor) (20kDa Kunitz-related protein)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	α A (SUB) [anti-insect]
<i>Triticum</i> tetrameric α AI (cereal TRY/ α AI family; chloroform/methanol (CM) soluble subunit types CM1, CM3, CM16) (glycosylated 16kDa subunit tetrameric proteins)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	α A ([allergenic, anti-insect]; major famines involving wheat as a major staple in India (eighteenth, nineteenth, & twentieth centuries), China (nineteenth & twentieth centuries), Russia (1921), China (1928–1930), Ukraine (1928–1930), Europe, China & India (Second World War), China (Great Leap Forward, 1959–1962))
<i>Zea</i> CHFI (Corn Human Activated Hageman Factor [Factor XII] Inhibitor = Popcorn Inhibitor) (14kDa, 10 Cys, 5 S-S protein)	<i>Zea mays</i> (corn, maize) (Poaceae) [seed]	α A (insect) (β -Factor XIIa (human, pig) [anti-insect])
<i>Zea</i> TRY/ α AI (22kDa, 16 Cys, 8 S-S)	<i>Zea mays</i> (corn, maize) (Poaceae) [seed]	α A (TRY) [homologous to plant sweet defensive protein Thaumatin; antifungal, anti-insect]

Table 13.3 Plant polygalacturonase-inhibiting proteins

<i>Compound (details)</i>	<i>Plant source (family) / plant part</i>	<i>Target (other targets) / in vivo effects</i>
Polygalacturonase (PG) inhibiting protein (PGIP)		13.3
<i>Arabidopsis</i> PGIP-like proteins (~24kDa, 40kDa proteins)	<i>Arabidopsis thaliana</i> (Brassicaceae)	PG
<i>Gossypium</i> PGIP (34kDa monomer, 66 kDa dimeric protein)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [root, stem]	PG [15nM]

(continued)

Table 13.3 (Continued)

Compound (details)	Plant source (family) plant part	Target (other targets) in vivo effects
<i>Lycopersicon</i> PGIP (35–41 kDa native; 34 kDa protein aglycone)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [fruit]	PG
<i>Medicago</i> PGIP (protein)	<i>Medicago sativa</i> (alfalfa) (Fabaceae)	PG
<i>Phaseolus</i> PGIP (~37 kDa protein)	<i>Phaseolus vulgaris</i> (French bean) (Fabaceae)	PG
<i>Pyrus</i> PGIP (~37 kDa protein)	<i>Pyrus communis</i> (pear) (Rosaceae)	PG
<i>Rubus</i> PGIP (39 kDa protein)	<i>Rubus idaeus</i> (raspberry) (Rosaceae) [fruit]	PG [0.8]
<i>Solanum</i> PGIP (41 kDa protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [leaf]	PG [wounding-, salicylic acid- & fungal elicitor-induced]

Table 13.4 Inhibition of proteases by plant non-protein compounds

Compound (details)	Plant source (family) plant part	Target (other targets) in vivo effects
Aspartate protease (ASPPR)		13.4
[Pepstatin A] (peptide)	Synthetic	ASPPR
HIV-1 Protease (HIV-1PR)		13.4A
Phenolic		13.4Ap
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	<i>Ocimum sanctum</i> (basil) Lamiaceae [leaf, stem], ferns [leaf surface]; glycosides widespread e.g. <i>Apium graveolens</i> (celery), <i>Petroselinum</i> (parsley) (Apiaceae), <i>Cosmos bipinnatus</i> , <i>Erigeron annuus</i> <i>Dahlia variabilis</i> (Asteraceae) [flower], <i>Amorpha fruticosa</i> (Fabaceae)	HIV-1 PR (60) (ADH, COX, PGP TR, PK, RTK) [blocks COX-2 & iNOS induction per IκB kinase inhibition; antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
Amariin (hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae)	HIV-1 PR (<53)
Butein (chalcone)	<i>Robinia pseudoacacia</i> , <i>Vicia faba</i> (Fabaceae); as 4'-glucoside Coreopsin in <i>Bidens</i> sp., <i>Coreopsis douglassii</i> (Asteraceae)	HIV-1 PR
Corilagin (hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae)	HIV-1 PR (21)
[3,2'-Dihydroxyflavone] (flavone)	Semi-synthetic	HIV-1 PR (12)
Epigallocatechin- (4β → 8, 2β → O-7)-epicatechin (tannin)	<i>Xanthoceras sorbifolia</i> (Sapindaceae) [wood]	HIV-1 PR (121)

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
Fisetin (= 5-Deoxy- quercetin; 3,7,3',4'- Tetrahydroxyflavone) (flavonol)	<i>Rhus cotinus</i> , <i>R. rhodantha</i> (Anacardiaceae), <i>Acacia</i> spp., <i>Glycine max</i> (Fabaceae) [heartwood]; as glycosides in <i>Rhus succedanea</i> (Anacardiaceae) [wood], <i>Dalbergia odorifera</i> [wood], <i>Trifolium subterraneum</i> (Fabaceae)	HIV-1 PR (50) (ITDI, HIV-1 INT, LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TPO) [allergenic, antibacterial, apoptotic, ↓SM contraction & histamine release]
Gardenin A (flavone)	Gardenin B in <i>Ocimum</i> sp. (Lamiaceae)	HIV-1 PR (11)
Geraniin (hydrolysable tannin)	<i>Acer</i> (Aceraceae), <i>Cercidiphyllum</i> (Cercidiphyllaceae), <i>Coriaria</i> (Coriariaceae), <i>Erythroxylum</i> (Erythroxylaceae), <i>Mallotus</i> , <i>Phyllanthus</i> (Euphorbiaceae), <i>Geranium</i> (Geraniaceae), <i>Fuchsia</i> (Onagraceae)	HIV-1 PR (< 79)
Gossypin (= Gossypetin 8- O-glucoside; 3,5,7,8,3',4'- Hexahydroxyflavone 8-O- glucoside) (flavonol O-glycoside)	<i>Gossypium indicum</i> , <i>Hibiscus vitifolius</i> [flower] (Malvaceae)	HIV-1 PR (~104) [AI, analgesic, anti-gastroulcerative]
Isoquercetrin (= Quercetin 3-O-glucoside)	Widespread; <i>Gossypium herbaceum</i> (Malvaceae) [flower], <i>Morus alba</i> (mulberry) (Moraceae) [leaf], <i>Ailanthus altissima</i> (Simaroubaceae) [leaf]	HIV-1 PR (< 108) (AR) [antibacterial, feeding attractant]
Luteolin (= 5,7,3',4'- Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium graveolens</i> (Apiaceae); widespread as glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	HIV-1 PR (ACE, AR, AROM, ITD, NADH DH, Na ⁺ , K ⁺ - ATPase, NEP, PK, RTK, succinate DH, TOPII, TPO) [antibacterial, AI, apoptotic, nodulation signal]
α-Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	HIV-1 PR (5) (CDPK, MLCK, PKA) [antibacterial, AI, antiulcer]
γ-Mangostin (prenylated xanthone)	<i>Garcinia mangostana</i> (Guttiferae) [fruit peel, resin]	HIV-1 PR (5) (CDPK, MLCK, PKA)
Morin (= 3,5,7,2',4'- Pentahydroxyflavone) (flavonol)	<i>Morus alba</i> , <i>M.</i> spp., <i>Chlorophora tinctoria</i> , <i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> (Moraceae)	HIV-1 PR (24) (5-LOX) [antiviral, antibacterial, allergenic, feeding attractant]
Myricetin (= 3,5,7,3',4', 5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplopappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	HIV-1 PR (22) (AROM, DNAL, DNAP, F ₁ -ATPase, HIV-1 INT, HIV-1 RT, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ - ATPase, Nase, NEP, PGK, PK, 5αR, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic, apoptotic]
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Oenothera biennis</i> (Onagraceae), <i>Koelreuteria henryi</i> (Sapindaceae); widespread as glycosides	HIV-1 PR (36; 59) (AR, cAMP PDE, HIV-1 PR, LOX, PK, RTK, TK, PS - EF-1α, TOPII) [allergenic, antibacterial, AI, anti- <i>Leishmania</i> , antiviral]

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) [plant part]	Target (other targets) / in vivo effects/
Repandusic acid (hydrolysable tannin)	<i>Phyllanthus amarus</i> (Euphorbiaceae)	HIV-1 PR (13)
Robinin (= Kaempferol 3- <i>O</i> -galactosyl-rhamnosyl-7- <i>O</i> -rhamnoside) (flavonol <i>O</i> -glycoside)	<i>Vinca minor</i> (Apocynaceae), <i>Pueraria</i> spp., <i>Robinia pseudoacacia</i> , <i>Vigna</i> spp. (Fabaceae)	HIV-1 PR (<68)
Rutin (= Quercetin 3- <i>O</i> -rutinoside; Rutoside) (flavonol <i>O</i> -glycoside)	Widespread; <i>Sophora japonica</i> (Fabaceae), <i>Polygonum</i> spp. (Polygonaceae), <i>Ruta graveolens</i> (Rutaceae), <i>Viola tricolor</i> (Violaceae)	HIV-1 PR (<82)
Tannin (Epicatechin, Epiafzelechin units) (condensed tannin)	<i>Xanthoceras sorbifolia</i> (Sapindaceae) [wood]	HIV-1 PR (~4)
Terpene		13.4At
Agastanol (diterpene)	<i>Agastache rugosa</i> (Lamiaceae) [root]	HIV-1 PR (360)
Agastaquinone (diterpene)	<i>Agastache rugosa</i> (Lamiaceae) [root]	HIV-1 PR (87)
α -Amyrin (= α -Amyrenol; Viminalol) (ursene triterpene)	<i>Alstonia boonei</i> (Apocycaceae) [root], <i>Balanophora elongata</i> (Balanophoraceae), <i>Ficus variegata</i> (Moraceae), <i>Hevea</i> (Euphorbiaceae), <i>Erythroxylum coca</i> (Erythroxylaceae)	HIV-1 PR (80) (CABPase, CDPK, collagenase, PKA, PKC) [anti-arthritic, AI, anti-insect]
Betulinic acid (lupene triterpene)	Widespread; <i>Rhododendron arboreum</i> (Ericaceae) [bark], <i>Psophocarpus</i> <i>tetragonolobus</i> (Fabaceae), <i>Syzygium</i> <i>claviflorum</i> (Myrtaceae) [leaf]	HIV-1 PR (9) (CDPK, PKA, PKC, TOPI, TOPII) [antineoplastic]
Carnosic acid (abietane diterpene)	<i>Rosmarinus officinalis</i> (rosemary) (Lamiaceae)	HIV-1 PR (<0.2) [anti-HIV-1 (<1)]
2 α ,19 α -Dihydroxy-3-oxo- 12-ursen-28-oic acid (ursane triterpene)	<i>Geum japonica</i> (Rosaceae) [plant]	HIV-1 PR
Escin Ia (triterpene saponin)	<i>Aesculus chinensis</i> (Hippocastanaceae) [seed]	HIV-1 PR (35)
Escin Ib (triterpene saponin)	<i>Aesculus chinensis</i> (Hippocastanaceae) [seed]	HIV-1 PR (50)
Isoescin Ia (triterpene saponin)	<i>Aesculus chinensis</i> (Hippocastanaceae) [seed]	HIV-1 PR (>100)
Maslinic acid (triterpene)	<i>Geum japonica</i> (Rosaceae) [plant]	HIV-1 PR
Oleanolic acid (oleanene triterpene)	<i>Luffa cylindrica</i> (Cucurbitaceae); <i>Centaurium umbellatum</i> , <i>Swertia japonica</i> (Gentianaceae), <i>Rosmarinus officinalis</i> (Lamiaceae), <i>Viscum album</i> (Loranthaceae), <i>Syzygium aromaticum</i> (Myrtaceae), <i>Olea europaea</i> (Oleaceae), <i>Xanthoceras sorbifolia</i> (Sapindaceae); as glycoside in <i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae)	HIV-1 PR (8; 22) (C3- convertase, CDPK, ELA, PKA, PKC) (DNAP) [AI]
3-Oxotirucalla-7,24-diene- 21-oic acid (triterpene)	<i>Xanthoceras sorbifolia</i> (Sapindaceae) [wood]	HIV-1 PR (~40)

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (ursene triterpene)	Widespread; <i>Cynomorium songaricum</i> (Cynomoriaceae), <i>Arctostaphylos</i> <i>uva-ursi</i> , <i>Rhododendron hymenanthes</i> , <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Prunella vulgaris</i> , <i>Salvia triloba</i> (Lamiaceae), <i>Crataegus pinnatifida</i> , <i>Geum</i> <i>japonica</i> , <i>Malus</i> sp., <i>Pyrus</i> sp. (Rosaceae)	HIV-1 PR (8) (CDPK, CHS, DNAP, ELA, PKA, PKC, RT, TOPI, TOPII) [AI, cytotoxic, antineoplastic]
Ursolic acid hydrogen malonate (= 3-O-Malonyl ursolic acid hemiester) (triterpene)	<i>Cynomorium songaricum</i> (Cynomoriaceae) [stem]	HIV-1 PR (6)
[Ursolic acid methyl ester] (ursene triterpene)	Semi-synthetic from ursolic acid	HIV-1 PR (14)
Uvaol (= Urs-12-ene-3, 28-diol) (ursene triterpene)	<i>Crataegus pinnatifida</i> (Rosaceae)	HIV-1 PR (6)
Non-plant reference		13.4An
[Acetylpepstatin] (peptide)	Synthetic	HIV-1 PR (90 nM)
[Amprenavir] (tetrahydrofuran aniline sulphonamide)	Synthetic, clinically used non-peptide anti-HIV-1 drug; globally 22 million dead from AIDS (4–5 million children), 40 million infected with HIV-1 (2000)	HIV-1 PR [~ 1 nM] [clinically used anti-HIV-1 (0.1)]
[Cyclopiazonic acid] (pentacyclic alkaloid mycotoxin)	<i>Aspergillus</i> & <i>Penicillium</i> spp. (fungi)	HIV-1 PR, HIV-2 PR – Fe(III)-CPA [100 nM], Tb(III)- CPA [20 nM] (Ca^{2+} -ATPase)
[EDF] (peptide)	Synthetic (based on TFP domain of HIV-1 PR precursor)	HIV-1 PR [25]
[EDL] (peptide)	Synthetic (part of TFP domain of HIV-1 PR precursor)	HIV-1 PR [50]
[EDLA] (peptide)	Synthetic (part of TFP domain of HIV-1 PR precursor)	HIV-1 PR [160]
[FLREDLAF] (peptide)	Synthetic (part of TFP domain of HIV-1 PR precursor)	HIV-1 PR [98]
[Ganoderic acid] (triterpene)	<i>Ganoderma lucidum</i> (mushroom) (Polyporaceae)	HIV-1 PR (190)
[Ganoderic acid B] (triterpene)	<i>Ganoderma lucidum</i> (mushroom) (Polyporaceae)	HIV-1 PR (170)
[Ganoderic acid C] (triterpene)	<i>Ganoderma lucidum</i> (mushroom) (Polyporaceae)	HIV-1 PR (180)
[Ganoderic acid H] (triterpene)	<i>Ganoderma lucidum</i> (mushroom) (Polyporaceae)	HIV-1 PR (200)
[Ganoderiol A] (triterpene)	<i>Ganoderma lucidum</i> (mushroom) (Polyporaceae)	HIV-1 PR (230)
[Ganoderiol B] (triterpene)	<i>Ganoderma lucidum</i> (mushroom) (Polyporaceae)	HIV-1 PR (170)
[Ganoderiol F] (triterpene)	<i>Ganoderma lucidum</i> (mushroom) (Polyporaceae)	HIV-1 PR (320)
[Indinavir] (indene piperidine pyridine peptide)	Synthetic, clinically used peptidomimetic anti-HIV-1 drug	HIV-1 PR [0.3 nM], HIV-2 PR [3 nM] [clinically used anti-HIV-1 (0.1)]

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
[Nelfinavir (= Viracept)] (isoquinoline)	Synthetic, clinically used non-peptide anti-HIV-1 drug	HIV-1 PR [2nM] [clinically used anti-HIV-1 (0.1)]
[Phenprocoumon (= 1- (4'-Hydroxy-3'- coumarinyl)-1-phenyl- propane)] (coumarin)	Synthetic	HIV-1 PR [1], HIV-2 PR [1]
[Ritonavir] (<i>N</i> -methyl peptide thiazole)	Synthetic, clinically used peptidomimetic anti-HIV-1 drug	HIV-1 PR [~0.1 nM] [clinically used anti-HIV-1]
[Saquinavir] [peptide isoquinoline quinoline]	Synthetic, clinically used peptidomimetic anti-HIV-1 drug	HIV-1 PR [0.1 nM], HIV-2 PR [< 1 nM] [clinically used anti-HIV-1]
[Warfarin (= 1-(4'- Hydroxy-3'-coumarinyl)- 1-phenyl-3-butanone)] (coumarin)	Synthetic coumarin	HIV-1 PR (30) [anticoagulant, rodenticide]
Pepsin	Crystalline pepsin & pepsinogen isolated by John Northrop (USA, Nobel Prize, Chemistry, 1946, pure enzyme & viral protein isolation)	13.4B
<i>Anchusa</i> Pepsin I (63kDa macromolecule)	<i>Anchusa strigosa</i> (Boraginaceae) [root]	Pepsin [20 nM]
Metalloproteases (MPRs)		13.4C-G
Aminopeptidases (AP)		13.4C
Betulinic acid (lupane triterpene)	Widespread; <i>Rhododendron arboreum</i> (Ericaceae) [bark], <i>Psophocarpus</i> <i>tetragonolobus</i> (Fabaceae), <i>Syzygium</i> <i>claviflorum</i> (Myrtaceae) [leaf]	AP – AP N (7) (ATP-K ⁺ CH, CDPK, HIV-1 PR, PKA, PKC) [antimelanoma, antineoplastic]
[Bestatin (= (3-Amino- 2-hydroxy-4-phenyl- butanoyl)-L-leucine) (amino acid)]	Synthetic	AP – AP N (16)
Angiotensin I converting enzyme (ACE)		13.4D
Alkaloid		13.4Da
Cycleahomine (bisbenzylisoquinoline)	<i>Stephania tetrandra</i> (Menispermaceae) [root]	ACE
Fangchinoline (bisbenzylisoquinoline)	<i>Isopyrum thalictroides</i> , <i>Pachygone dasycarpa</i> [stem bark], <i>Stephania erecta</i> (Menispermaceae)	ACE [AI, PAI, inhibits TXB2 formation]
Fenfangjine A (bisbenzylisoquinoline)	<i>Stephania tetrandra</i> (Menispermaceae) [root]	ACE
Fenfangjine B (bisbenzylisoquinoline)	<i>Stephania tetrandra</i> (Menispermaceae) [root]	ACE
Fenfangjine C (bisbenzylisoquinoline)	<i>Stephania tetrandra</i> (Menispermaceae) [root]	ACE
Fenfangjine D (bisbenzylisoquinoline)	<i>Stephania tetrandra</i> (Menispermaceae) [root]	ACE

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
Nicotianamine (= <i>N</i> -[<i>N</i> -(3-Amino-3-carboxypropyl)-3-amino-3-carboxypropyl]-azetidine-2-carboxylic acid) (azetidine carboxylic acid)	<i>Glycine max</i> (soyabean) (Fabaceae) [soy sauce (fermented soyabean)], <i>Angelica keiskei</i> (Apiaceae) [leaf]	ACE (0.3)
(+)-Tetrandine (bisbenzylisoquinoline)	<i>Cissampelos pareira</i> , <i>Cyclea barbata</i> , <i>C. peltata</i> , <i>Pachygone dasycarpa</i> , <i>Stephania discolor</i> , <i>S. tetrandra</i> (Menispermaceae)	ACE [AI, analgesic, antipyretic, inhibits TXB2 formation, PAI]
Phenolic		13.4Dp
Areca II-5-C (tannin)	<i>Areca catechu</i> (betel nut) (Palmae) [seed]	ACE [antihypertensive]
<i>Eriosema</i> compound B (prenylated xanthone)	<i>Eriosema tuberosum</i> (Fabaceae) [root]	ACE (195) (NEP)
<i>Hypericum</i> compound H8 (prenylated xanthone)	<i>Hypericum roeperanum</i> (Hypericaceae) [root]	ACE (104) (NEP)
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; widespread as glycosides in Cruciferae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Apium graveolens</i> (Apiaceae)	ACE (< 300) (AR, CDPK, ITD, MLCK, NADH DH, NEP, PKA, PKC, succinate DH, TOPII) [antibacterial, AI, nodulation signal]
Procyanidin B-5 3,3'-di- <i>O</i> -gallate (condensed tannin)	<i>Rheum palmatum</i> (rhubarb) (Polygonaceae) [rhizome]	ACE (1)
Procyanidin C-1 3,3',3''-tri- <i>O</i> -gallate (condensed tannin)	<i>Rheum palmatum</i> (rhubarb) (Polygonaceae) [rhizome]	ACE (1) [high specificity for ACE – 100× higher concentration to inhibit TRY, CHY, LAP, carboxypeptidase & urinary kallikrein]
Procyanidins (condensed tannins)	<i>Lespedeza capitata</i> (Fabaceae)	ACE
Procyanidin polymer (condensed tannin)	<i>Pistacia lentiscus</i> (Anacardiaceae)	ACE
Quercetrin (= Quercetin 3- <i>O</i> -rhamnoside; 3,5,7,3',4'-Pentahydroxyflavone) (flavonol <i>O</i> -glycoside)	Widespread; <i>Polygonum</i> spp. (Polygonaceae), <i>Quercus tinctoria</i> (Fagaceae) [bark]	ACE (300) (AR, MLCK, PKA) [antibacterial, antimutagenic, antiviral, feeding deterrent & stimulant]
Terpene		13.4Dt
Oleacein (iridoid monoterpene)	<i>Jasminum grandiflorum</i> (Oleaceae) [aerial]	ACE (30)
Sambacein I (iridoid monoterpene)	<i>Jasminum azoricum</i> (Oleaceae) [aerial]	ACE (30)
Sambacein II (iridoid monoterpene)	<i>Jasminum azoricum</i> (Oleaceae) [aerial]	ACE (30)
Sambacein III (iridoid monoterpene)	<i>Jasminum azoricum</i> (Oleaceae) [aerial]	ACE (30)
Non-plant reference		13.4Dn
[Enalapril (= Enalaprilat ethyl ester) (aryl peptide ester)]	Synthetic; Enalaprilat ethyl ester; pro-drug & yields ACE inhibitor Enalaprilat; Vasotec = Enalapril maleate salt	ACE [major antihypertensive drug]

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) plant part	Target (other targets) in vivo effects
[Enalaprilat (= N-(1-Carboxy-3-phenylpropyl)-L-Ala-L-Pro)] (aryl peptide)	Synthetic; hypertension a major diagnosed problem in Western over-50s	ACE [major antihypertensive drug]
Endothelin-converting enzyme (ECE)		13.4E
Daleformis (pterocarpinoid phytoalexin)	<i>Dalea filiciformis</i> (Fabaceae) [root]	ECE (9)
Neutral endopeptidase (NEP)		13.4F
Phenolic		13.4Fp
<i>Eriosema</i> compound B (prenylated xanthone)	<i>Eriosema tuberosum</i> (Fabaceae) [root]	NEP (50) ACE
Fisetin (= 5-Deoxy- quercetin; 3,7,3',4'- Tetrahydroxyflavone) (flavonol)	<i>Rhus cotinus</i> , <i>R. rhodantha</i> (Anacardiaceae), <i>Acacia</i> spp., <i>Glycine max</i> (Fabaceae) [heartwood]; as glycosides in <i>Rhus succedanea</i> (Anacardiaceae) [wood], <i>Trifolium subterraneum</i> (Fabaceae)	NEP (220) (ITD, LOX, NADH DH, PK, succinate DH) [allergenic, antibacterial, inhibits smooth muscle contraction & histamine release]
<i>Hypericum</i> compound H8 (prenylated xanthone)	<i>Hypericum roeperanum</i> (Hypericaceae) [root]	NEP (81) (ACE)
Luteolin (= 5,7,3',4'- Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Apium graveolens</i> (Apiaceae); widespread as glycosides in Cruciferae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]	NEP (127) (ACE, AR, CDPK, ITD, MLCK, NADH DH, PKA, PKC, succinate DH, TOPII) [antibacterial, AI, nodulation signal]
Myricetin (= 3,5,7,3',4', 5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soyimida febrifuga</i> (Meliaceae), <i>Haplopappus canescens</i> (Asteraceae); glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Myrica rubra</i> (Moraceae), <i>Primula sinsensis</i> (Primulaceae), <i>Camellia sinsensis</i> (Theaceae)	NEP (42) (CDPK, IKK, 5- LOX, NADH DH, MLCK, PKA, succinate DH, TOPII) [antibacterial, antigonadotropic]
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	NEP (192) (AR, cAMP PDE, LOX, PK, PS-EF-1 α , RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
Other metalloproteases		13.4G
Phenolic		13.4Gp
(-)-Epicatechin-3-gallate (flavan-3-ol, gallotannin)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	Collagenase (at 200), MMP-2 (Gelatinase A) (95), MMP-9 (Gelatinase B) (28), MMP-12 (< 1) (EGF-RTK) [AI]
(-)-Epigallocatechin-3- gallate (flavan-3-ol, gallotannin)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	Collagenase (at 200), MMP-2 (Gelatinase A) (6), MMP-9 (Gelatinase B) (0.3), MMP-12 (< 1) (β -A R, D1 R, D2 R, O R, PKC) [AI, blocks COX-2 & iNOS induction]

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
Nobiletin (= 5,6,7,8,3',4'-Hexamethoxyflavone) (flavone)	<i>Citrus aurantium</i> , <i>C. depressa</i> (Rutaceae) [fruit juice]	[suppresses MMP-9/gelatinase B expression (rabbit synovial cells)]
Theaflavin (polycyclic benzopyran)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	MMP-2, MMP-9
Theaflavin digallate (polycyclic benzopyran)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	MMP-2, MMP-9
Terpene		13.4Gt
α -Amyrin (= α -Amyrenol; Viminalol) (ursane triterpene)	<i>Alstonia boonei</i> (Apocycaceae), <i>Balanophora elongata</i> (Balanophoraceae), <i>Ficus variegata</i> (Moraceae), <i>Hevea brasiliensis</i> (Euphorbiaceae), <i>Erythroxylum coca</i> (Erythroxylaceae),	Collagenase (< 100) (CABPase, CHY, CDPK, HIV-1 PR, PKA, PKC, TRY) [anti-arthritic, AI, anti-insect]
α -Amyrin linoleate (= α -Amyrin <i>cis</i> -9, <i>cis</i> -12-octadecadienoic acid ester) (ursane triterpene FA ester)	Semi-synthetic from α -Amyrin	Collagenase (< 100) (CABPase, CHY, 5-LOX, MLCK, PKA, PKC, TRY) [AI]
α -Amyrin palmitate (= α -Amyrin hexadecanoic acid ester) (ursane triterpene FA ester)	<i>Lobelia inflata</i> (Campanulaceae) [leaf]; Semi-synthetic from α -Amyrin	Collagenase (< 100) (CABPase, CHY, PKA, PKC) [AI]
β -Dolabrin (tropolone monoterpene)	<i>Thujaopsis</i> (<i>Thuja</i>) <i>dolobrata</i> , <i>T. plicata</i> (Cupressaceae) [wood]	CPA (20), Collagenase (<i>Clostridium histolyticum</i>) (89)
Hinokitiol (tropolone monoterpene)	<i>Thujaopsis</i> (<i>Thuja</i>) <i>dolobrata</i> , <i>T. plicata</i> (Cupressaceae) [wood]	CPA (3), collagenase (24), thermolysin (61) (COMT) [antifungal]
Phorbol esters (diterpene diesters)	<i>Croton tiglium</i> (Euphorbiaceae)	Induce collagenase synthesis via collagenase promoter activation
α -Thujaplicin (= 2-Isopropyltropolone) (tropolone monoterpene)	<i>Thujaopsis</i> (<i>Thuja</i>) <i>dolobrata</i> (Cupressaceae) [wood]	CPA [antibacterial, cytotoxic]
γ -Thujaplicin (tropolone monoterpene)	<i>Thujaopsis</i> (<i>Thuja</i>) <i>dolobrata</i> , <i>T. plicata</i> (Cupressaceae) [wood]	CPA (bovine) (11), collagenase (19), thermolysin (69) [antifungal]
Serine proteases – e.g. chymotrypsin (CHY), trypsin (TRY), elastase (ELA)	Crystalline TRY & CHY isolated by John Northrop (USA, Nobel Prize, Chemistry, 1946, pure enzyme & viral protein isolation)	13.4H
Phenolic		13.4Hp
Dicoumarol (= Dicumarol; Dicumol; Dicoumarin; Dufalone; Melitoxin) (coumarin)	<i>Melilotus</i> sp. (Fabaceae), <i>Anthoxanthum</i> sp. (Poaceae) [in decomposing hay from 4-Hydroxycoumarin] cf. Warfarin	Inhibits Vitamin K-dependent protein glutamate carboxylation (\rightarrow Ca ²⁺ -binding to Gla & blood clotting protease activation, signalling & bone formation) [anticoagulant]

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) plant part	Target (other targets) in vivo effects
(-)-Epigallocatechin 3-gallate (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	Proteasome CHY-like activity (0.1–0.2) (EST-R, PKA, PKC, 5 α R, RTK, TK) [cell-EGF- RTK (<5); oxidation products give tea taste]
Rosmarinic acid (phenylpropanoid)	<i>Anethum</i> , <i>Astrantia</i> , <i>Levisticum</i> , <i>Sanicula</i> (Apiaceae), <i>Symphytum</i> (Boraginaceae), <i>Melissa</i> , <i>Mentha</i> , <i>Ocimum</i> , <i>Origanum</i> , <i>Rosmarinus</i> , <i>Salvia</i> , <i>Teucrium</i> (Lamiaceae) spp.	C3b convertase (covalent attachment via C3b thioester) (COX-1, COX-2, ITD) [AI, inhibits classical & alternative pathway complement activation]
Vitamin K ₁ (= Phylloquinone; 3-Phytomenadione) (naphthoquinone); Vitamin K requirement for blood clotting found independ- ently by Henrik Dam (Denmark) & Edward Doisy (USA) (Nobel Prize, Medicine, 1943, Vitamin K)	Widespread; e.g. <i>Vaccinium corymbosum</i> (Ericaceae), <i>Medicago sativa</i> (alfalfa) (Fabaceae), <i>Castanea</i> sp. (chestnut) (Fagaceae) [leaf], <i>Triticum aestivum</i> (Poaceae); Dihydro form (KH ₂) coenzyme for γ -carboxyglutamic acid formation on procoagulant factors II, VII, IX & X, anticoagulant proteins C & S, matrix Gla protein & osteocalcin	Vitamin K (koagulations- Vitamin)-dependent protein glutamate carboxylation (\rightarrow Ca ²⁺ -binding to Gla for blood clotting protease activation, signalling & bone formation) [pro-coagulant]; see Vitamin K ₂ & Vitamin K ₃
Terpene Acetyl-11-keto- β -boswellic acid (triterpene)	<i>Boswellia serrata</i> (Indian frankincense); one of the offerings of the three Magi (Kings, Wise men) to the infant Jesus	13.4Ht Leucocyte ELA (15) (5-LOX) [AI]
Amidiol (= Taraxast- 20(30)-ene-3 β ,16 β -diol) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (96) [53], TRY (195) [143] [AI (Phorbol ester- induced inflammation)]
α -Amyrin (= α -Amyrenol; Viminalol) (ursane triterpene)	<i>Alstonia boonei</i> (Apocycaceae), <i>Balanophora elongata</i> (Balanophoraceae), <i>Ficus variegata</i> (Moraceae), <i>Hevea brasiliensis</i> (Euphorbiaceae), <i>Erythroxylum coca</i> (Erythroxylaceae),	CHY (23) [18], leucocyte ELA (at 20), TRY (41) [29] (CABPase, CDPK, collagenase, HIV-1 PR, PKA, PKC) [anti- arthritic, AI, anti-insect]
[α -Amyrin linoleate (= α - Amyrin <i>cis</i> -9, <i>cis</i> -12- octadecadienoic acid ester] (ursane triterpene FA ester)	Semi-synthetic from α -Amyrin	CHY (16) [28], TRY (15) [16] (CABPase, collagenase, 5- LOX, MLCK, PKA, PKC) [AI]
[α -Amyrin palmitate (= α -Amyrin hexadecanoic acid ester)] (ursane triterpene FA ester)	Semi-synthetic from α -Amyrin	CHY (24) [6] (CABPase, collagenase, PKA, PKC) [AI]
Andrographolide (diterpene)	<i>Andrographis paniculata</i> (Acanthaceae)	Furin (proprotein convertase) [200]; furin required for cancer invasiveness & hence good chemotherapy target

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) plant part	Target (other targets) in vivo effects
β -Boswellic acid (triterpene)	<i>Boswellia serrata</i> (Indian frankincense); one of the offerings of the three Magi (Kings, Wise men) to the infant Jesus	Leucocyte ELA (at 20) [AI]
Brein (= Urs- 12-ene-3 β ,16 β -diol) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (120) [110], TRY (~100) [AI (Phorbol ester-induced inflammation)]
Brein 3- <i>O</i> -myristate (= Urs-12-ene-3 β ,16 β -diol 3- <i>O</i> -myristate) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (78) [114] [AI (Phorbol ester-induced inflammation)]
Brein 3- <i>O</i> -palmitate (= Urs-12-ene-3 β ,16 β -diol 3- <i>O</i> -palmitate) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (42) [110] [AI (Phorbol ester-induced inflammation)]
Calenduladiol (= Lup- 20(29)-ene-3 β ,16 β -diol) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (120) [57], TRY (~100) [AI (Phorbol ester-induced inflammation)]
Cycloartenol (= Cycloart- 24-en-3 β -ol) (triterpene)	<i>Taraxacum officinale</i> (dandelion) (Asteraceae) [flower]	CHY (140) [420], TRY (82) [25] [AI (Phorbol ester-induced inflammation)]
Dammaradienol (= Dammara-20,24-dien- 3 β -ol) (triterpene)	<i>Helianthus annuus</i> (sunflower) (Asteraceae) [flower]	CHY (130) [60] [AI (Phorbol ester-induced inflammation)]
Erythrodiol (triterpene)	<i>Coryza filaginoides</i> , <i>Solidago virga-aurea</i> (Asteraceae), <i>Olea europaea</i> (Oleaceae) [oil]	Leucocyte ELA
Faradiol (= Taraxast-20- ene-3 β ,16 β -diol) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (160) [68], TRY (130) [113] [AI (Phorbol ester- induced inflammation)]
Faradiol 3- <i>O</i> -myristate (= Taraxast-20-ene-3 β , 16 β -diol 3- <i>O</i> -myristate) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (32) [30], TRY (> 100) [AI (Phorbol ester-induced inflammation)]
Faradiol 3- <i>O</i> -palmitate (= Taraxast-20-ene-3 β , 16 β -diol 3- <i>O</i> -palmitate) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (72) [58], TRY (82) [86] [AI (Phorbol ester-induced inflammation)]
Genistein (= Genisteol; Prunetol; Sophoricol; 4', 5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Trifolium brachycalycinum</i> , <i>T. subterraneum</i> (clover) (Fabaceae); glycosides in <i>Genista tinctoria</i> , <i>Glycine</i> <i>max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora</i> <i>japonica</i> (Fabaceae)	Inhibits thrombin activation (AD-R, GABAA-R, lipase, peroxidase, PK, RTK, TOPII) [antifungal, oestrogenic]
18- β -Glycyrrhetic acid (Glycyrrhetic acid; Glycyrrhetin) (triterpene saponenin)	<i>Glycyrrhiza glabra</i> (licorice) (Fabaceae) [root, rhizome]	ELA (ALDO-R, β HSDH, PKA, PKC) [AI, anti-ulcerogenic, anti-diuretic]
Hederagenin (triterpene)	<i>Hedera helix</i> (ivy) (Araliaceae), <i>Spinacia</i> <i>oleracea</i> (Chenopodiaceae)	Leucocyte ELA, pancreatic ELA (41)
Heliantriol C (= Taraxast- 20-ene-3 β ,16 β ,22 α -triol) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (> 100) [AI (Phorbol ester-induced inflammation)]

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) plant part	Target (other targets) in vivo effects
Heliantriol C 3- <i>O</i> -myristate (= Taraxast-20-ene-3 β ,16 β ,22 α -triol 3- <i>O</i> -myristate) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	TRY (34) [40] [AI (Phorbol ester-induced inflammation)]
Heliantriol C 3- <i>O</i> -palmitate (= Taraxast-20-ene-3 β ,16 β ,22 α -triol 3- <i>O</i> -palmitate) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (> 100) [AI (Phorbol ester-induced inflammation)]
Lupeol (= Fagasterol; Monogynol B; β -Viscol) (lupane triterpene)	<i>Alstonia boonei</i> (Apocynaceae) [bark, seed], Asteraceae [flower], <i>Phyllanthus emblica</i> (Euphorbiaceae), <i>Lupinus luteus</i> (Fabaceae) [seed]	CHY (22) [8], TRY (34) [22] (CAB Pase, FPT, PKA, PKC, TOPII) [anti-arthritis, AI, antitumour]
[Lupeol linoleate (= Lupeol-9, <i>cis</i> -12-octadecadienoic acid ester)] (lupane triterpene FA ester)	Semi-synthetic from Lupeol	CHY (> 50), TRY (10) [7] (CABPase, PKA, PKC) [AI]
[Lupeol palmitate (= Lupeol hexadecanoic acid ester)] (lupane triterpene FA ester)	Semi-synthetic from Lupeol	CHY (> 50), TRY (6) [10] (CABPase, PKA)[AI]
Maniladiol (= Olean-12-ene-3 β ,16 β -diol) (triterpene)	<i>Helianthus annuus</i> (sunflower) (Asteraceae) [flower]	CHY (~100) [AI (Phorbol ester-induced inflammation)]
Maniladiol 3- <i>O</i> -myristate (= Olean-12-ene-3 β ,16 β -diol 3- <i>O</i> -myristate) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (78) [26], TRY (73) [267] [AI (Phorbol ester-induced inflammation)]
Maniladiol 3- <i>O</i> -palmitate (= Olean-12-ene-3 β ,16 β -diol 3- <i>O</i> -palmitate) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (84) [120], TRY (97) [190] [AI (Phorbol ester-induced inflammation)]
(24 <i>S</i>)-25-Methoxycycloartanediol (= (24 <i>S</i>)-25-Methoxycycloartane-3 β ,24-diol) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	TRY (110) [AI (Phorbol ester-induced inflammation)]
24-Methylenecycloartenol (= 24-Methylcycloart-24(24')-en-3 β -ol) (triterpene)	<i>Helianthus annuus</i> (sunflower) (Asteraceae) [flower]; Cycloartenol widespread	CHY (~100) [AI (Phorbol ester-induced inflammation)]
Neoandrographolide (= Andrographolide <i>O</i> -glucoside) (diterpene)	<i>Andrographis paniculata</i> (Acanthaceae)	PPC-1, PPC-7, Furin (a PPC) (54); furin required for cancer invasiveness & hence good chemotherapy targets
Oleanolic acid (oleanane triterpene)	<i>Luffa cylindrica</i> (Cucurbitaceae), <i>Centaurium umbellatum</i> , <i>Svertia japonica</i> (Gentianaceae), <i>Rosmarinus officinalis</i> (Lamiaceae), <i>Viscum album</i> (Loranthaceae), <i>Syzygium aromaticum</i> (Myrtaceae), <i>Olea europaea</i> (Oleaceae), <i>Xanthoceras sorbifolia</i> (Sapindaceae)	C3-convertase (at 200 μ M), leucocyte ELA [6], pancreatic ELA (5) (CDPK, CHS, DNAP, PKA, PKC) [AI]

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
Ruscogenin (triterpene)	<i>Ruscus aculeatus</i> (Liliaceae) [rhizome]	Pancreatic ELA (120)
Succinoyl-andrographolide (diterpene)	<i>Andrographis paniculata</i> (Acanthaceae)	Furin (a PPC) & PPC-1, PPC-7 [< 30]; furin required for cancer invasiveness & hence good chemotherapy targets
Taraxerol (= Taraxer-14- en-3 β -ol) (triterpene)	<i>Taraxacum officinale</i> (dandelion) (Asteraceae) [flower]	TRY (> 100) [AI (Phorbol ester- induced inflammation)]
Δ^7 -Tirucallol (= Tirucalla- 7,24-dien-3 β -ol) (triterpene)	<i>Chrysanthemum mortifolium</i> (chrysanthemum) (Asteraceae) [flower]	CHY (98) [72], TRY (140) [152] [AI (Phorbol ester- induced inflammation)]
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (triterpene)	Widespread; <i>Cynomorium songaricum</i> (Cynomoriaceae), <i>Vaccinium macrocarpon</i> , <i>Arctostaphylos uva-ursi</i> (Ericaceae), <i>Prunella vulgaris</i> , <i>Salvia triloba</i> (Lamiaceae), <i>Malus</i> , <i>Pyrus</i> (Rosaceae)	Leucocyte ELA [4] (CDPK, DNAP, HIV-1 PR, PKA, PKC RT, TOPI, TOPII) [AI, cytotoxic, antineoplastic]
Non-plant reference		13.4Hn
[Leupeptin] (peptide)	Synthetic	TRY, CYS PR [anti-apoptotic]
[Vitamin K ₂ (= Menaquinone)] (naphthoquinone); isolated by Edward Doisy (USA) (Nobel Prize, Medicine, 1943, with Henrik Dam, Vitamin K)	Intestinal bacteria; dihydro form (KH ₂) coenzyme for γ -carboxyglutamic acid formation on procagulant factors II, VII, IX & X, anticoagulant proteins C & S, matrix Gla protein & osteocalcin	Vitamin K-dependent protein glutamate carboxylation (\rightarrow Ca ²⁺ -binding to Gla for blood clotting protease activation, signalling & bone formation) [pro-coagulant]
[Vitamin K ₃ (= Menadione)] (naphthoquinone)	Synthetic; dihydro form (KH ₂) coenzyme for γ -carboxyglutamic acid formation on procagulant factors II, VII, IX, & X, anticoagulant proteins C & S, matrix Gla protein & osteocalcin	Vitamin K-dependent protein glutamate carboxylation (\rightarrow Ca ²⁺ -binding to Gla for blood clotting protease activation, signalling & bone formation) [pro-coagulant]
[Warfarin (= 1-(4'- Hydroxy-3'-coumarinyl)- 1-phenyl-3-butanone)] (coumarin)	Synthetic cf. Dicoumarol, Vitamins K ₁ , K ₂ & K ₃	Inhibits Vitamin K-dependent protein glutamate carboxylation (thus inhibits Ca ²⁺ -binding to Gla & blood clotting protease activation, signalling & bone formation) (HIV-1 PR) [anticoagulant]
Prolyl endopeptidase (PEP)		13.4I
Phenolics		13.4Ip
Arbutin (= Hydroquinone- β -D-glucopyranoside) (phenol glucoside)	<i>Rhodiola sacra</i> (Crassulaceae), <i>Arctostaphylos uva-ursi</i> , <i>Chimaphila umbellata</i> , <i>Vaccinium vitis-idaea</i> (Ericaceae), <i>Origanum majorana</i> (Lamiaceae), <i>Pyrus communis</i> (Rosaceae), <i>Bergenia crassifolia</i> (Saxifragaceae)	PEP (391) (weak) [antibacterial, antitussive, inhibits insulin degradation]

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) plant part	Target (other targets) in vivo effects
(-)-Epicatechin (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), <i>Pterocarpus</i> spp., (Fabaceae), <i>Crataegus monogyna</i> (Rosaceae), <i>Podocarpus nagi</i> (Podocarpaceae), <i>Rheum palmatum</i> (Polygonaceae), <i>Camellia sinensis</i> (Theaceae)	PEP [antibacterial, AI]
(-)-Epicatechin 3- O-gallate (flavan-3-ol gallic acid ester)	<i>Cinnamomum</i> sp. (Lauraceae), <i>Rheum palmatum</i> (Polygonaceae), <i>Camellia sinensis</i> (Theaceae)	PEP (52 nM) [products give taste to tea]
(-)-Epigallocatechin 3-O-gallate (flavan-3-ol gallic acid ester)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Cinnamomum</i> sp. (Lauraceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	PEP (1470 nM) [products give taste to tea]; PEP inhibitors are potential anti-amnesics since PEP involved in metabolism of memory-linked vasopressin, substance P & thyrotropin releasing hormone (TRH)
Gallic acid (= 3,4,5- Trihydroxybenzoic acid) (phenolic acid)	Widespread; basic constituent of the hydrolysable tannins (gallotannins); <i>Mangifera indica</i> (Anacardiaceae)	PEP (487) (weak)
Gallic acid 4-O-β-D-(6-O- galloyl)glucopyranoside (glucose gallic acid ester)	<i>Rhodiola sacra</i> (Crassulaceae) [root], <i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
3-O-Galloyl- epigallocatechin-(4β → 8)-epigallocatechin-3-O- gallate ester (condensed tannin)	<i>Camellia sinensis</i> (tea) (Theaceae), [leaf] <i>Rhodiola sacra</i> (Crassulaceae) [root]	PEP (437 nM)
4-O-(β-D- Glucopyranoside)-gallic acid (phenolic glycoside)	<i>Rhodiola sacra</i> (Crassulaceae) [root]	PEP (215) (weak)
4(4-Hydroxyphenyl)-2- butanone 4'-O-β-D-(2,6-di-O-galloyl) glucopyranoside (phenolic glycoside)	<i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
4(4-Hydroxyphenyl)-2- butanone 4'-O-β-D-(2-O- galloyl-6-O-cinnamoyl)- Glc (phenolic glycoside)	<i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
4(4-Hydroxyphenyl)-2- butanone 4'-O-β-D-(6-O- galloyl-2-O-cinnamoyl)- Glc (phenolic glycoside)	<i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
Licuraside (= Iso- liquiritigenin-4-β-D- apiofuranosyl-2'-β-D-Glc; 2',4',4'-Trihydroxychalcone- 4-β-D-apiofuranosyl-2'-β- D-Glc) (chalcone glycoside)	<i>Glycyrrhiza glabra</i> (licorice) [root] (Fabaceae)	PEP

(continued)

Table 13.4 (Continued)

Compound (details)	Plant source (family) plant part	Target (other targets) in vivo effects
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread, Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Apium graveolens</i> (Apiaceae)	PEP
Protocatechuic acid (= 3,4-Dihydroxybenzoic acid) (phenolic acid)	Widespread; <i>Allium cepa</i> (Liliaceae), <i>Helianthus</i> (Asteraceae), <i>Erica</i> (Ericaceae), <i>Hibiscus</i> (Malvaceae), <i>Eucalyptus</i> (Myrtaceae), <i>Picea</i> (Pinaceae), <i>Picrorhiza</i> (Scrophulariaceae), fern, <i>Actinidia</i> (Actinidiaceae), <i>Olea</i> (Oleaceae) <i>Rheum</i> (Polygonaceae) spp.	PEP (28) [antifungal, AI]
Purpurogallin (= 2,3,4,6-Tetrahydroxy-5H-benzocyclohepten-5-one) (bicyclic phenolic)	<i>Dryophanta divisa</i> gall on <i>Quercus pedunculata</i> (Fagaceae)	PEP (16) (EGF-RTK, XO) [antioxidant, red pigment]
1,2,6-Tri- <i>O</i> -galloylglucose (glucose gallic acid ester)	<i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
<i>cis</i> -3,5,4'-Trihydroxystilbene 4'- <i>O</i> - β -D-(6- <i>O</i> -galloyl)-Glc (= <i>cis</i> -Resveratrol 4'- <i>O</i> - β -D-(6- <i>O</i> -galloyl)-Glc) (stilbene glycoside)	<i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
3,5,4'-Trihydroxystilbene 4'- <i>O</i> - β -D-(2- <i>O</i> -galloyl)-Glc (= Resveratrol 4'- <i>O</i> - β -D-(2- <i>O</i> -galloyl)-Glc) (stilbene glycoside)	<i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
3,5,4'-Trihydroxystilbene 4'- <i>O</i> - β -D-(6- <i>O</i> -galloyl)-Glc (= Resveratrol 4'- <i>O</i> - β -D-(6- <i>O</i> -galloyl)-Glc) (stilbene glycoside)	<i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
3,5,4'-Trihydroxystilbene 4'- <i>O</i> - β -D-Glc (= Resveratrol 4'- <i>O</i> - β -D-Glc) (stilbene glycoside)	<i>Rheum palmatum</i> (Polygonaceae) [rhizome]	PEP
Terpene		13.4It
Sacranoside A (monoterpene glycoside)	<i>Rhodiola sacra</i> (Crassulaceae) [root]	PEP (348) (weak)
β -Sitosterol-3- <i>O</i> - β -D-Glc (= Sitosterin-3- <i>O</i> - β -D-Glc) (phytosterol glycoside)	Widespread; <i>Caryophyllus flos</i> (Myrtaceae)	PEP

Table 13.5 Inhibition of proteases by plant proteins

Protein (molecular mass; number of cysteines; other properties)	Plant source (family) [plant part]	Target (other targets) / in vivo effects/
Aspartate protease (ASPPR)		13.5A
<i>Cucurbita</i> ASPPR I-1, I-2 (11 kDa monomer; homodimeric)	<i>Cucurbita pepo</i> (squash) (Cucurbitaceae) [fruit]	Pepsin [2 nM], <i>Glomerella cingulata</i> (fungus) ASPPR [20 nM]
<i>Lycopersicon</i> ASPPR Is (protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [leaf – induced by Jasmonic acid (at 50–100)]	ASPPR – cathepsin D
<i>Solanum</i> A-class genes encode ASPPR Is, e.g. 1 (21 kDa), 2 (22 kDa), 3 (22 kDa), 4 (= Cathepsin D inhibitor = PDI) (19 kDa), 5 (22 kDa), 6 (22 kDa)	<i>Solanum tuberosum</i> (Solanaceae) [tuber] (some ASPPR Is induced by Jasmonic acid (at 50–100))	ASPPR Is (1–6), TRY I, ASPPR I (6), Cathepsin D (4 = PDI) (Kunitz PI homologues)
<i>Solanum dulcamara</i> ASPPR Is (protein)	<i>Solanum dulcamara</i> (Solanaceae) [induced by Jasmonic acid (at 50–100)]	ASPPR
<i>Solanum melongena</i> ASPPR Is (protein)	<i>Solanum melongena</i> (Solanaceae) [induced by Jasmonic acid (at 50–100)]	ASPPR
<i>Vicia</i> Cathepsin D I (protein)	<i>Vicia sativa</i> (vetch) (Fabaceae) [seed]	Cathepsin D
Cysteine Protease (CYSPR)		13.5B
<i>Ananas</i> BI–I, BI–II, BI–III, BI–IV, BI–V, BI–VI (6 kDa; A (41 aa, 7 Cys)–(S–S) ₂ –B (11 aa; 2 Cys); triple stranded antiparallel β sheet)	<i>Ananas comosus</i> (pineapple) (Bromeliaceae) [stem] [Homology to BBIs]	Bromelain [0.7], Cathepsin L [0.2], Papain [3]
<i>Carica</i> papain pro-region (107 aa)	<i>Carica papaya</i> (papaya, paw-paw) (Caricaceae) [recombinant]	Papain [2 nM], chymopapain [12 nM], caricain [8 nM], papaya proteinase IV [3]
<i>Carica</i> proteinase IV pro-region (106 aa)	<i>Carica papaya</i> (paw-paw) (Caricaceae) [recombinant]	Papain [20 nM], chymopapain [15 nM], caricain [34 nM], papaya proteinase IV [1]
<i>Chelidonium</i> Chelidostatin (10 kDa phytocystatin)	<i>Chelidonium majus</i> (celandine) (Papaveraceae) [leaf, stem]	Cathepsin H [8 nM], Cathepsin L [56 pM], Papain [110 pM]
<i>Daucus</i> phytocystatin EIP18 (18 kDa phytocystatin)	<i>Daucus carota</i> (Apiaceae)	CYSPR
<i>Glycine</i> Cystatins L1, N2 (Soyacystatin; scN; soybean CYSPR inhibitor N), R1 (11 kDa phytocystatins)	<i>Glycine max</i> (soybean) (Fabaceae) [seed] (L1 constitutive; N2 & R1 induced by wounding & Methyljasmonate)	Papain – L1 [19], N2 [57 nM], R1 [21 nM]; insect gut CYSPRs
<i>Helianthus</i> phytocystatins Sca, Scb (10 kDa phytocystatins)	<i>Helianthus annuus</i> (<i>Helianthus annuus</i>) (Asteraceae)	CYSPR – papain
<i>Hordeum</i> Lipid Transfer Proteins 1 & 2 (= LTP 1 & 2) (7 kDa protein)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	CYSPRs (barley malt endoproteases) (< 2) [antifungal]

(continued)

Table 13.5 (Continued)

<i>Protein (molecular mass; number of cysteines; other properties)</i>	<i>Plant source (family) / plant part/</i>	<i>Target (other targets) / in vivo effects/</i>
<i>Oryza</i> Oryzacystatin-I (11 kDa; phycocystatin; α -helix- 5 antiparallel β sheets)	<i>Oryza sativa</i> (Poaceae) [seed]	Cathepsin H [790nM], Papain [9; 30nM] [anti-polioviral (at 8)]
<i>Oryza</i> Oryzacystatin-II (11 kDa; phycocystatin; α -helix- 5 antiparallel β sheets)	<i>Oryza sativa</i> (Poaceae) [seed]	Cathepsin H [10nM], Papain [830nM]
<i>Pennisetum</i> CYSPR I (24kDa protein)	<i>Pennisetum glaucum</i> (pearl millet) (Poaceae) [seed]	CYSPR – Papain [antifungal]
<i>Solanum</i> Cysteine Protease Inhibitor (PCPI) (20kDa)	<i>Solanum tuberosum</i> (Solanaceae) [tuber]	CYSPR (STI (Kunitz PI) homologue) – lysosomal cathepsin L (70pM)
<i>Sorghum</i> CYSPR I (26kDa pre-protein phycocystatin)	<i>Sorghum bicolor</i> (Poaceae) [seedling]	CYSPR – Papain
<i>Wisteria</i> WCPI-3 (Wisteria CYSPR I) (17kDa phycocystatin)	<i>Wisteria floribunda</i> (Fabaceae) [seed]	CYSPR – Papain [6nM]
<i>Zea</i> Cystatin (= CC; Corn Cystatin) (11 kDa; phycocystatin)	<i>Zea mays</i> (corn) (Poaceae) [seed]	CYSPR – corn proteinases, papain (0.2), cathepsin H (0.1), cathepsin L
Non-plant reference		13.5Bn
[Animal Cystatins (Type 2 animal Cystatins)] (Egg white Cystatin, Cystatins C, D & S) (12kDa; Cys = 4; α -helix-5 antiparallel β sheets)	Animal (human, mammalian, bird, insect, snake Cystatins) [extracellular]	CYSPR (e.g. papain)
[Animal Stefins (Type 1 animal Cystatins) (Stefins A, B & D)] (11 kDa; acidic; α -helix-5 antiparallel β sheets)	Animal (e.g. bovine, human mouse, rat Stefins A & B, bovine Stefin C & pig Stefin D) [intracellular & extracellular]	CYSPR (e.g. papain)
[Kininogens (High MW Kininogen (HK), Low MW Kininogens (LK), T-Kininogen (TK) (single chain glycoproteins; Cystatin-like domains)	Animals; single chain cleaved by Kallikrein \rightarrow S-S-linked heavy & light chains + Kinin (e.g. Bradykinin)	CYSPR (e.g. papain, cathepsins B, H & L) [infection response, inflammation, vascular regulation, vasodilation]
Metalloproteases (MPRs)		13.5C–D
Angiotensin-I converting enzyme (ACE)		13.5C
AF (= Ala–Phe) (dipeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (15)
APGAGVY (= Ala–Pro–Gly–Ala–Gly–Val–Tyr) (septapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (2)

(continued)

Table 13.5 (Continued)

<i>Protein (molecular mass; number of cysteines; other properties)</i>	<i>Plant source (family plant part)</i>	<i>Target (other targets) / in vivo effects </i>
DIGYY (= Asp-Ile-Gly-Tyr-Tyr) (pentapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (3)
DYVGN (= Asp-Tyr-Val-Gly-Asn) (pentapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (0.7)
FY (= Phe-Tyr) (dipeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (25)
GGVIPN (= Gly-Gly-Val-Ile-Pro-Asn) (hexapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (0.7)
IRA (= Ile-Arg-Ala) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (6)
IRAQQ (= Ile-Arg-Ala-Gln-Gln) (pentapeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (160)
IVY (= Ile-Val-Tyr) (tripeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (0.5) [0.1] [antihypertensive]
IY (= Ile-Tyr) (dipeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (2)
LAA (= Leu-Ala-Ala) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (13)
LAY (= Leu-Ala-Tyr) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (4)
LLP (= Leu-Leu-Pro) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (57)
LNP (= Leu-Asn-Pro) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (43)
LQP (= Leu-Gln-Pro) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (2)
LQQ (= Leu-Gln-Gln) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (100)
LRP (= Leu-Arg-Pro) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (0.3)
LSP (= Leu-Ser-Pro) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (2)
LY (= Leu-Tyr) (dipeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (6)
TAPY (= Thr-Ala-Pro-Tyr) (tetrapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (14)
TF (= Thr-Phe) (dipeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (18)
TPVY (= Thr-Val-Pro-Tyr) (tetrapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (2)

(continued)

Table 13.5 (Continued)

<i>Protein (molecular mass; number of cysteines; other properties)</i>	<i>Plant source (family plant part)</i>	<i>Target (other targets) in vivo effects </i>
TVVPG (= Thr–Val– Val–Pro–Gly) (pentapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (2)
TYLGS (= Thr–Tyr– Leu–Gly–Ser) (pentapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (0.9)
VAA (= Val–Ala–Ala) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (13)
VAY (= Val–Ala–Tyr) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (16)
VF (= Val–Phe) (dipeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (18)
VFPS (= Val–Phe–Pro–Ser) (tetrapeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (0.5)
VSP (= Val–Ser–Pro) (tripeptide)	<i>Zea mays</i> (corn) (Poaceae) [α -Zein (seed protein) hydrolysate]	ACE (10)
VY (= Val–Tyr) (tripeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE [3]
YL (= Tyr–Leu) (dipeptide)	<i>Triticum aestivum</i> (wheat) (Poaceae) [wheatgerm proteolytic hydrolysate]	ACE (16)
Carboxypeptidase (CPA)	Crystalline carboxypeptidase	13.5D
	isolated by John Northrop	
	(USA, Nobel Prize,	
	Chemistry Chemistry, 1946,	
	pure enzyme & viral	
	protein isolation)	
<i>Solanum</i> Carboxypeptidase inhibitor (= PCI) (4kDa, 6 Cys, “cystine knot” or “T-knot” protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	CPA [2nM] [EGF-R antagonist]
<i>Lycopersicon</i> Metallo-carboxypeptidase inhibitor (= MCPI) (protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [leaf]	CPA
Matrix metalloproteases (MMPs)		13.5E
<i>Bauhinia</i> lectin (196kDa, homotetramer)	<i>Bauhinia purpurea</i> (Fabaceae)	↓ MMP-9 production by activated leucocytes (CHO) [mitogenic]
<i>Calystegia</i> lectin (CHO-binding protein)	<i>Calystegia sepium</i> (Convolvulaceae)	Induction of leucocyte MMP-9 (CHO = carbohydrate)
<i>Convolvulus</i> lectin (CHO-binding protein)	<i>Convolvulus arvensis</i> (Convolvulaceae)	Induction of leucocyte MMP-9 (CHO)

(continued)

Table 13.5 (Continued)

<i>Protein (molecular mass; number of cysteines; other properties)</i>	<i>Plant source (family plant part)</i>	<i>Target (other targets) / in vivo effects </i>
<i>Colchicum</i> lectin (CHO-binding protein)	<i>Colchicum autumnale</i> (Liliaceae)	Induction of leucocyte MMP-9 (CHO = carbohydrate)
<i>Datura</i> lectin (86 kDa, $\alpha_2\beta_2$)	<i>Datura stramonium</i> (Solanaceae)	↓ MMP-9 production by activated leucocytes (CHO)
<i>Glycine</i> Concanavalin A (110 kDa lectin, homotetramer)	<i>Glycine max</i> (Fabaceae)	Induction of leucocyte MMP-9 (CHO)
<i>Maackia</i> lectin (130 kDa, $\alpha_2\beta_2$)	<i>Maackia amurensis</i> (Fabaceae)	↓ MMP-9 production by activated leucocytes (CHO) [mitogenic]
<i>Phaseolus</i> Phytohaemagglutinin (PHA-L4) (126 kDa, homotetramer)	<i>Phaseolus vulgaris</i> (bean) (Fabaceae) [seed]	Induction of MMP-9 production by leucocytes (CHO) [mitogenic]
<i>Triticum</i> lectin (36 kDa, dimer)	<i>Triticum aestivum</i> (wheat) (Poaceae)	↓ MMP-9 production by activated leucocytes (CHO) [mitogenic]
<i>Urtica</i> lectin (CHO-binding protein)	<i>Urtica dioica</i> (Urticaceae)	Induction of leucocyte MMP-9 (CHO)
<i>Viscum</i> lectin (115 kDa, $\alpha_1\beta_1$)	<i>Viscum album</i> (mistletoe) (Viscaceae)	↓ MMP-9 production by activated leucocytes (CHO)
Serine proteases – elastase (ELA), chymotrypsin (CHY), subtilisin (SUB), trypsin (TRY)		
Monocot Bowman–Birk serine protease inhibitors (BBIs)		13.5F
<i>Coix</i> BBI TI-1; TI-2 (7 kDa; 10 Cys)	<i>Coix lachryma jobi</i> (Job's tears) (Poaceae) [seed]	TRY
<i>Hordeum</i> BBI (16 kDa; 20 Cys)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	TRY
<i>Oryza</i> BBI (16 kDa; 18 Cys)	<i>Oryza sativa</i> (rice) (Poaceae) [seed]	TRY
<i>Setaria</i> FMTI-II; FMTI-III (7 kDa; 10 Cys)	<i>Setaria italica</i> (foxtail millet) (Poaceae) [seed]	TRY
<i>Triticum</i> Type I – I, I-2a, I-2b, I-2c (15 kDa; 18 Cys)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	TRY (double-headed)
<i>Triticum</i> BBI Type II – II-4, II-5, II-6a, II-6b, II-7a (7 kDa; 9 Cys)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	TRY (single-headed)
<i>Zea</i> WIP1 (gene) (11 kDa; 11 Cys)	<i>Zea mays</i> (Poaceae) [seed]	TRY (putative)
Non-Poaceae Bowman– Birk serine protease inhibitors (BBIs)		13.5G
<i>Ananas</i> BI-I, BI-II, BI-III, BI-IV, BI-V, BI-VI (6 kDa; A (41 aa, 7 Cys)- (S-S) ₂ -B (11 aa; 2 Cys) [Homology to BBIs]	<i>Ananas comosus</i> (pineapple) (Bromeliaceae) [stem]	TRY (Bromelain, Cathepsin L, Papain)

(continued)

Table 13.5 (Continued)

Protein (molecular mass; number of cysteines; other properties)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
<i>Arachis</i> A-I, A-II, B-I, B-II, B-III (7–8 kDa; 14 Cys)	<i>Arachis hypogaea</i> (peanut) (Fabaceae) [seed]	CHY, TRY
<i>Canavalia</i> CLTI-I, CLTI-II (8 kDa)	<i>Canavalia lineata</i> (Fabaceae) [seed]	CHY, TRY
<i>Dioclea</i> DgTI (7 kDa; 14 Cys)	<i>Dioclea glabra</i> (Fabaceae) [seed]	TRY [0.5 nM] (2 TRY-binding sites)
<i>Erythrina</i> EBI (7 kDa; 14 Cys)	<i>Erythrina variegata</i> (Fabaceae) [seed]	CHY (weaker), TRY
<i>Glycine</i> BBI-1 (8 kDa protein; 14 Cys)	<i>Glycine max</i> (soyabean) (Fabaceae) [seed]	CHY (0.5), TRY (0.3) (Thrombin PAR)
<i>Glycine</i> C-II, D-II (8 kDa; 14 Cys), E-I (7 kDa; 14 Cys)	<i>Glycine max</i> (soyabean) (Fabaceae) [seed]	CHY, TRY; CHY, ELA, TRY (C-II)
<i>Lonchocarpus</i> DE-4 (8 kDa; 14 Cys)	<i>Lonchocarpus capassa</i> (apple leaf seed) (Fabaceae) [seed]	CHY, TRY
<i>Macrotyloma</i> DE-3, DE-4 (8 kDa; 14 Cys)	<i>Macrotyloma axillaris</i> (Fabaceae) [seed]	TRY
<i>Medicago</i> MsTI [seed] (7 kDa; 14 Cys)	<i>Medicago sativa</i> (alfalfa) (Fabaceae) [seed]	TRY [2 nM]
<i>Medicago</i> ATI (Alfalfa TI), ATI- 18, ATI-21 (7 kDa; 14 Cys)	<i>Medicago sativa</i> (alfalfa) (Fabaceae) [leaf]	TRY [ATI first wound- induced leaf BBI found]
<i>Phaseolus</i> I, I-A (9 kDa), I-B, I- A' (8 kDa), II (9 kDa), II', II-A (8–9 kDa; 14 Cys)	<i>Phaseolus angularis</i> (<i>Vigna angularis</i>) (adzuki bean) Fabaceae) [seed]	TRY
<i>Phaseolus</i> BBI (8 kDa; 14 Cys)	<i>Phaseolus aureus</i> (<i>Vigna radiata</i>) (mung bean) (Fabaceae)	TRY
<i>Phaseolus</i> BBI (8 kDa; 14 Cys)	<i>Phaseolus lunatus</i> (lima bean) (Fabaceae) [seed]	CHY, TRY
<i>Phaseolus</i> PVI-3, PVI-4 (8 kDa; 14 Cys)	<i>Phaseolus vulgaris</i> (kidney bean) (Fabaceae) [seed]	CHY, TRY
<i>Phaseolus</i> TI-II, TI-II' (8 kDa; 14 Cys)	<i>Phaseolus vulgaris</i> (kidney bean) (Fabaceae) [seed]	ELA, TRY
<i>Pisum</i> PsTI-I, PsTI-II, PsTI-IVA, PsTI-IVB (8 kDa; 14 Cys)	<i>Pisum sativum</i> (pea) (Fabaceae) [seed]	CHY, TRY
<i>Vicia</i> BBI (8 kDa; 14 Cys)	<i>Vicia angustifolia</i> (common vetch) (Fabaceae) [seed]	CHY, TRY
<i>Vicia</i> FBI (8 kDa; 14 Cys)	<i>Vicia faba</i> (broad bean, fava bean) (Fabaceae) [seed]	CHY, TRY
<i>Vigna</i> BTCl (8 kDa; 14 Cys)	<i>Vigna unguiculata</i> (cowpea) (Fabaceae) [seed]	CHY, TRY
<i>Solanum</i> BBI (homologue of <i>Glycine</i> C-II) (8 kDa)	<i>Solanum tuberosum</i> (Solanaceae) [tuber]	SERPR
<i>Torresea</i> BBI (13 kDa)	<i>Torresea cearensis</i> (Fabaceae) [seed]	TRY, factor XIIa
Cyclotide BBI		13.5H
<i>Helianthus</i> BBI SFTI-1 (14 aa, 2 Cys, cyclotide)	<i>Helianthus annuum</i> (sunflower) (<i>Helianthus annuus</i> (Asteraceae) [seed])	TRY [0.5 nM] (acyclic SFTI-1 [12 nM]), cathepsin G
[acyclic <i>Helianthus</i> BBI SFTI-1] (14 aa, 2 Cys)	Synthetic acyclic analogue of <i>Helianthus</i> SFTI-1	TRY [12 nM]

(continued)

Table 13.5 (Continued)

Protein (molecular mass; number of cysteines; other properties)	Plant source (family) [plant part]	Target (other targets) / in vivo effects/
Brassicaceae 7kDa protease inhibitors		
<i>Arabidopsis</i> ATTI-A, ATTI-B, ATTI-C (7kDa; 8 Cys)	<i>Arabidopsis thaliana</i> (Brassicaceae) gene translation	Putative SERPR inhibitors
<i>Brassica</i> RTI-IIIA, RTI-IIIB, RTI-IIIC (7kDa; 8 Cys)	<i>Brassica napus</i> (Brassicaceae) [seed]	CHY [410nM], TRY [300pM]
<i>Brassica</i> thrombin inhibitor (~10kDa; possible member of RTI family)	<i>Brassica oleraceae</i> (cabbage) (Brassicaceae) [seed]	TRY (at 0.3), thrombin, factor Xa, factor XIIa, plasmin
<i>Sinapis</i> MTI-2A, MTI-2B, MTI-2C, MTI-2D, MTI-2E, MTI-2F (7kDa; 8 Cys)	<i>Sinapis alba</i> (Brassicaceae) [seed]	CHY [500nM], TRY [160pM]
Defensin (γ-thionin) PIs		
<i>Brassica</i> Type II PI (cf. γ -thionin = defensin; cf. <i>Arabidopsis</i> Type II PI) (8kDa; 8 Cys)	<i>Brassica rapa</i> (turnip) (Brassicaceae)	13.5J SERPR
<i>Cassia</i> 5467 Da defensin PI (5kDa; 8 Cys)	<i>Cassia fistula</i> (Fabaceae) [seed]	TRY (2) [homologous <i>C. fistula</i> Defensin with Tyr-25 instead of Lys-25 is inactive]
<i>Phaseolus</i> 5412 Da Defensin PI (5kDa; 8 Cys)	<i>Phaseolus angularis</i> (adzuki bean) (Fabaceae) [seed]	TRY (0.5) [<i>P. angularis</i> Defensin lacking N-terminal Arg may also be a TI]
Kunitz serine protease inhibitors (KPI)		
<i>Acacia</i> ACTI-A (ACTI-A (14kDa)-S-S-ACTI-B (4kDa) heterodimeric KPI)	<i>Acacia confusa</i> (Fabaceae) [seed]	TRY [also active as non-processed gene product]
<i>Adenanthera</i> DE5 (α chain (14kDa)-S-S- β chain (4kDa) heterodimeric KPI)	<i>Adenanthera pavonina</i> (Fabaceae) [seed]	TRY
<i>Albizia</i> A-II, A-III (22kDa), B-I, B-II (19kDa) (A chain-S-S-B chain heterodimeric KPIs)	<i>Albizia julibrissin</i> (Fabaceae) [seed]	TRY, CHY (A-II, A-III), bovine CHY, porcine ELA (B-I, B-II)
<i>Alocasia</i> KTI (18kDa)	<i>Alocasia macrorrhiza</i> (giant taro) (Araceae) [tuber]	CHY, TRY
<i>Arabidopsis</i> KPI-like protein (gene)	<i>Arabidopsis thaliana</i> (Brassicaceae)	Putative SERPR inhibitor
<i>Bauhinia</i> KPIs (20kDa)	<i>Bauhinia bauhinoides</i> , <i>B. mollis</i> , <i>B. pentandra</i> (Fabaceae)	TRY, kallikrein (<i>B. bauhinoides</i> , <i>B. pentandra</i>), factor XIIa (<i>B. pentandra</i>)
<i>Brassica</i> KPI-like BnD22 (22kDa)	<i>Brassica napus</i> (rape) (Brassicaceae) [drought-induced]	Putative SERPR inhibitor
<i>Brassica</i> KPI (22kDa)	<i>Brassica oleraceae</i> (cabbage) (Brassicaceae)	TRY

(continued)

Table 13.5 (Continued)

Protein (molecular mass; number of cysteines; other properties)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
<i>Canavalia</i> CLSI-II, CLSI-III (21 kDa; glycoproteins)	<i>Canavalia lineata</i> (Fabaceae) [seed]	SUB
<i>Canavalia</i> CLTI-III (21 kDa)	<i>Canavalia lineata</i> (Fabaceae) [seed]	TRY [5 nM]
<i>Carica papaya</i> KTI-like Latex SERPR inhibitor (~20 kDa; glycosylated)	<i>Carica papaya</i> (Caricaceae) [latex]	CHY, TRY
<i>Citrus</i> Miraculin-like proteins 1 & 2 (24 kDa)	<i>Citrus paradisi</i> (grapefruit) (Rutaceae)	Miraculin and KPI homologues
<i>Enterolobium</i> ECTI (α (15 kDa), β (4 kDa) heterodimeric KPI)	<i>Enterolobium contorsiliquum</i> (Fabaceae) [seed]	CHY [120 nM], Factor XIIa [150], human plasma kallikrein [5 nM], plasmin [18], TRY [2 nM]
<i>Erythrina</i> DE-3 (17 kDa)	<i>Erythrina caffra</i> (Fabaceae) [seed]	TRY, PA
<i>Erythrina</i> DE-3 (17 kDa)	<i>Erythrina latissima</i> (Fabaceae) [seed]	TRY
<i>Erythrina</i> ETI-A (19 kDa), ETI-B (20 kDa), ECI (18 kDa)	<i>Erythrina variegata</i> (Fabaceae) [seed]	CHY (ECI), TRY (ETI-A, ETI-B)
<i>Glycine</i> KPIs – STI (= Soybean trypsin inhibitor; STI-A; B- KESL; KTI-3; KTI-A; major KTI) (18 kDa); STI-B (18 kDa); STI-C (18 kDa); 10 KTI genes encoding KTI-1, KTI-2 etc.	<i>Glycine max</i> (soybean) (Fabaceae) [seed]	TRY (STI [3 pM])
<i>Hordeum</i> KTI-like α -Amylase- Subtilisin Inhibitor BASI (Barley α A & Subtilisin I) (20 kDa Kunitz-related protein)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	SUB (α -A)
<i>Ipomoea</i> putative KTI-like proteins (Sporamin A & B precursors) (at least 5 genes encoding A and B type proteins) (22 kDa)	<i>Ipomoea batatas</i> (sweet potato) (Solanaceae)	Putative SERPR inhibitor
<i>Lycopersicon</i> putative KTI (23 kDa)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	Putative SERPR inhibitor
<i>Lycopersicon</i> Miraculin-like protein (LeMir) (23 kDa)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	KTI-like protein (converts sour taste to sweet)
<i>Oryza</i> KTI-like α -Amylase- Subtilisin Inhibitor (20 kDa Kunitz-related protein)	<i>Oryza sativa</i> (rice) (Poaceae) [seed]	SUB (α -A) [antifungal, anti-insect]
<i>Phaseolus</i> KPI (~20 kDa)	<i>Phaseolus coccineus</i> (Fabaceae)	Putative SERPR inhibitor
<i>Populus</i> KTI-like (20 kDa)	<i>Populus balsamifera</i> (poplar) (Salicaceae)	Putative SERPR inhibitor
<i>Populus</i> KTI-like TI1 (22 kDa) TI2 (21 kDa), TI3 (21 kDa)	<i>Populus tremuloides</i> (poplar) (Salicaceae)	Putative SERPR inhibitor

(continued)

Table 13.5 (Continued)

<i>Protein (molecular mass; number of cysteines; other properties)</i>	<i>Plant source (family) / plant part/</i>	<i>Target (other targets) / in vivo effects/</i>
<i>Prosopis</i> 2-chain KPI (α chain (14kDa)-S-S- β -chain (4kDa) heterodimeric KPI)	<i>Prosopis juliflora</i> (Fabaceae) [seed]	TRY
<i>Psophocarpus</i> Nodulin KPI (20kDa), WBTI-1a, WBTI-1b (19kDa; basic), WBTI-2 (19kDa; acidic), WBTI-2a (19kDa; acidic)	<i>Psophocarpus tetragonolobus</i> (winged bean) (Fabaceae) [seed]	TRY – WTBI-1a [3 nM]
<i>Psophocarpus</i> Psophocarpin B1(20kDa), WCI-2, WCI-3, WCI-X (21 kDa), putative CHYI-X (21 kDa)	<i>Psophocarpus tetragonolobus</i> (winged bean) (Fabaceae) [seed]	CHY
<i>Richadella</i> Miraculin (25kDa; glycoprotein)	<i>Richadella dulcifica</i> (miracle fruit) (Sapotaceae) [fruit]	Soybean KPI homologue
<i>Salix viminalis</i> putative KTI (20kDa)	<i>Salix viminalis</i> (Salicaceae)	Putative SERPR inhibitor
<i>Schizolobium</i> CHYI (20kDa; 4 Cys)	<i>Schizolobium parahybum</i> (Fabaceae) [seed]	CHY [59nM]
<i>Solanum</i> Cysteine Protease Inhibitor (PCPI) (22kDa)	<i>Solanum tuberosum</i> (Solanaceae) [tuber]	STI (KPI) homologue (CYSPR)
<i>Solanum</i> KPIs – B- & C-class genes encode SERPR Is	<i>Solanum tuberosum</i> (Solanaceae) [tuber]	SERPR (CYSPR)
<i>Solanum</i> KPIs – A-class genes encode ASPPR Is e.g. 1 (21 kDa), 2 (22kDa), 3 (22kDa), 4 (= Cathepsin D inhibitor = PDI) (19kDa), 5 (22kDa), 6 (22kDa), 7, 8, 9 (= PKI-1, PKI-2, PKI-1-like), 10 (putative KPI), potato serine protease inhibitors PSPI-21-5.2 (21 kDa, pI 5.2), PSPI-21-6.3 (21 kDa, pI 6.3), 23kDa KPI	<i>Solanum tuberosum</i> (Solanaceae) [tuber]	SERPR (1–6, ASPPR Is), 6 (TRY I, ASPPR I), 7, 8, 9 (TRY Is), PSPI-21- 5.2 & PSPI-21-6.3 (ELA more sensitive than TRY & CHY)
<i>Solanum</i> KPI – 21kDa SERPR Is PSPI-21-5.2 & PSPI- 21-6.3 (S–S-linked 17kDa & 5kDa subunit heterodimers)	<i>Solanum tuberosum</i> (Solanaceae) [tuber]	SERPR – CHY, ELA, TRY
<i>Theobroma</i> KTI (21kDa)	<i>Theobroma cacao</i> (cocoa) (Malvaceae) [seed]	SERPR – CHY [2], TRY [95 nM]
<i>Triticum</i> WASI (Wheat α A & Subtilisin inhibitor) (20kDa Kunitz-related protein)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	SUB (α -A)

(continued)

Table 13.5 (Continued)

Protein (molecular mass; number of cysteines; other properties)	Plant source (family plant part)	Target (other targets) in vivo effects/
Lipid transfer protein (LTP) PIs		13.5L
<i>Eleusine</i> double-headed TRY – α AI inhibitor I-2 (LTP homologue)	<i>Eleusine coracana</i> (ragi, finger millet) (Poaceae) [seed]	SUB (α AI) (double-headed inhibitor)
<i>Phaseolus</i> 9kDa LTP PI (9kDa) [antifungal]	<i>Phaseolus angularis</i> (adzuki bean) (Fabaceae) [seed]	TRY (0.4) [10kDa glycosylated forms of this LTP are inactive]
Napin PIs (14kDa proteins; S-S- linked 4kDa S-10kDa L heterodimers)		13.5M
<i>Brassica</i> TIBN (14kDa)	<i>Brassica napus</i> (kohlrabi) (Brassicaceae)	TRY [50]
<i>Brassica</i> BN (16kDa)	<i>Brassica nigra</i> (Brassicaceae)	CHY (at 2), Subtilisin (at 2) TRY [20]
<i>Sinapis</i> TISA-1, TISA-2 (16kDa)	<i>Sinapis arvensis</i> (charlock) (Brassicaceae) [seed]	CHY (at 2), Subtilisin (at 2), TRY [7]
Potato inhibitor 1 family		13.5N
<i>Amaranthus</i> ATI (7kDa; 2 Cys)	<i>Amaranthus hypochondriacus</i> (Amaranthaceae) [seed]	CHY, TRY
<i>Amaranthus</i> ATSI (7kDa; 2 Cys)	<i>Amaranthus caudatus</i> (Amaranthaceae) [seed]	Cathepsin G [122 nM], CHY [0.4 nM], Factor XIIa [440 nM], Plasmin [38 nM], Subtilisin [0.4 nM], TRY [0.3 nM]
<i>Canavalia</i> CLSI-1 (7kDa; 0 Cys)	<i>Canavalia lineata</i> (Fabaceae) [seed]	Subtilisin
<i>Cucurbita</i> PI (7kDa; 2 Cys)	<i>Cucurbita maxima</i> (squash) (Cucurbitaceae) [seed]	Activated Hageman Factor (XIIa) [41 nM], TRY [16 nM]
<i>Cucurbita</i> PFTI (7kDa; 0 Cys)	<i>Cucurbita maxima</i> (squash) (Cucurbitaceae) [seed]	TRY
<i>Fagopyrum</i> BW-1, BW-2, BW- 3; IT1, IT2, IT4 (BTI-1, BTI-2, BTI-3); BWI-4a (8kDa; 2 Cys)	<i>Fagopyrum esculentum</i> (buckwheat) (Polygonaceae) [seed]	TRY
<i>Hordeum</i> CI-1, CI-2 (0 Cys), 5 other variants (8kDa; various Cys)	<i>Hordeum vulgare</i> (barley) (Poaceae)	CHY
<i>Linum</i> LUTI, LUTI A (8kDa; 2 Cys)	<i>Linum usitatissimum</i> (flax) (Linaceae) [seed]	Cathepsin G, CHY, SUB, TRY
<i>Lycopersicon</i> PI-1; 2 other variants (8kDa; 2 Cys)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	SERPR
<i>Momordica</i> BGIA (7kDa; 2 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	<i>S. aureus</i> Glutamate endopeptidase [70 nM], SUB
<i>Momordica</i> MCI-3 (7kDa; 0 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	TRY
<i>Nicotiana</i> PI-Ia, PI-Ib, TIMPa, TIMPb (8kDa; 2 Cys)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	SERPR

(continued)

Table 13.5 (Continued)

Protein (molecular mass; number of cysteines; other properties)	Plant source (family plant part)	Target (other targets) / in vivo effects/
<i>Solanum</i> PI-1A, B, C, D; other variants (8 kDa; 2 Cys)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	CHY, TRY [wounding- & pathogen-induced, anti-carcinogen]
<i>Vicia</i> VSI (7 kDa; 0 Cys)	<i>Vicia faba</i> (broad bean) (Fabaceae) [seed]	SUB
<i>Vigna</i> Subtilisin I & processing variant (N-terminal 19aa) (11 kDa)	<i>Vigna (Phaseolus) angularis</i> (adzuki bean) (Fabaceae) [seed]	SUB
<i>Zea</i> PI (gene) (8 kDa; 1 Cys)	<i>Zea mays</i> (corn) (Poaceae) [seed]	Putatively CHY & SUB
Potato inhibitor II family		13.50
<i>Arabidopsis</i> Type II PI II (cf. γ -thionin = defensin; cf. Brassica Type II PI) (9 kDa; 8 Cys)	<i>Arabidopsis thaliana</i> (Brassicaceae)	SERPR
<i>Brassica</i> Type II PI (cf. γ -thionin = defensin; cf. <i>Arabidopsis</i> Type II PI) (8 kDa; 8 Cys)	<i>Brassica rapa</i> (turnip) (Brassicaceae)	SERPR
<i>Capsicum</i> PSI-I, PSI-2 (pepper seed PIs); PLPI-1, PLPI-2, PLPI-3, PLPI-4, PLPI-5, PLPI-6, PLPI-7 (Pepper leaf PIs 1-7) (6 kDa; 8 Cys)	<i>Capsicum annuum</i> (paprika) (Solanaceae) [seed; leaf - wounding-inducible]	PSI-I activity - TRY [0.5 nM], CHY [47 nM], PRO [59 nM]; PLPIs 1-7 activities - CHY (all) [80 pM to 1 nM]; TRY (1, 2, 6 & 7) [4-10 nM]
<i>Lycopersicon</i> PI-II precursor (3 TRYI domains) (Cys-rich protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	TRY [wound induced]
<i>Lycopersicon</i> PI-II (Cys-rich protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	CHY, TRY [wound induced]
<i>Lycopersicon</i> AT1 (Cys-rich protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	Putative SERPR I
<i>Nicotiana</i> Precursor NaProPI (43 kDa)	<i>Nicotiana glauca</i> (ornamental tobacco) (Solanaceae) [stigma]	CHY, TRY [precursor of 6 kDa T1-T4 & C1]
<i>Nicotiana</i> T1, T2, T3, T4 (6 kDa; 8 Cys)	<i>Nicotiana glauca</i> (ornamental tobacco) (Solanaceae) [stigma]	TRY
<i>Nicotiana</i> C1 (6 kDa; 8 Cys)	<i>Nicotiana glauca</i> (ornamental tobacco) (Solanaceae) [stigma]	CHY
<i>Nicotiana</i> C2 (2 chain CHY I from processing Precursor NaProPI) (Cys-rich 2-chain protein)	<i>Nicotiana glauca</i> (ornamental tobacco) (Solanaceae) [stigma]	CHY
<i>Nicotiana</i> TTI-1, TTI-2, TTI-3, TTI-4, TTI-5, TTI-6 (6 kDa)	<i>Nicotiana tabacum</i> (tobacco) (Solanaceae) [stigma]	TRY
<i>Nicotiana</i> Precursors NGPI-1 (8 repeated PI domains), NGPI-2 (6 repeated PI domains)	<i>Nicotiana glutinosa</i> (Solanaceae) [flower, leaf expression]	Putative SERPR Is [pathogen- & wounding-induced]
<i>Solanum</i> (6 kDa; 8 Cys)	<i>Solanum melongena</i> (aubergine) (Solanaceae) [fruit]	TRY

(continued)

Table 13.5 (Continued)

Protein (molecular mass; number of cysteines; other properties)	Plant source (family) plant part	Target (other targets) in vivo effects
<i>Solanum</i> PI-II (12 kDa; 16 Cys)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]; fungal pathogen <i>Phytophthora infestans</i>-induced famine in Scotland & Ireland (1840s)	2 PI domains – 1. CHY [0.9 nM], TRY [0.4 nM]; 2. CHY [2 nM] [wounding- & pathogen-induced, anti-carcinogen, anti-insect]; Irish famine (1845–1852) killed 1.5 million, exiled 1 million CHY, <i>S. griseus</i> proteinase B
<i>Solanum</i> PCI-I (6 kDa; 8 Cys)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	
<i>Solanum</i> TRY I (6 kDa; 8 Cys)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	TRY
<i>Solanum</i> PCI-1 (Potato CHY I) (6 kDa; 8 Cys)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	CHY
<i>Solanum</i> PI-II CM-7 (Cys-rich protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	CHY
Squash family trypsin inhibitors		13.5P
<i>Bryonia dioica</i> BDTI-II (3 kDa; 6 Cys)	<i>Bryonia dioica</i> (red bryony) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Citrullus</i> CVTI-1 (3 kDa; 6 Cys)	<i>Citrullus vulgaris</i> (watermelon) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Cucumis</i> CMCTI-I (3 kDa; 6 Cys)	<i>Cucumis melo</i> (oriental pickling melon) (Cucurbitaceae) [seed]	TRY (bovine) [127 pM], LYSEP (<i>S. aureus</i>) [207 pM]
<i>Cucumis</i> CMCTI-II (= CMeTI-A) (3 kDa; 6 Cys)	<i>Cucumis melo</i> (oriental pickling melon) (Cucurbitaceae) [seed]	TRY (bovine) [118 pM; 160 pM], LYSEP (<i>S. aureus</i>) [15 pM]
<i>Cucumis</i> CMCTI-III (3 kDa; 6 Cys; N-terminal < E)	<i>Cucumis melo</i> (oriental pickling melon) (Cucurbitaceae) [seed]	TRY (bovine) [78 pM], LYSEP (<i>S. aureus</i>) [62 pM]
<i>Cucumis</i> CMeTI-B (3 kDa; 6 Cys)	<i>Cucumis melo</i> (oriental pickling melon) (Cucurbitaceae) [seed]	TRY (bovine) [470 pM]
<i>Cucumis</i> CSTI-IIb (3 kDa; 6 Cys)	<i>Cucumis sativus</i> (cucumber) (Cucurbitaceae) [seed]	TRY (bovine) [1 pM]
<i>Cucumis</i> CSTI-IV (3 kDa; 6 Cys)	<i>Cucumis sativus</i> (cucumber) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Cucumis</i> HM TI-I (3 kDa; 6 Cys)	<i>Cucumis melo</i> (Chinese melon, Hami melon) (Cucurbitaceae)	TRY (at nM)
<i>Cucurbita</i> CMTI-I (3 kDa; 6 Cys)	<i>Cucurbita maxima</i> (pumpkin) (Cucurbitaceae) [seed]	TRY (bovine) [3 pM]
<i>Cucurbita</i> CMTI-III (3 kDa; 6 Cys)	<i>Cucurbita maxima</i> (pumpkin) (Cucurbitaceae) [seed]	Xa [23], XIIa [70 nM], KAL [130], TRY (bovine) [1 pM]
<i>Cucurbita</i> CMTI-IV (3 kDa; 6 Cys)	<i>Cucurbita maxima</i> (pumpkin) (Cucurbitaceae) [seed]	TRY (bovine) [17 pM]
<i>Cucurbita</i> CMTI-V (7 kDa)	<i>Cucurbita maxima</i> (pumpkin) (Cucurbitaceae) [seed]	TRY [16 pM], Hagemann factor (factor XIIa) [41 nM]
<i>Cucurbita</i> ITD I, ITD III (3 kDa; 6 Cys)	<i>Cucurbita maxima</i> (pumpkin) (Cucurbitaceae) [seed]	TRY
<i>Cucurbita</i> CPTI-I (3 kDa; 6 Cys)	<i>Cucurbita pepo</i> (marrow, pumpkin, squash) (Cucurbitaceae) [seed]	TRY (bovine) (at nM)

(continued)

Table 13.5 (Continued)

<i>Protein (molecular mass; number of cysteines; other properties)</i>	<i>Plant source (family) [plant part]</i>	<i>Target (other targets) / in vivo effects/</i>
<i>Cucurbita</i> CPTI-II (3 kDa; 6 Cys)	<i>Cucurbita pepo</i> (marrow, pumpkin, squash) (Cucurbitaceae) [seed]	TRY (bovine) [1 pM]
<i>Cucurbita</i> CPTI-III (3 kDa; 6 Cys)	<i>Cucurbita pepo</i> (marrow, pumpkin, squash) (Cucurbitaceae) [seed]	TRY (bovine) [8 pM]
<i>Ecballium</i> EETI-II (3 kDa; 6 Cys)	<i>Ecballium elaterium</i> (squirting cucumber) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Echinocystis</i> ELTI-I (3 kDa; 6 Cys)	<i>Echinocystis lobata</i> (Cucurbitaceae) [seed]	TRY (15 pM), cathepsin G (79 nM)
<i>Echinocystis</i> ELTI-II (3 kDa; 6 Cys)	<i>Echinocystis lobata</i> (Cucurbitaceae) [seed]	TRY (3 pM), cathepsin G (91 nM)
<i>Lagenaria</i> LLDTI-I (= LLTI-I = <E-LLDTI-II = <E-LLTI-II) (3 kDa; 6 Cys; N-terminal <E)	<i>Lagenaria leucantha</i> (bottle gourd) (Cucurbitaceae) [seed]	TRY (bovine) [240 pM; 360 pM]
<i>Lagenaria</i> LLDTI-II (= LLTI-II) (3 kDa; 6 Cys)	<i>Lagenaria leucantha</i> (bottle gourd) (Cucurbitaceae) [seed]	Xa [41], XIIa [1], KAL [27], TRY (bovine) [65 pM; 96 pM]
<i>Lagenaria</i> LLDTI-III (= LLTI-III) (3 kDa; 6 Cys)	<i>Lagenaria leucantha</i> (bottle gourd) (Cucurbitaceae) [seed]	Xa [19], XIIa [4], KAL [200], TRY (bovine) [30 pM; 96 pM]
<i>Luffa</i> LATI-I (3 kDa; 6 Cys)	<i>Luffa acutangula</i> (ribbed gourd) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Luffa</i> LATI-II (3 kDa; 6 Cys)	<i>Luffa acutangula</i> (ribbed gourd) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Luffa</i> LCTI-I (3 kDa; 6 Cys)	<i>Luffa cylindrica</i> (sponge gourd, towel gourd) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Luffa</i> LCTI-II (3 kDa; 6 Cys)	<i>Luffa cylindrica</i> (sponge gourd, towel gourd) (Cucurbitaceae) [seed]	Xa [780], XIIa [75 nM], KAL [20], TRY (at nM)
<i>Luffa</i> LCTI-III (3 kDa; 6 Cys)	<i>Luffa cylindrica</i> (sponge gourd, towel gourd) (Cucurbitaceae) [seed]	Xa [100], XIIa [4 nM], KAL [38], TRY (at nM)
<i>Luffa</i> TGTI-I (3 kDa; 6 Cys)	<i>Luffa cylindrica</i> (towel gourd) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Luffa</i> TGTI-II (3 kDa; 6 Cys)	<i>Luffa cylindrica</i> (towel gourd) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Momordica</i> MCTI-A (3 kDa; 6 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Momordica</i> MCEI-I (3 kDa; 6 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	ELA (pig pancreas) [300 nM; 970 nM]
<i>Momordica</i> MCEI-II (3 kDa; 6 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	ELA (pig pancreas) [9 nM]
<i>Momordica</i> MCEI-III (3 kDa; 6 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	ELA (pig pancreas) [4 nM]
<i>Momordica</i> MCEI-IV (3 kDa; 6 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	ELA (pig pancreas) [5 nM]

(continued)

Table 13.5 (Continued)

Protein (molecular mass; number of cysteines; other properties)	Plant source (family / plant part)	Target (other targets) / in vivo effects/
<i>Momordica</i> MCTI-I (3kDa; 6 Cys; N-terminal < E)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	Xa [100], XIIa [13 nM], KAL [110], TRY (bovine) [67 pM; 12 nM]
<i>Momordica</i> MCTI-II (3kDa; 6 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	Xa [1], X1a [18], XIIa [56 nM], KAL [100], TRY (bovine) [25 pM; 0.8 nM]
<i>Momordica</i> MCTI-II' (3kDa; 6 Cys)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Momordica</i> MCTI-III (3kDa; 6 Cys; N-terminal < E)	<i>Momordica charantia</i> (bitter gourd) (Cucurbitaceae) [seed]	Xa [59], XIIa [2], KAL [140], TRY (bovine) [190 nM]
<i>Momordica</i> MRTI-I (3kDa; 6 Cys)	<i>Momordica repens</i> (Cucurbitaceae) [seed]	TRY (at nM)
<i>Momordica</i> MCoTI-I (3kDa; 6 Cys; cyclic peptide)	<i>Momordica cochinchinensis</i> (Vietnamese squash) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Momordica</i> MCoTI-II (3kDa; 6 Cys; cyclic peptide)	<i>Momordica cochinchinensis</i> (Vietnamese squash) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Momordica</i> MCoTI-III (3kDa; 6 Cys; linear peptide; N-terminal pyroglutamyl)	<i>Momordica cochinchinensis</i> (Vietnamese squash) (Cucurbitaceae) [seed]	TRY (at nM)
<i>Tricosanthes</i> TKTI-I (3kDa; 6 Cys)	<i>Tricosanthes kirilowii</i> (Cucurbitaceae) [seed]	TRY (at nM)
<i>Tricosanthes</i> TKTI-II (3kDa; 6 Cys)	<i>Tricosanthes kirilowii</i> (Cucurbitaceae) [seed]	TRY (at nM)
Ragi/barley		13.5Q
bifunctional PIs		
<i>Eleusine</i> TRY- α AI = RBI (Ragi bifunctional I) = RATI (Ragi α A and Trypsin I) (122 aa; 13kDa protein; 10 Cys; 5 S-S; protein)	<i>Eleusine coracana</i> (ragi, Indian finger millet) (Poaceae) [seed]	α A (insect), TRY [anti-insect]
<i>Hordeum</i> CM α A-TRY I proteins a-e (Barley chloroform-methanol soluble proteins a-e) (16kDa monomers; tetrameric glycoproteins)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	α A (insect) (CMa), TRY (CMc, CMe) [anti-insect]
<i>Hordeum</i> TRY I (13kDa; 10 Cys)	<i>Hordeum vulgare</i> (barley) (Poaceae) [seed]	TRY
<i>Oryza</i> allergen (15kDa)	<i>Oryza sativa</i> (Poaceae) [seed]	Cereal α A/try I family homologue [allergenic]
<i>Secale</i> allergen (14kDa)	<i>Secale cereale</i> (Poaceae) [seed]	Cereal α A/try I family homologue [allergenic]
<i>Triticum</i> 0.28 α AI (14kDa; 11 Cys)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	α A [homologous to <i>Hordeum</i> TRY I]
<i>Triticum</i> 0.19 α AI (14kDa; 10 Cys)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	α A [homologous to <i>Hordeum</i> TRY I]

(continued)

Table 13.5 (Continued)

Protein (molecular mass; number of cysteines; other properties)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
<i>Zea</i> CHFI (Corn Human Activated Hageman Factor [Factor XII] Inhibitor = Popcorn Inhibitor) (14kDa, 10 Cys, 5 S-S protein)	<i>Zea mays</i> (corn, maize) (Poaceae) [seed]	α A (insect), β -Factor XIIa (human, pig) [anti-insect]
Other serine protease inhibitor proteins		13.5R
<i>Cucurbita</i> CmPS-1 (<i>Cucurbita maxima</i> phloem serpin-1) (42kDa)	<i>Cucurbita maxima</i> (Cucurbitaceae) [phloem]	ELA
<i>Phaseolus</i> enterokinase inhibitor (60kDa; 31kDa monomer homodimeric glycoprotein)	<i>Phaseolus vulgaris</i> (kidney bean) (Fabaceae)	Enterokinase
<i>Zea</i> TRY/ α A inhibitor (22kDa, 16 Cys, 8 S-S protein)	<i>Zea mays</i> (corn, maize) (Poaceae) [seed]	α A, TRY bifunctional inhibitor (α A) [homologous to plant sweet defensive protein Thaumatin; antifungal, anti-insect]

Table 13.6 Oxidative phosphorylation and photophosphorylation

Compound (class)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
F₁-ATPase	Paul Boyer (mechanochemical coupling) & John Walker (F₀-F₁ structure & function) (USA, Nobel Prize, chemistry, 1997); Ephraim Racker (coupling factors) (USA)	13.6A
Phenolic		13.6Ap
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	<i>Apium graveolens</i> (Apiaceae); Lamiaceae, ferns [leaf surface]; <i>Digitaria exilis</i> (Poaceae); as glycoside in <i>Apium</i> , <i>Petroselinum</i> (parsley) (Apiaceae), <i>Cosmos</i> , <i>Erigeron</i> , <i>Dahlia</i> (Asteraceae), <i>Amorpha</i> (Fabaceae) spp.	F ₁ -ATPase (100) (BZ-R-like R, EST-R, Na ⁺ /K ⁺ /Cl ⁻ TR, PK, RTK, TPO) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
Biochanin A (= 5,7-Dihydroxy-4'-methoxyisoflavone; Pratensol) (isoflavone)	<i>Baptisia</i> sp., <i>Cicer arietum</i> , <i>Dalbergia</i> sp., <i>Trifolium pratense</i> (Fabaceae) spp., <i>Virola cadudifolia</i> (Myristicaceae), <i>Cotoneaster pannosa</i> (Rosaceae)	F ₁ -ATPase (60) (EGF-RTK, EST-R, MLCK, PKA, TPO) [oestrogenic, hypolipidaemic]
Butein (= 2',4',3,4-Tetrahydroxychalcone) (chalcone)	<i>Vicia faba</i> (Fabaceae); 4'-glycoside (Butrin) in <i>Coreopsis douglasii</i> , <i>Bidens</i> spp., <i>Helianthus annuus</i> (Asteraceae) [flower]; 3,4'-diglycoside (Isobutrin) in <i>Butea monosperma</i> , <i>B. frondosa</i> (Fabaceae)	F ₁ -ATPase (< 73) (EGF-RTK, Na ⁺ , K ⁺ -ATPase, p60 ^{c-src} TK)

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) plant part	Target (other targets) / in vivo effects/
Curcumin (= Diferuloylmethane; Turmeric yellow) (phenylpropanoid)	<i>Curcuma longa</i> (turmeric), <i>C. aromatica</i> , <i>C. xanthorrhiza</i> , <i>Zingiber officinale</i> (Zingiberaceae) [root]	F ₁ -ATPase (45) (HIV-1-INT, PK, RTK) [AI, antioxidant, hypoglycaemic, cytotoxic]
Daidzein (= 4',7-Dihydroxyisoflavone) (isoflavone)	<i>Glycine max</i> , <i>Trifolium repens</i> (clover), <i>Ulex europaeus</i> (gorse) (Fabaceae); 7-O-glucoside (Daidzein) in <i>Baptisia</i> spp., <i>Glycine max</i> , <i>Pueraria</i> spp., <i>Trifolium pratense</i> (Fabaceae)	F ₁ -ATPase (100) (CFTR, DNAPOL, EST-R, GABAA-R, lipase, TOPII, TPO) [antifungal, phytoestrogen]
(-)-Epicatechin 3-O-gallate (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae)	F ₁ -ATPase (45) (collagenase, EST-R, 5 α R) [cell-EGF-RTK (<5)]
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	F ₁ -ATPase (17) (EST-R, PK, proteasome, 5 α R, RTK, TOPOIB) [cell-EGF-RTK (<5); oxidation products give tea taste]
Eriodictyol (= 5,7,3',4'-Tetrahydroxyflavanone) (flavanone)	Widespread; <i>Eriodictyon californicum</i> (Hydrophyllaceae); Asteraceae, Fabaceae, Lamiaceae; glycosides in <i>Lophophytum leandri</i> (Balanophoraceae), <i>Citrus paradisi</i> , <i>C. spp.</i> (Rutaceae)	F ₁ -ATPase (<139) [antibacterial, antilarval, induces rhizobial nodulation]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Trifolium brachycalycinum</i> , <i>T. spp.</i> (clover) (Fabaceae); glycosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Sophora japonica</i> , <i>Ulex nanus</i> (Fabaceae)	F ₁ -ATPase (60) (AD-R, GABAA-R, lipase, peroxidase, Na ⁺ /K ⁺ /Cl ⁻ TR, PK, RTK, TOPII, TPO) [antifungal, apoptotic, oestrogenic]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread; <i>Hypericum brasiliense</i> (Guttiferae) [leaf, flower], <i>Azadirachta indica</i> (Meliaceae); glycosides in Hippocastanaceae [aerial], Fabaceae [wood, leaf]	F ₁ -ATPase (60) (AR, ECMOX, ITD, MLCK, PKA, RTK (p56 ^{lck})) [antibacterial, antioxidant, AI, mutagenic]
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Morus alba</i> , <i>M. spp.</i> (mulberry), <i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> , <i>Chlorophora tinctoria</i> (Moraceae)	F ₁ -ATPase (60) (AR, ECMOX, ITD, 5-LOX, MLCK, PKA) [allergenic, antibacterial, antiviral, feeding attractant]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae), <i>Haplopappus canescens</i> (Asteraceae); glycosides in <i>Vaccinium</i> (Ericaceae), <i>Myrica</i> (Moraceae), <i>Primula</i> (Primulaceae), <i>Camellia</i> (Theaceae) spp.	F ₁ -ATPase (<25) (IKK, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TOPII) [antibacterial, antigonadotropin]
Phloretin (= 2',4,4',6'-Tetrahydroxydihydrochalcone) (dihydrochalcone)	<i>Malus domestica</i> (Rosaceae); as 2'-glucoside (Phloridzin) in <i>Kalmia latifolia</i> , <i>Pieris japonica</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>Malus</i> spp. (Rosaceae), <i>Symplocos</i> spp. (Symplocaceae)	F ₁ -ATPase (100) (ECMOX, EGFRK, ITD, ox. phos. (uncoupler), PKC) [antibacterial, AI, feeding deterrent]

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) plant part/	Target (other targets) / in vivo effects/
Piceatannol (= 3,3',4,5'-Tetrahydroxystilbene) (stilbene)	<i>Laburnum anagyroides</i> (Fabaceae), <i>Morus alba</i> (Moraceae), <i>Picea</i> spp., <i>Pinus</i> spp., <i>Tsuga canadensis</i> (Pinaceae)	F ₁ -ATPase (8) (CDPK, MLCK, PKA, PKC, p56 ^{lck} TK, p40 TK) [antifungal]
Proanthocyanidins (from grape seed) (tannin)	<i>Vitis vinifera</i> (grape) (Vitaceae) [seed]	F ₁ -ATPase (100)
Quercetagenin (= 6-Hydroxyquercetin; 3,5,6,7,3',4'-Hexahydroxyflavone) (flavonol)	<i>Eupatorium gracile</i> , <i>Tagetes erecta</i> , <i>T. patula</i> (Asteraceae), other Asteraceae [flower], <i>Acacia catechu</i> (Fabaceae); glycosides in <i>Tagetes erecta</i> (marigold) (Asteraceae) [flower]	F ₁ -ATPase (<50) (AR, CDPK, MLCK, Na ⁺ , K ⁺ -ATPase, PKA, TOPII) [antibacterial, yellow pigment]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	F ₁ -ATPase (<26; 60) (AR, cAMP PDE, LOX, K ⁺ -ATPase, MDR-TR, Na ⁺ , NEP, PS – EF-1 α , PK, PKC, RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
Resveratrol (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Vératrum grandiflorum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis</i> (Vitaceae) spp.	F ₁ -ATPase (19) (EST-R, p56 ^{lck} TK)
Tannic acid (gallotannin)	Widespread (fruit, bark); e.g. <i>Quercus</i> sp. (Fagaceae)	F ₁ -ATPase (5)
Theaflavins (condensed tannins)	<i>Camellia sinensis</i> (tea) (Theaceae)	F ₁ -ATPase (35)
Other		13.6Ao
<i>Solanum</i> ATPase inhibitor protein (8kDa protein)	<i>Solanum tuberosum</i> (Solanaceae) [tuber mitochondria]	F ₁ -ATPase (potato & yeast)
Non-plant reference		13.6An
ATPase inhibitor proteins (9–10kDa proteins)	Yeast, animal, bacteria	F ₁ -ATPase
Oligomycins A, B, C & D (macrolides)	<i>Streptomyces diastatochromogenes</i> (fungus)	F ₁ -ATPase
Mitochondrial electron transport chain (ETC) (complexes I–IV) David Keilin isolated cytochrome c	Eugene Kennedy & Albert Lehninger discovered mitochondrial site of oxidative phosphorylation; Hans Krebs (Germany/UK, Nobel Prize, Physiology/Medicine, 1953, Krebs = Citric acid = Tricarboxylic acid cycle generating reduced coenzymes for ox. phos.)	13.6B Fritz Lipmann (Germany/USA, Nobel Prize, Physiology/Medicine, 1953, acetylCoA involved in TCA cycle, FA synthesis & oxidation)

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) plant part	Target (other targets) / in vivo effects
Alkaloid		13.6Ba
Riboflavin (= Vitamin B ₂) (glycosylated isoalloxazine); synthesized by Richard Kuhn (Germany, Nobel Prize, 1938, Chemistry, carotenes & vitamins, forbidden to accept award by Nazis)	Leafy vegetables; malted seed of <i>Hordeum vulgare</i> (barley) (Poaceae); Riboflavin also synthesized by Paul Karrer (Russia/Switzerland, Nobel Prize, Chemistry, 1937, carotenoids, vitamins); FMN-linked Glucose oxidase (“old yellow enzyme”) studied by Otto Warburg, (Germany Nobel Prize, Medicine, 1931, oxidation reactions)	Riboflavin part of key oxidation-reduction coenzymes FMN/FMNH₂ & FAD/FADH₂; FMN-linked Glucose oxidase studied by Axel Theorell (Sweden, Nobel Prize, Medicine, 1955, biological oxidation reactions)
Salsolinol (tetrahydroisoquinoline)	<i>Musa</i> sp. (banana) (Musaceae), <i>Theobroma cacao</i> (cocoa) (Sterculiaceae)	ETC – NADH–CoQ reductase complex I; succinate-CoQ reductase complex II
Phenolic		13.6Bp
Assamicaine B (tannin)	<i>Camellia sinensis</i> (Theaceae) [tea leaf]	ETC – NADH DH complex I (3–9)
Casuarinin (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Liquidambar</i> (Hamamelidaceae), <i>Osbeckia</i> (Melastomaceae), <i>Eucalyptus</i> , <i>Feijoa</i> (Myrtaceae), <i>Punica granatum</i> (Punicaceae), <i>Stachyurus</i> (Stachyuraceae)	ETC – NADH DH complex – no inhibition
Deguelin (benzopyran)	<i>Lonchocarpus utilis</i> , <i>L. urucu</i> (Fabaceae) [root]	ETC – NADH DH complex I (7nM)
(–)-Epigallocatechin-3-gallate (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae), <i>Hamamelis virginiana</i> (Hamamelidaceae), <i>Camellia sinensis</i> (Theaceae)	ETC – NADH DH (7) [AI, blocks COX-2 & iNOS induction]
(–)-Glyceollin I (pterocarpan isoflavanone)	<i>Glycine</i> spp., <i>Psoralea</i> spp. (Fabaceae) [leaf phytoalexin]	ETC (EST-R) [antibacterial, antifungal]
(–)-Glyceollin II (pterocarpan isoflavanone)	<i>Glycine</i> spp., <i>Psoralea</i> spp. (Fabaceae) [leaf phytoalexin]	ETC (EST-R) [antibacterial, antifungal]
[Lauryl gallate] (phenolic acid ester)	Semi-synthetic from gallic acid	ETC – NADH DH complex I (9)
Oolonghomobisflavan A (tannin)	<i>Camellia sinensis</i> (Theaceae) [tea leaf]	ETC – NADH DH complex I (0.8–4)
Pedunculagin (ellagitannin)	<i>Casuarina</i> (Casuarinaceae), <i>Quercus</i> (Fagaceae), <i>Juglans</i> (Juglandaceae), <i>Rubus</i> , <i>Potentilla</i> (Rosaceae), <i>Stachyurus</i> (Stachyuraceae), <i>Camellia</i> (Theaceae) spp.	ETC – NADH DH complex I (> 10)
Pentagalloyl-β-D-glucose (gallotannin)	<i>Acer</i> (Aceraceae), <i>Cotinus</i> , <i>Rhus</i> , <i>Schinus</i> (Anacardiaceae), <i>Terminalia</i> (Combretaceae), <i>Quercus</i> (Fagaceae), <i>Geranium</i> (Geraniaceae), <i>Nuphar</i> (Nymphaeaceae), <i>Epilobium</i> , <i>Fuchsia</i> (Onagraceae), <i>Paeollia</i> , <i>Paeonia</i> (Paeonaceae), <i>Rosa</i> (Rosaceae), <i>Camellia</i> (Theaceae)	ETC – NADH DH complex I (0.2–7) (αGase, H ⁺ , K ⁺ -ATPase, Na ⁺ , K ⁺ -ATPase, XO) [anti-gastritis, anti-peptic ulcer]

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) / plant part/	Target (other targets) / in vivo effects/
Procyanidin C-1 (condensed tannin)	<i>Kandelia candel</i> (Rhizophoraceae)	ETC – NADH DH complex I (> 10)
Procyanidin polymer (condensed tannin)	<i>Kandelia candel</i> (Rhizophoraceae)	ETC – NADH DH complex I (0.8–6)
Procyanidin tetramer (condensed tannin)	<i>Kandelia candel</i> (Rhizophoraceae)	ETC – NADH DH complex I (2–9)
Prodelphinidin B-2 3, 3'-di-O-gallate (gallotannin)	<i>Camellia sinensis</i> (Theaceae) [tea leaf]	ETC – NADH DH complex I (1–9)
Rotenolone (benzopyran)	<i>Lonchocarpus utilis</i> , <i>L. urucu</i> (Fabaceae) [root]	ETC – NADH DH complex I (0.3)
Rotenone (benzopyran)	<i>Lonchocarpus nicou</i> , <i>L. utilis</i> , <i>L. urucu</i> , <i>Pachyrhizus erosus</i> (Fabaceae) [root]	ETC – NADH DH complex I (6nM; 28nM) [4nM]
Sanguiinin H-2 (tannin)	<i>Sanguisorba officinalis</i> (Rosaceae)	ETC – NADH DH complex I (4–7)
Sanguiinin H-6 (tannin)	<i>Sanguisorba officinalis</i> (Rosaceae)	ETC – NADH DH complex I (2–7)
Sanguiinin H-11 (tannin)	<i>Sanguisorba officinalis</i> (Rosaceae)	ETC – NADH DH complex I (0.6–2)
Stenophyllanin A (tannin)	<i>Casuarina glauca</i> (Casuarinaceae)	ETC – NADH DH complex I (1)
Tephrosin (benzopyran)	<i>Lonchocarpus utilis</i> , <i>L. urucu</i> (Fabaceae) [root]	ETC – NADH DH complex I (0.1)
1,2,3,6-Tetra-O-galloyl- D-glucose (gallotannin)	<i>Quercus pedunculata</i> (Fagaceae)	ETC – NADH DH complex I (0.8); succinate DH complex II [0.1–2]
Δ^1 -Tetrahydro- cannabinol (= Dronabinol; Δ^9 - Tetrahydro- cannabinol; (-)- Δ^1 -3,4- <i>trans</i> - Tetrahydrocannabinol (dibenzopyranol)	<i>Cannabis sativa</i> (marijuana, hemp) (Cannabaceae) [cannabis leaf resin (hashish), marijuana leaf extract (bhang), smoked leaf (ganja)]	ETC – NADH DH complex I (at 10) (AND-R, CBI R) [AI, anti-emetic, hallucinogenic , intoxicant, psychotropic]
Theaflavine 3,3'-di- O-gallate (tannin)	<i>Camellia sinensis</i> (Theaceae) [tea leaf]	ETC – NADH DH complex I (0.8–9)
Theaflavine 3'-O-gallate (tannin)	<i>Camellia sinensis</i> (Theaceae) [tea leaf]	ETC – NADH DH complex I (0.6–5)
Theasinensin A (condensed tannin)	<i>Camellia sinensis</i> (Theaceae) [tea leaf]	ETC – NADH DH complex I (4–7)
1,2,6-Tri-O-galloyl- D-glucose (gallotannin)	<i>Mallotus japonica</i> (Euphorbiaceae)	ETC – NADH DH complex I (2) (α -Glucosidase)
Other		13.6Bo
Annomontacin (tetrahydrofuran acetogenin)	<i>Goniothalamus giganteus</i> (Annonaceae) [stem bark]	ETC – NADH-UQ OR complex I (0.4)
Annonacin (tetrahydrofuran acetogenin)	<i>Annona muricata</i> (Annonaceae) [seed]	ETC – NADH-UQ OR complex I (0.5)
<i>cis</i> -Annonacin-10-one (tetrahydrofuran acetogenin)	<i>Annona muricata</i> (Annonaceae) [seed]	ETC – NADH-UQ OR complex I (0.2)

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) [plant part]	Target (other targets) / in vivo effects/
Asimicin (tetrahydrofuran acetogenin)	<i>Asimina triloba</i> (Annonaceae) [stem bark]	ETC – NADH-UQ OR complex I (30nM)
Bullatacin (= Rolliniastatin-2) (tetrahydrofuran acetogenin)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (2nM; 70nM; 330nM) [0.6]
Bullatacinone (tetrahydrofuran acetogenin)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (50nM)
Bullatalicin (tetrahydrofuran acetogenin)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (17nM; 80nM)
Bullatalicinone (tetrahydrofuran acetogenin)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (30nM)
Bullatanocin (tetrahydrofuran acetogenin)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (70nM)
Bullatanocinone (alkyl tetrahydrofuran)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (0.1)
Cyanide ion (= CN ⁻ ; protonated HCN = Hydrocyanic acid; Prussic acid) (hydrogen cyanide); James Price took Prussic acid & died before the Royal Society committee having failed to demonstrate lead to gold transmutation (1782)	Generated from Cyanogenic glycosides notably <i>ex Manihot esculentum</i> (bitter cassava) (Euphobiaceae) [widespread tropical staple] & <i>Sorghum</i> spp. (Poaceae) [stock forage sorghum]; cassava poisoning avoided by processing but $S_2O_3^{2-} + CN^- \rightarrow SO_3^{2-} + SCN^-$ (thiocyanate) → long-term toxicosis	ETC – cytochrome oxidase (complex III) [deadly within minutes at 300ppm]; generated from Zyklon B in Second World War Holocaust mass murder of Jews in Auschwitz-Birkenau
Carbon monoxide (= CO) (carbon monoxide); used for execution of criminals by Romans & Greeks; biggest gaseous cause of human death; >6% motor vehicle exhaust	From incomplete combustion of carbon-containing compounds; brain neurotransmitter formed by heme oxygenase (HO) type HO2; motor vehicle exhaust CO used in mass murder of Jews in Second World War SS Einsatzgruppen mobile gas chambers	ETC – cytochrome oxidase (GC activation, Hb) [extremely toxic – prevents O ₂ -Hb formation]
Corrossolin (tetrahydrofuran acetogenin)	<i>Annona glabra</i> (Annonaceae) [seed]	ETC – NADH-UQ OR complex I (6nM)
4-Deoxyasimicin (alkyl tetrahydrofuran)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (0.7)
4-Deoxybullatacin (alkyl tetrahydrofuran)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (0.8)

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) plant part/	Target (other targets) / in vivo effects/
Gigantetrocin A (alkyl tetrahydrofuran)	<i>Goniiothalamus giganteus</i> (Annonaceae) [stem bark]	ETC – NADH-UQ OR complex I (3nM; 0.3)
Gigantetrocin B (alkyl tetrahydrofuran)	<i>Annona muricata</i> (Annonaceae) [seed]	ETC – NADH-UQ OR complex I (0.3)
30-Hydroxybullatacinone (alkyl tetrahydrofuran)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (20 nM)
31-Hydroxybullatacinone (alkyl tetrahydrofuran)	<i>Annona bullata</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (20 nM)
10-Hydroxy-4- deoxybullatacin (= Bullatin) (alkyl tetrahydrofuran)	<i>Asimina triloba</i> (Annonaceae) [stem bark]	ETC – NADH-UQ OR complex I (0.2)
30-Hydroxy-4- deoxybullatacin (= Bullanin) (alkyl tetrahydrofuran)	<i>Asimina triloba</i> (Annonaceae) [stem bark]	ETC – NADH-UQ OR complex I (20 nM)
Isoannonacin (alkyl tetrahydrofuran)	<i>Annona muricata</i> (Annonaceae) [seed]	ETC – NADH-UQ OR complex I (0.2)
Longimicin C (tetrahydrofuran acetogenin)	(Annonaceae)	ETC – NADH-UQ OR complex I (6 nM)
Longimicin D (tetrahydrofuran acetogenin)	(Annonaceae)	ETC – NADH-UQ OR complex I (21 nM)
Molvizarin (tetrahydrofuran acetogenin)	<i>Annona cherimola</i> , <i>A. reticulata</i> , <i>A. squamosa</i> (Annonaceae) [stem bark]	ETC – NADH-UQ OR complex I (2 nM) [1 nM]
Muricatetrocin B (tetrahydrofuran acetogenin)	<i>Annona glabra</i> (Annonaceae) [seed]	ETC – NADH-UQ OR complex I (26 nM)
Otivarin (tetrahydrofuran acetogenin)	(Annonaceae)	ETC – NADH-UQ OR complex I (3 nM) [0.8 nM]
Oxygen (= O ₂) (oxygen); Joseph Priestley, Antoine Lavoisier (“oxygen”)	Global atmospheric O ₂ (21%) <i>ex</i> photolysis of H ₂ O per photosynthesis Photosystem II	ETC – terminal electron acceptor per cytochrome oxidase (Hb)
Parviflorin (tetrahydrofuran acetogenin)	<i>Asimina parviflora</i> (Annonaceae) [bark]	ETC – NADH-UQ OR complex I (4 nM)
Rolliniastatin-1 (tetrahydrofuran acetogenin)	<i>Rollinia sylvatica</i> (Annonaceae)	ETC – NADH-UQ OR complex I (0.3 nM; 1 nM)
Rolliniastatin-2 (tetrahydrofuran acetogenin)	<i>Rollinia sylvatica</i> (Annonaceae)	ETC – NADH-UQ OR complex I (0.6 nM)
Sylvaticin (tetrahydrofuran acetogenin)	<i>Rollinia sylvatica</i> (Annonaceae)	ETC – NADH-UQ OR complex I (9 nM)
Squamocin (tetrahydrofuran acetogenin)	<i>Annona reticulata</i> [seed], <i>Rollinia emarginata</i> (Annonaceae)	ETC – NADH-UQ OR complex I (2 nM; 3 nM) [0.4 nM]

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) plant part	Target (other targets) / in vivo effects/
Squamocin B (tetrahydrofuran acetogenin)	(Annonaceae)	ETC – NADH-UQ OR complex I (2 nM)
Trilobacin (tetrahydrofuran acetogenin)	<i>Asimina triloba</i> (Annonaceae) [stem bark]	ETC – NADH-UQ OR complex I (80 nM; 4 nM)
Non-plant reference		13.6Bn
Piericidin A (isoprenyl pyridine)	<i>Streptomyces</i> sp. (fungus); ubiquinone analogue	ETC – NADH-UQ OR complex I (3 nM) [1 nM]
Ox. Phos. Uncouplers	Peter Mitchell (UK, Nobel Prize, Chemistry, 1978, chemiosmotic theory – energy conservation via proton & electrochemical gradients)	13.6C Critical evidence for chemiosmotic model by André Jagendorf (USA)
Phenolic		13.6Cp
Atranorin (phenolic)	<i>Parmelia tinctorum</i> (lichen)	Uncoupler (<5)
Chalcone (chalcone)	<i>Glycyrrhiza echinata</i> (Fabaceae)	Uncoupler
3,4'-Dihydroxychalcone (chalcone)	<i>Glycyrrhiza echinata</i> (Fabaceae)	Uncoupler
Echinatin (chalcone)	<i>Glycyrrhiza echinata</i> (Fabaceae)	Uncoupler
4'-Hydroxychalcone (chalcone)	<i>Glycyrrhiza echinata</i> (Fabaceae)	Uncoupler
Isoliquiritigenin (= 2',4',4'-Trihydroxy- chalcone) (chalcone)	<i>Glycyrrhiza glabra</i> (Fabaceae); as glycoside in <i>Dahlia variabilis</i> (Asteraceae) [flower], <i>Glycyrrhiza glabra</i> (Fabaceae) [root, rhizome]	Uncoupler (COX, 5-LOX) [PAI, yellow]
Okanin (= 2',3',4',3,4- Pentahydroxychalcone) (chalcone)	As 4'-O-glycoside (Merein) in <i>Bidens</i> sp., <i>Coreopsis</i> sp. (Asteraceae) [flower]	Uncoupler [yellow]
<i>trans</i> -Resveratrol (= 3,5,4'-Trihydroxy- stilbene) (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), spp., <i>Vitis vinifera</i> (Vitaceae)	Causes mitochondrial depolarization (& thence caspase 9 activation & apoptosis) (AO/FRS, COX, LOX)
(+)-Usnic acid (benzofuran)	<i>Usnea articulata</i> (lichen)	Uncoupler (<1)
Vulpinic acid (phenolic)	<i>Letharia vulpina</i> (lichen)	Uncoupler (<5)
Other		13.6Co
Nitric oxide (= NO) (nitrogen oxide)	Universal; generated in plants via NOS & nitrate reductase	Uncouples the plant cytochrome oxidase (but not alternative) ETC pathway [inhibits $\Delta\Psi_{\text{in}}$, ATP synthesis]
Non-plant reference		13.6Cn
[2,4-Dinitrophenol] (phenol)	Synthetic; "classic" uncoupler	Uncoupler (<50)

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) plant part	Target (other targets) / in vivo effects
Oxidative phosphorylation (ox. phos.) – other inhibition		13.6D
Phenolic		13.6Dp
Alizarin (= 1,2-Dihydroxyanthraquinone) (anthraquinone)	<i>Rheum palmatum</i> (Polygonaceae), <i>Rubia cordifolia</i> , <i>R. tinctorum</i> (madder), <i>Asperula</i> , <i>Galium</i> , <i>Morinda</i> spp. (Rubiaceae)	Ox. Phos.
Terpene		13.6Dt
Helenalin (pseudoguaianolide sesquiterpene lactone)	<i>Anaphalis</i> , <i>Arnica</i> , <i>Balduina</i> , <i>Eupatorium</i> , <i>Gaillardia</i> , <i>Helenium</i> spp., <i>Inula helenium</i> (Asteraceae)	Ox Phos. [antineoplastic, cytotoxic, toxic]
Dihydrogriesenin (seco-guaianolide sesquiterpene lactone)	<i>Geigeria africanum</i> (Asteraceae)	Ox. Phos. [toxic]
Helenin (pseudoguaianolide sesquiterpenoid lactone)	<i>Anaphalis</i> , <i>Balduina</i> , <i>Gaillardia</i> , <i>Helenium</i> spp., <i>Inula helenium</i> (Asteraceae)	Ox. Phos.
Hymenoxon (seco-pseudoguaianolide sesquiterpene lactone)	<i>Helenium hoopesii</i> , <i>Hymenoxys odorata</i> (Asteraceae)	Ox. Phos. (DNA) [toxic]
Mexicanin E (norpseudoguaianolide sesquiterpene lactone)	<i>Helenium mexicanum</i> , <i>H.</i> spp. (Asteraceae)	Ox. Phos. [cytotoxic, antitumour, toxic]
Psilotropin (sesquiterpene lactone)	<i>Geigeria</i> spp. (Asteraceae)	Ox. Phos.
Tenulin (pseudoguaianolide sesquiterpene lactone)	<i>Helenium tenuifolium</i> , <i>H.</i> spp. (Asteraceae)	Ox. Phos. [cytotoxic, antitumour, toxic]
Photosynthetic electron transport	Richard Willstätter (Nobel Prize, Chemistry, 1915, plant pigments & chlorophyll; fled Nazis); Hans Fischer (Germany, Nobel Prize, Chemistry, 1930, chlorophyll; synthesis of bilirubin & haemin)	13.6E
Animals consume & plants generate oxygen – Joseph Priestley (“dephlogisticated air”), Antoine Lavoisier (“oxygen”)		Johann Deisenhofer, Robert Huber & Hartmut Michel (Germany, Nobel Prize, Chemistry, 1988, photosynthetic reaction centre 3D structure)
Chalepensis (coumarin)	<i>Ruta graveolens</i> , <i>Stauranthus perforatus</i> (Rutaceae)	PSII (50)
3-(1',1'-Dimethylallyl)-xanthyletin (coumarin)	<i>Stauranthus perforatus</i> (Rutaceae)	PSII (50)
Xanthyletin (coumarin)	<i>Stauranthus perforatus</i> (Rutaceae)	PS I (50), PSII (30)
Photophosphorylation uncoupler		13.6F
Chalepensis (coumarin)	<i>Ruta graveolens</i> , <i>Stauranthus perforatus</i> (Rutaceae)	Uncoupler (at 100)
3-(1',1'-Dimethylallyl)-xanthyletin (coumarin)	<i>Stauranthus perforatus</i> (Rutaceae)	Uncoupler (50)

(continued)

Table 13.6 (Continued)

Compound (class)	Plant source (family) plant part	Target (other targets) / in vivo effects/
Photophosphorylation	Daniel Arnon (discovered process); André Jagendorf (dissected mechanism)	13.6G
Chalepensin (coumarin)	<i>Ruta graveolens</i> , <i>Stauranthus perforatus</i> (Rutaceae)	Photophos. (30)
3-(1',1'-Dimethylallyl)-xanthyletin (coumarin)	<i>Stauranthus perforatus</i> (Rutaceae)	Photophos. (40)
Xanthyletin (coumarin)	<i>Stauranthus perforatus</i> (Rutaceae)	Photophos. (60)

Table 13.7 Multidrug resistance, glucose and other transporters

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
ADP/ATP transporter (ADP/ATP-TR) (ADP/ATP antiporter)		13.7A
Atractyloside (= Atractylin)(kaurane diterpenoid glycoside sulphate ester)	<i>Atractylis gummifera</i> (thistle) (Asteraceae)	ADP/ATP-TR (antiporter; mitochondrial inner membrane) [very toxic, strychnine-like]
[Bongkrekkic acid] (alkene carboxylic acid)	<i>Pseudomonas cocovenenans</i> (bacterium infecting Indonesian moulded coconut product bongkrekk)	ADP/ATP-TR [very toxic]
Amino acid transport (AA-TR)		13.7B
Cyclochampedol (prenylated flavone)	<i>Artocarpus champeden</i> (Moraceae)	AA-TR [250]
Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) (ABC transporter; cAMP-regulated chloride transporter)	Cystic fibrosis from defective CFTR (major mutation yielding defective CFTR folding & greatly decreased functional CFTR)	13.7C
<i>Croton</i> SP-303 (condensed tannins; proanthocyanidin oligomer mixture)	<i>Croton lechleri</i> (Euphorbiaceae) [latex]	CFTR [inhibits cAMP-mediated Cl ⁻ & fluid secretion; antidiarrhoeal, blocks cholera toxin-induced diarrhoea]
<i>Oryza</i> factor (= rice factor) (structure unknown)	<i>Oryza sativa</i> (Poaceae) [boiled rice seed]; Bengalis cook rice (the Bengali staple) with a 3-fold excess of water which is drained & used; starving Bengalis (1943/44) begged for rice water	CFTR [inhibits cAMP-mediated Cl ⁻ & fluid secretion; antidiarrhoeal; potential for blocking cholera toxin-induced diarrhoea]

(continued)

Table 13.7 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Ethanol absorption	Pleasant effects of fermented grain likely to have encouraged cereal agriculture-based civilization	13.7D
3 α -Acetoxyeudesma-1,4(15),11(13)-trien-12,6 α -olide (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae)	Ethanol absorption inhibited
Costunolide (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae)	Ethanol absorption inhibited
Dehydrocostus lactone (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae)	Ethanol absorption inhibited
Elatosides A & B (oleanolic acid glycosides) (triterpene glycosides)	<i>Aralia elata</i> (Araliaceae)	Ethanol absorption inhibited
3-Oxo-eudesma-1,4,11(13)-trien-12,6 α -olide (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae)	Ethanol absorption inhibited
Reynosin (sesquiterpene)	<i>Chrysanthemum parthenium</i> (Asteraceae), <i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae)	Ethanol absorption inhibited
Santamarine (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae)	Ethanol absorption inhibited
Zaluzanin D (sesquiterpene)	<i>Laurus nobilis</i> (bay leaf, laurel) (Lauraceae)	Ethanol absorption inhibited
Glucose transporter (Glc-TR)		13.7E
Phenolic		13.7Ep
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Trifolium brachycalycinum</i> , <i>T.</i> spp. (clover) (Fabaceae); glycosides in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora japonica</i> (Fabaceae)	Glc-TR – GLUT1 (hexose TR; human HL-60 cells) [12], GLUT1 (human RBC) [7], GLUT1 (Chinese hamster ovary CHO cells) [isoflavone Daidzein inactive]
Phloridizin (= Phloretin 2'-O-glycoside) (dihydrochalcone O-glycoside)	<i>Kalmia</i> , <i>Pieris</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>Malus</i> spp. (Rosaceae) [apple leaf, fruit skin], <i>Symplocos</i> spp. (Symplocaceae)	Glc-TR (EGF-RTK, Glc-R (GIP)) [bitter, feeding deterrent]
Terpene		13.7Et
Escin Ia (triterpene glycoside, saponin)	<i>Aesculus hippocastanum</i> (horse chestnut), <i>A. chinensis</i> (Hippocastanaceae); very toxic	Glc-TR [blocks gastric emptying, hypoglycaemic]
Escin IIa (triterpene glycoside, saponin)	<i>Aesculus hippocastanum</i> (horse chestnut), <i>A. chinensis</i> (Hippocastanaceae); very toxic	Glc-TR [blocks gastric emptying, hypoglycaemic]

(continued)

Table 13.7 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Forskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae) [root]	Glc-TR (PM; rat adipocyte) (Cytochalasin binding inhibited) [0.2], Insulin-stimulated Glucose TR (rat adipocyte) [0.2] [independent of AC activation (q.v.)]
Gymnemic saponins GiA-2, GiA-5 & GiA-7 (oleanane triterpene glycosides)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	Glc-TR [hypoglycaemic]
Senegin II (triterpene glycoside, saponin)	<i>Polygala senega</i> (Polygalaceae)	Glc-TR [blocks gastric emptying, hypoglycaemic]
Glucose-6-phosphate transporter (G-6-P-TR)		13.7F
Palmitoyl-coenzyme A (=Hexadecanoyl- coenzyme A) (fatty acyl coenzyme A thioesters)	Widespread; <i>Brassica napus</i> (rape) (Brassicaceae) [embryo]	G-6-P-TR (rape plastid) (at 1)
Oleoyl-coenzyme A (= <i>cis</i> -9-Octadecanoyl- coenzyme A) (unsaturated fatty acyl Coenzyme A thioester)	Widespread; <i>Brassica napus</i> (rape) (Brassicaceae) [embryo]	G-6-P-TR (rape plastid) (at 1)
Haemoglobin (Hb) (tetrameric hemoprotein blood oxygen transporter); crystallized by Hoppe-Seyler (1864)	Hans Fischer (Germany, Nobel Prize, Chemistry, 1930, chlorophyll, synthesis of bilirubin & haemin)	13.7G
Carbon monoxide (= CO) (carbon oxide)	From incomplete combustion of carbon-containing compounds; brain neurotransmitter formed by heme oxygenase (HO) type HO2; biggest gaseous cause of human death; > 6% motor vehicle exhaust – used in vehicular mass murder of Jews by Second World War SS squads	Hb (forms cherry-red CO–Hb complex) (cytochrome oxidase, GC) [extremely toxic; prevents O ₂ -Hb formation; treatment – ventilation, O ₂]; used for execution of criminals by Romans & Greeks
Oxygen (= O ₂) (oxygen)	Global atmospheric O ₂ (21%) <i>ex</i> photolysis of H ₂ O per photosynthesis Photosystem II	Hb – forms O ₂ -Hb (ETC)
Multidrug-resistance transporter (MDR- TR) = P-glycoprotein transporter (PGP-TR)		13.7H

(continued)

Table 13.7 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Alkaloid		
5- <i>O</i> -Benzoyltaxinine (taxoid)	<i>Taxus cuspidata</i> (Japanese yew) (Taxaceae) [leaf]	13.7Ha MDR-TR
2'-Desacetoxyaustrospicatin (taxoid)	<i>Taxus cuspidata</i> (Japanese yew) (Taxaceae) [leaf]	MDR-TR
Desacetoxytaxinine J (taxoid)	<i>Taxus cuspidata</i> (Japanese yew) (Taxaceae) [leaf]	MDR-TR
Cyclopamine (= 11- Deoxyjervine) (steroidal)	<i>Veratrum album</i> , <i>V. californicum</i> (Liliaceae)	MDR-TR [teratogenic]
Pheophorbide (indole)	Universal; <i>Berberis</i> sp. (Berberidaceae)	MDR-TR [synergizes antibacterial activity of Berberine]
Quinidine (= Conchicine; Conquinine; Pitayine; β -Quinine) (quinoline)	<i>Cinchona officinalis</i> , <i>C.</i> spp., <i>Remijia pedunculata</i> (Rubiaceae)	MDR-TR [antitumour, immunosuppressive]
Quinine (quinoline)	<i>Cinchona officinalis</i> , <i>C.</i> spp., <i>Remijia pedunculata</i> (Rubiaceae)	MDR-TR (competitive modulator) (V-K ⁺ CH) [antibrillatory, antimalarial, very bitter]
Reserpine (indole)	<i>Catharanthus roseus</i> , <i>Rauwolfia serpentina</i> , <i>R. vomitoria</i> (Apocynaceae)	MDR-TR (MA-TR, VM-TR) [antihypertensive, tranquillizer, co-carcinogenic]
Taxuspine (taxoid)	<i>Taxus cuspidata</i> (Japanese yew) (Taxaceae) [leaf]	MDR-TR
Thaliblastine (= Thalicarpine) (bisbenzylisoquinoline)	<i>Thalictrum dasycarpum</i> , <i>T. flavum</i> , <i>T. polygamum</i> (Ranunculaceae)	MDR-TR [hypotensive, antimicrobial, antitumour, toxic, vasodilatory]
Tomatidine (steroidal)	<i>Lycopersicon esculentum</i> (tomato) [root], <i>Solanum demissum</i> (Solanaceae); as glycoside in <i>Lycopersicon</i> , <i>Solanum</i> (Solanaceae) spp.	MDR-TR (AChE) [antidermatitic, antifungal, insect repellent]
Vinblastine (= Vincalukoblastine; VLB) (indole)	<i>Vinca rosea</i> (periwinkle) (Apocynaceae) [leaf]	MDR-TR (MTI) [antitumour]
Phenolic		
Acacetin (= Apigenin 4'-methyl ether) (flavone)	<i>Buddleja officinalis</i> , <i>B.</i> spp. (Buddlejaceae)[flower], some Betulaceae [leaf bud surface], some Asteraceae [leaf surface], <i>Agastache foeniculum</i> (Lamiaceae)	13.7Hp MDR-TR (<i>Leishmania tropica</i> NBD2 domain) [21] (COX) [inhibits histamine release, AI, allergen]
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	<i>Apium graveolens</i> (Apiaceae), <i>Ocimum sanctum</i> (Lamiaceae), ferns; 7-apiosylglucoside (= Apiin; Apioside) in <i>Apium graveolens</i> , <i>Petroselinum</i> (Apiaceae); as glycoside in <i>Amorpha fruticosa</i> (Fabaceae), <i>Cosmos bipinnatus</i> , <i>Erigeron annuus</i> , <i>Dahlia variabilis</i> (Asteraceae)	MDR-TR (<i>Leishmania tropica</i> NBD2 domain) [16] (COX-1, COX-2, IKK, PGP TR, PK, RTK) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]

(continued)

Table 13.7 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Chrysin (= 5,7-Dihydroxyflavone) (flavone)	<i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (poplar) (Salicaceae) [leaf bud], <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	MDR-TR (mouse H ₆ -NBD2 domain) [9], (<i>Leishmania tropica</i> NBD2 domain) [18] (AR, cAMP PDE, ITD) [AI, antibacterial, inhibits histamine release]
[8-(1,1-Dimethylallyl)-apigenin] (flavone)	Semi-synthetic from Apigenin	MDR-TR (<i>Leishmania tropica</i> NBD2 domain) [0.7]
[8-(1,1-Dimethylallyl)-chrysin] (flavone)	Semi-synthetic from Chrysin	MDR-TR (<i>Leishmania tropica</i> NBD2 domain) [1.4]
[8-(1,1-Dimethylallyl)-kaempferide] (flavone)	Semi-synthetic from Kaempferide	MDR-TR (<i>Leishmania tropica</i> NBD2 domain) [0.7]
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae), <i>Hamamelis virginiana</i> (Hamamelidaceae), <i>Camellia sinensis</i> (Theaceae)	MDR (blocks efflux of Doxorubicin); ↑ MDR-TR expression (Na ⁺ /glucose symport TR PKC) [AI]
Flavone (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	MDR-TR (mouse H ₆ -NBD2 domain) [34] (cAMP PDE, COX, 5-LOX) [AI, APA, antifungal, inhibits basophil histamine release, pro-apoptotic]
Galangin (= 3,5,7-Trihydroxyflavone) (flavonol)	Betulaceae, Salicaceae [bud excretion], ferns [frond], Lamiaceae [leaf], <i>Datisca cannabina</i> (Datiscaceae) [leaf], <i>Escallonia</i> spp. (Saxifragaceae), <i>Alpinia officinarum</i> (Zingiberaceae)	MDR-TR (mouse H ₆ -NBD2 domain) [5], (<i>Leishmania tropica</i> NBD2 domain) [9] (cAMP PDE, COX) [antibacterial]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Trifolium brachycalycinum</i> , <i>T.</i> spp. (clover) (Fabaceae); as glycoside in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> , <i>Sophora japonica</i> (Fabaceae)	↑ MDR-TR expression (AD-R, EGF-RTK (human) (3; 22), GABAA-R, HISK, Lipase, MLCK, Peroxidase, PKA, pp60 ^{v-src} TK, pp110 ^{gag-fcs} TK, TOPII) [antifungal, oestrogenic]
3,5,6,7,8,3',4'-Heptamethoxyflavone (flavone)	<i>Citrus sinsensis</i> (orange) (Rutaceae) [fruit juice]	MDR-TR (intestinal epithelial cells) (at 50)
5,6,7,8,3',4'-Hexamethoxyflavone (flavone)	<i>Citrus sinsensis</i> (orange) (Rutaceae) [fruit juice]	MDR-TR (intestinal epithelial cells) (at 50)
[3-Hydroxyflavone (= Flavonol)] (flavonol)	Synthetic; flavonol parent	MDR-TR (mouse H ₆ -NBD2 domain) [10], (<i>Leishmania</i> NBD2 domain) [19] (cAMP PDE, PGP TR)
7-Hydroxyflavone (flavone)	<i>Clerodendron phlomidis</i> (Verbenaceae) [flower, leaf]	MDR-TR (mouse H ₆ -NBD2 domain) [10], (<i>Leishmania</i> NBD2 domain) [84] (ADH, AROM, 17βHSOR, cAMP PDE) [antinociceptive]

(continued)

Table 13.7 (Continued)

Compound (class)	Plant (family) / part	Target (other targets) / in vivo effects
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread; Hippocastanaceae [aerial], Fabaceae [wood, leaf], <i>Azadirachta indica</i> (Meliaceae)	MDR-TR (mouse H ₆ -NBD2 domain) [7] (AO/FRS, cAMP PDE, ITD, 5-LOX, myosin ATPase, Pases, PK) [blocks COX-2 & iNOS induction; AI, antibacterial, mutagenic]
Kaempferide (= Kaempferol 4'-methyl ether) (flavonol)	<i>Pityrogramma triangularis</i> (fern) (Adiantaceae), Betulaceae, <i>Baccharis</i> spp. (Asteraceae), Salicaceae, <i>Prunus</i> spp. (Rosaceae), <i>Linaria dalmatica</i> (Scrophulariaceae), <i>Alpinia galanga</i> (Zingiberaceae); glycoside in <i>Dillenia indica</i> (Dilleniaceae)	MDR-TR (mouse H ₆ -NBD2 domain) [5], (<i>Leishmania tropica</i> NBD2 domain) [14] [AI (TPA-induced)]
5'-Methoxyhydnocarpin-D (flavonolignan)	<i>Berberis fremontii</i> (Berberidaceae)	MDR-TR (bacterial)
5,6,7,8,4'-Pentamethoxyflavone (= Tangeretin) (flavone)	<i>Citrus sinensis</i> (orange) (Rutaceae) [fruit juice]	MDR-TR (human intestinal epithelial Caco-2 cells) (at 50)
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae, <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	MDR-TR modulator (AR, cAMP PDE, LOX, NEP, PK, PS-EF-1 α , RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
[3',4',7-Trimethoxyquercetin] (flavonol)	Semi-synthetic	MDR-TR
Silybin (flavanolignan)	<i>Silybum marianum</i> (Asteraceae)	MDR-TR (bacterial) ["Silymarin" component; hepatoprotectant]
Terpene		13.7Ht
8-Acetoxy-9-benzoyloxy-15(2)-methylbutyroyloxy-2-nicotinoyloxy-1,4,6-trihydroxy-dihydro- β -agarofuran (sesquiterpene)	<i>Crossopetalum tonduzii</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) (binds to NBD) [reversion of drug resistant phenotype by inhibiting MDR-TR (at 30)]
1-Acetoxy-9-benzoyloxy-8,15-di-(2)-methylbutyroyloxy-2,4,6-trihydroxy-dihydro- β -agarofuran (sesquiterpene)	<i>Crossopetalum tonduzii</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) (binds to NBD) [\downarrow drug resistance via MDR-TR (at 15)]
8-Acetoxy-1,9-dibenzoyloxy-15(2)-methylbutyroyloxy-2,4,6-trihydroxy-dihydro- β -agarofuran (sesquiterpene)	<i>Crossopetalum tonduzii</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) (binds to NBD) [\downarrow drug resistance via MDR-TR (at 15)]
9-Benzoyloxy-1,6-diacetoxy-4-hydroxy-15(2)-methylbutyroyloxy-8-nicotinoyloxy-dihydro- β -agarofuran (sesquiterpene)	<i>Crossopetalum tonduzii</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) (binds to NBD) [\downarrow drug resistance via MDR-TR (at 15)]

(continued)

Table 13.7 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
9-Benzoyloxy-4,6-dihydroxy-15(2)-methylbutyroyloxy-1,2,8-triacetoxy-dihydro- β -agarofuran (sesquiterpene)	<i>Crossopetalum tonduzii</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) (binds to NBD at 50) [\downarrow drug resistance via MDR-TR (at 30)]
9-Benzoyloxy-4-hydroxy-15(2)-methylbutyroyloxy-8-nicotynoyloxy-1,2,6-triacetoxy-dihydro- β -agarofuran (sesquiterpene)	<i>Crossopetalum tonduzii</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) (binds to NBD at 50) [\downarrow drug resistance via MDR-TR (at 30)]
9-Benzoyloxy-4-hydroxy-15(2)-methylbutyroyloxy-1,2,6,8-tetraacetoxy-dihydro- β -agarofuran (sesquiterpene)	<i>Crossopetalum tonduzii</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) (binds to NBD at 50) [reversion of drug resistant phenotype by inhibiting MDR-TR (at 30)]
9-Benzoyloxy-4-hydroxy-1,6,8,15-tetraacetoxy-dihydro- β -agarofuran (sesquiterpene)	<i>Maytenus macrocarpa</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) (binds to NBD) [\downarrow drug resistance via MDR-TR (at 30)]
6,8-Diacetoxy-1,9-dibenzoyloxy-2,4-dihydroxy-15(2)-methylbutyroyloxy-dihydro- β -agarofuran (sesquiterpene)	<i>Crossopetalum tonduzii</i> (Celastraceae) [aerial]	MDR-TR (<i>Leishmania</i>) [\downarrow drug resistance via MDR-TR (at 15)]
1,9-Dideoxyforskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae)	MDR-TR (nACh-R antagonist, Ca^{2+} CH, inactive as AC activator)
Forskolin (labdane diterpenoid)	<i>Coleus forskohlii</i> (Lamiaceae)	MDR-TR (AC activator, nACh-R, Ca^{2+} CH,) [hypotensive per arterial SM relaxation, increases cAMP, increases heart rate]
Lycaconitine (= <i>N</i> -Succinylanthranoyllycotonine) (diterpene)	<i>Aconitum lycoctonum</i> , <i>Delphinium cashmirianum</i> (Ranunculaceae)	MDR-TR (110)
Other		13.7Ho
Attractylsucrose I, II & III (disaccharides)	<i>Atractylodis lanceae</i> (Asteraceae) [rhizome]	MDR-TR
<i>Feijoa</i> Fraction A4 (unpurified)	<i>Feijoa</i> sp. (pineapple guava) (Myrtaceae) [fruit peel]	MDR-TR [\approx Verapamil]
<i>Rosmarinus</i> extract (unpurified)	<i>Rosmarinus officinalis</i> (Lamiaceae)	MDR-TR (competitive)
Theanine (amino acid)	<i>Camellia sinensis</i> (Theaceae) [leaf]	MDR (blocks efflux of Doxorubicin)
Non-plant reference		13.7Hn
[Verapamil] (aryl tertiary amine)	Synthetic	MDR-TR (Ca^{2+} CH) [coronary vasodilator, hypotensive]

(continued)

Table 13.7 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Na⁺ /glucose symport transporter (Na⁺ / Glc TR)		13.7I
Cycasin (= Methylazoxymethanol-glucoside) (Azoxymethanolglucoside)	<i>Cycas circinalis</i> , (Cycad, sago palm), <i>C. revoluta</i> (Cycadaceae) [leaf, seed]	Substrate for Na ⁺ /Glc TR [toxic, teratogenic, neurotoxic (Parkinsonism dementia), defensive use by non-susceptible insect]
(-)-Epicatechin 3-gallate (= ECG) (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	Na ⁺ /Glc TR SGLT1 (rabbit intestinal brush-border) (EGF-RTK)
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (Theaceae) [leaf]	Na ⁺ /Glc TR SGLT1 (rabbit intestinal brush-border) (PKC) [AI]
Phloridzin (= Phloretin 2'- O-glucoside; Phlorizin) (dihydrochalcone O-glycoside)	<i>Kalmia latifolia</i> , <i>Pieris japonica</i> , <i>Rhododendron</i> spp. (Ericaceae), <i>Malus</i> spp. (apple) (Rosaceae) [leaf, skin], <i>Symplocos</i> spp. (Symplocaceae)	Na ⁺ /Glc TR (kidney, intestinal brush-border) [bitter taste, glucosuria, anti- feedant]

Table 13.8 Various enzymes

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Aconitase		13.8A
Fluoroacetate (aliphatic acid)	<i>Palicourea maregravii</i> (Rubiaceae)	Converted to aconitase inhibitor Fluorocitrate [toxic to livestock e.g. horses & cattle]
Fluorocitrate (aliphatic acid)	From metabolism of Fluoroacetate	Aconitase
AcylCoA: cholesterol O-acyltransferase (ACAT)		13.8B
Yakuchinone B (= 1-(4'- Hydroxy-3'-methoxyphenyl)- 7-phenylhept-1-en-3-one) (phenyl propanoid, aryl heptenoid)	<i>Alpinia oxyphylla</i> , <i>A. officinarum</i> (Zingiberaceae) [rhizome]	ACAT (206) (COX, TYR) [anti-tumour potential: ↓ TPA- induced AP-1 activation & ODC, TNF-α & O ₂ -production]
Alcohol dehydrogenase (ADH)		13.8C
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	<i>Apium graveolens</i> (Apiaceae), <i>Ocimum sanctum</i> (basil) Lamiaceae, ferns; glycosides widespread e.g. <i>Apium graveolens</i> , <i>Petroselinum</i> (Apiaceae), <i>Cosmos bipinnatus</i> , <i>Erigeron annuus</i> <i>Dahlia variabilis</i> (Asteraceae), <i>Amorpha fruticosa</i> (Fabaceae)	ADH (COX, PGP TR, PK, RTK) [blocks COX-2 & iNOS induction per IκB kinase inhibition; antibacterial, AI, diuretic, hypotensive, nodulation stimulant]

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Galangin (= 3,5,7-Trihydroxyflavone) (flavonol)	Betulaceae, Salicaceae, ferns, Lamiaceae, <i>Datisca cannabina</i> (Datisceae), <i>Escallonia</i> spp. (Saxifragaceae), <i>Alpinia officinarum</i> (Zingiberaceae)	ADH (cAMP PDE, COX) [antibacterial]
Genistein (= Genisteol; Prunetol; Sophoricol; 4',5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (Rosaceae), <i>Genista</i> , <i>Trifolium brachycalycinum</i> , <i>T. spp.</i> (Fabaceae); 7-O-glucoside (= Genistin; Genistoid) in <i>Genista tinctoria</i> , <i>Glycine max</i> , <i>Lupinus luteus</i> , <i>Ulex nanus</i> (Fabaceae); 4'-O-glucoside (= Sophocoroside) in <i>Sophora japonica</i> (Fabaceae) [pod]	ADH [0.1] (AD-R, F1-ATPase, GABAA-R, lipase, peroxidase, Na ⁺ /K ⁺ /Cl ⁻ TR, PK, RTK, TOPII, TPO) [antifungal, apoptotic, oestrogenic]
7-Hydroxyflavone (flavone)	<i>Clerodendron phlomidis</i> (Verbenaceae) [flower, leaf]	ADH (AROM) [antinociceptive]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Azadirachta indica</i> (Meliaceae), <i>Cuscuta reflexa</i> (Convolvulaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koelreuteria henryi</i> (Sapindaceae)	ADH (AROM, CDPK, CFTR, EGF-RTK, EST-R, MLCK, PKA, p56 ^{lck} TK, TPO)
Prunetin (= 5-Hydroxy-7,4'-dimethoxyisoflavone) (isoflavone)	<i>Pterocarpus angolensis</i> , <i>Dalbergia miscolobium</i> (Fabaceae), <i>Prunus</i> spp. (Rosaceae)	ADH (EGF-RTK)
Aldehyde dehydrogenase (ALDH)		13.8D
1-Aminocyclopropanol (alicyclic amine)	From Coprine	ALDH (50)
[Coprine (= 1-Aminocyclopropanol γ -glutamyl amide)] (amino acid amide)	<i>Coprinus atramentarius</i> (inky cap mushroom)	Yields ALDH inhibitor [& alcohol intake deterrent] 1-Amino-cyclopropanol [toxic]
[Disulfiram (= Bis-(diethylthiocarbamoyl)-disulfide)] (alkyl thiocarbamoyl disulfide)	Synthetic	ALDH [alcohol consumption deterrent – increases acetaldehyde in blood]
Hypoglycin A (= Methylene-cyclopropyl-L-alanine) (methylene-cyclopropyl amino acid)	<i>Billia hippocastanum</i> (Hippocastanaceae), <i>Blighia sapida</i> (ackee) (Sapindaceae), [unripe ackee fruit, seed]	Yields ALDH inhibitor (Methylene-cyclopropyl)-acetylCoA [toxic]
Hypoglycin B (= 1- γ -Glutamyl-L-hypoglycin A) (methylene-cyclopropyl amino acid)	<i>Billia hippocastanum</i> (Hippocastanaceae), <i>Blighia sapida</i> (ackee) (Sapindaceae), [unripe ackee fruit, seed]	Yields ALDH inhibitor (Methylene-cyclopropyl)-acetylCoA [toxic]
[(Methylene-cyclopropyl)-acetic acid] (cyclopropyl, carboxylic acid)	Metabolic product of hypoglycin A	Metabolic product from hypoglycin A & precursor of Methylene-cyclopropyl-acetylCoA [toxic]

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
[(Methylenecyclopropyl)-acetylCoA] (cyclopropyl, thioester)	Metabolic product from hypoglycin A	ALDH – inactivates short – and medium-chain (but not long chain) ALDH
α -Methylenecyclopropyl-L-glycine (methylenecyclopropyl amino acid)	<i>Acer pseudoplatanus</i> (sycamore) (Aceraceae), <i>Billia hippocastanum</i> (Hippocastanaceae), <i>Litchi sinensis</i> (Sapindaceae)	Yields ALDH inhibitor (Methylenecyclopropyl)-acetylCoA [hypoglycaemic, toxic]
Alkaline phosphatase (Alk Pase)		13.8E
Canavanine (= 2-Amino-4-(guanidinoxy)butyric acid) (guanidine amino acid)	<i>Canavalia ensiformis</i> (jack bean) (Fabaceae); other Fabaceae seeds	Alk Pase (Arginase, NOS) [arginine antimetabolite, cytotoxic]
Amine oxidase		13.8F
Serotonin (= 5-Hydroxy-tryptamine; 5HT) (indole)	<i>Ananas comosus</i> (Bromeliaceae), <i>Juglans regia</i> (Juglandaceae), <i>Mucuna pruriens</i> (Fabaceae), <i>Musa sapientum</i> (Musaceae), <i>Phalaris</i> spp. (Poaceae), <i>Lycopersicon esculentum</i> (Solanaceae), <i>Theobroma cacao</i> (Sterculiaceae), <i>Urtica dioica</i> (Urticaceae)	Suicide substrate (irreversible inhibitor minus O ₂) (5HT-R) [CNS stimulatory NT, inhibits insulin secretion]
Tryptamine (= 3-(2-Aminoethyl)indole) (indole)	Widespread; <i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [fruit]	Suicide substrate (irreversible inhibitor minus O ₂) [Precursor of indole-3-acetic acid (IAA, auxin) & hallucinogen Dimethyltryptamine]
Arginase		13.8G
Indospicine (= 1-2-Amino-6-amidinohexanoic acid) (amino acid)	<i>Indigofera spicata</i> , <i>I.</i> spp. (Fabaceae)	Arginase (NOS) [abortefacient, hepatotoxic, teratogenic]
Asparagine synthetase (ASNS)		13.8H
Albizziine (ureido amino acid)	<i>Acacia</i> , <i>Albizia</i> spp. (Fabaceae)	ASNS
Carbonic anhydrase (CA)		13.8I
Phenolic		13.8Ip
Casuarinine (ellagitannin)	<i>Punica granatum</i> (Punicaceae) [pericarp]	CA (0.3)
Corilagin (ellagitannin)	<i>Punica granatum</i> (Punicaceae) [pericarp]	CA (> 5)
Ellagic acid (phenol)	Widespread; <i>Punica granatum</i> (Punicaceae) [pericarp]	CA (> 10)
Galic acid (phenol)	Widespread; <i>Punica granatum</i> (Punicaceae) [pericarp]	CA (> 10)
Gallagylidilactone (ellagitannin)	<i>Punica granatum</i> (Punicaceae) [pericarp]	CA (0.2)
Granatin A (ellagitannin)	<i>Punica granatum</i> (Punicaceae) [pericarp]	CA (> 6)
Granatin B (ellagitannin)	<i>Punica granatum</i> (Punicaceae) [pericarp]	CA (0.4)

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Pedunculagin (ellagitannin)	<i>Punica granatum</i> (Punicaceae) [pericarp]	CA (0.6)
Punicalagin (ellagitannin)	<i>Terminalia catappa</i> (Combretaceae), <i>Punica granatum</i> (Punicaceae) [pericarp]	CA (0.2) (AO/FRS)
Punicalin (ellagitannin)	<i>Terminalia catappa</i> (Combretaceae), <i>Punica granatum</i> (Punicaceae) [pericarp]	CA (1) (AO/FRS, HIV-1 RT)
Tellimagrandin 1 (ellagitannin)	<i>Punica granatum</i> (Punicaceae) [pericarp]	CA (0.3)
Non-plant reference		13.8In
[Acetazolamide (= 2-Acetylamino-1,3,4-thiadiazole-5-sulphonamide)] (thiadiazole sulphonamide)	Synthetic	CA (0.2)
Chitin synthetase (CHS)		13.8J
Phenolic		13.8Jp
Corilagin (ellagitannin)	<i>Terminalia chebula</i> (Combretaceae), <i>Euphorbia pekinensis</i> (Euphorbiaceae), <i>Punica granatum</i> (Punicaceae) [pericarp]	CHS II (at 100) (CA)
Ellagic acid (phenol)	Widespread; <i>Euphorbia pekinensis</i> (Euphorbiaceae), <i>Punica granatum</i> (Punicaceae), <i>Fragaria</i> spp. (Rosaceae)	CHS II (at 100) (CA)
Gallic acid (phenol)	Widespread; <i>Mangifera indica</i> (Anacardiaceae), <i>Euphorbia pekinensis</i> (Euphorbiaceae), <i>Punica granatum</i> (Punicaceae) [pericarp]	CHS II (at 100) (CA)
3- <i>O</i> -Galloyl-(−)-shikimic acid (gallotannin)	<i>Euphorbia pekinensis</i> (Euphorbiaceae)	CHS II (18)
Geraniin (ellagitannin)	<i>Erythroxylum coca</i> (Erythroxylaceae), <i>Euphorbia pekinensis</i> (Euphorbiaceae)	CHS II (at 100)
Kaempferol (= 3,5,7,4'- Tetrahydroxyflavone) (flavonol)	Widespread as aglycone & glycosides; <i>Cuscuta reflexa</i> (Convolvulaceae), <i>Azadirachta indica</i> (Meliaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Citrus paradisi</i> (Rutaceae), <i>Koelreuteria</i> <i>henryi</i> (Sapindaceae)	CHS II (at 100) (ADH, AROM, CDPK, CFTR, EGF- RTK, EST-R, MLCK, PKA, p56 ^{lck} TK, TPO)
Kaempferol-3- <i>O</i> -(2''- <i>O</i> - galloyl)-β-D-glucoside (flavonol gallate ester)	<i>Euphorbia pekinensis</i> (Euphorbiaceae)	CHS II (at 100)
Methylgallate (gallate ester)	<i>Euphorbia pekinensis</i> (Euphorbiaceae)	CHS II (at 100)
Plumbagin (naphthoquinone)	<i>Dionaea muscipula</i> , <i>Drosera</i> (Droseraceae), <i>Aristea</i> , <i>Sisyrinchium</i> , <i>Sparaxis</i> (Iridaceae), <i>Diospyros</i> (Ebenaceae), <i>Pera</i> (Euphorbiaceae) spp., <i>Plumbago europaea</i> (Plumbaginaceae) [root]	CHS (CYP, ECMOX, MLCK, PKA, TOPII)

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae, <i>Oenothera biennis</i> (Onagraceae), <i>Koelerutera henryi</i> (Sapindaceae); widespread as glycosides	CHS II (at 100) (AR, cAMP PDE, CFTR, DNAP, F ₁ -ATPase, HIV-1 RT, 11 β HSDH, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, Nase, NEP, NQOR, PK, PS-EF-1 α , RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
Quercetin-3-O-(2''-O-galloyl)- β -D-glucoside (flavonol gallate ester)	<i>Euphorbia peginensis</i> (Euphorbiaceae)	CHS II (at 100)
Quercetin-3-O-(2''-O-galloyl)- β -D-rutinoside (flavonol gallate ester)	<i>Euphorbia peginensis</i> (Euphorbiaceae)	CHS II (at 100)
Quercitrin (= Quercetin 3-O-rhamnoside; 3,5,7,3',4'-Pentahydroxyflavone) (flavonol O-glycoside)	Widespread; <i>Quercus tinctoria</i> (Fagaceae) [bark], <i>Eucalyptus globulus</i> (Tasmanian blue gum) (Myrtaceae), <i>Polygonum</i> spp. (Polygonaceae)	CHS II (at 100) (ACE, AR, MLCK, PKA) [antibacterial, antimutagenic, antiviral, feeding deterrent & stimulant]
Rutin (= Quercetin 3-O-rutinoside; Quercetin 3-O-rhamnosyl-glucoside) (flavonol O-glycoside)	Widespread; <i>Polygonum</i> spp. (Polygonaceae), <i>Ruta graveolens</i> (Rutaceae), <i>Viola tricolor</i> (Violaceae)	CHS II (at 100) (AR, 5-LOX, MLCK, PKA) [antioxidant, feeding attractant, feeding deterrent, oviposition stimulant]
Terpene		13.8Jt
Betulinic acid (triterpene)	<i>Centella asiatica</i> (Apiaceae), <i>Crataegus pinnatifida</i> (Rosaceae) [leaf]	CHS II (223)
α -Hederin (= Sapindoside A) (triterpene glycoside, saponin)	<i>Hedera helix</i> (ivy) (Araliaceae) [leaf], <i>Crataegus pinnatifida</i> (Rosaceae) [leaf]	CHS II (86)
Oleanolic acid (oleanane triterpene)	<i>Luffa</i> (Cucurbitaceae), <i>Centaurium</i> , <i>Sivertia</i> (Gentianaceae), <i>Rosmarinus</i> (Lamiaceae) <i>Viscum</i> (Loranthaceae), <i>Syzygium</i> (Myrtaceae), <i>Olea</i> (Oleaceae), <i>Xanthoceras</i> (Sapindaceae) spp.	CHS II (12) (C3-convertase, CDPK, DNAP, ELA, PKA, PKC) [AI]
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (ursene triterpene)	Widespread; <i>Cynomorium</i> (Cynomoriaceae), <i>Arctostaphylos</i> , <i>Rhododendron</i> , <i>Vaccinium</i> (Ericaceae), <i>Prunella</i> , <i>Salvia</i> (Lamiaceae), <i>Crataegus</i> , <i>Geum</i> , <i>Malus</i> , <i>Pyrus</i> (Rosaceae) spp.	CHS II (2) (CDPK, CHS, DNAP, ELA, HIV-1 PR, PKA, PKC, RT, TOPI, TOPII) [AI, cytotoxic, antineoplastic]
Cytochrome P450 oxygenase (CYP)		13.8K
Phenolic		13.8Kp
Anthraquinones (anthraquinones)	Many plants	CYP [antimutagenic, anti-genotoxic, block xenobiotic conversion to genotoxics]
Baicalin (flavone)	<i>Scutellaria baicalensis</i> (Lamiaceae) [root], <i>Plantago major</i> (Plantaginaceae)	CYP – CYP3A4 (17)

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
4,6-Dihydroxychalcone (chalcone)	<i>Dracaena cinnabari</i> (Agavaceae)	CYP
2-Hydroxychalcone (chalcone)	<i>Dracaena cinnabari</i> (Agavaceae)	CYP
Juglone (= 2-Demethyl- plumbagin; 5-Hydroxy-1,4- naphthalenedione; Mucin; Natural Brown 7; Regianin) (naphthoquinone)	<i>Juglans cinerea</i> , <i>J. nigra</i> [stem bark], <i>J. regia</i> , <i>Carya ovata</i> , <i>C. ilinoensis</i> [leaf, nut] (Juglandaceae), <i>Lomatia</i> spp. (Proteaceae)	CYP (ECMOX, MLCK, PKA, PKC, pp60 ^{c-src}) [antifungal, antiviral, molluscicidal, feeding deterrent, walnut allelopathic]
Kaempferol (= 3,5,7,4'- Tetrahydroxyflavone) (flavonol)	Widespread; Hippocastanaceae [aerial], Fabaceae [wood, leaf]; <i>Azadirachta indica</i> (Meliaceae), <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice]	CYP IIIA4 – AROM (at 0.5) (AO/FRS, COX-1, 5-LOX) [blocks COX-2 & iNOS induction; AI, antibacterial, mutagenic, radical scavenger]
Naringin (flavanone glycoside)	<i>Citrus paradisi</i> (grapefruit) (Rutaceae)	CYP1A2 (caffeine 3- demethylation) [7–29]
Naringenin (= 5,7,4'- Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia</i> spp. (Asteraceae), <i>Citrus sinensis</i> , <i>C. paradisi</i> (Rutaceae) [grapefruit juice]	CYP IIIA4 – AROM (at 0.5) (AR, cAMP PDE, EST-R) [antibacterial, antifungal]
Oleuropein (seco-iridoid monoterpene glucoside)	<i>Ligustrum japonicum</i> , <i>L. lucidum</i> , <i>L. obtusifolium</i> (privet), <i>Olea europaea</i> (olive) (Oleaceae)	CYP inactivation [22] (forms reactive aglycone that yields imine protein adduct) [protein denaturant; spasmolytic]
Oroxylin A (flavone)	<i>Scutellaria baicalensis</i> (Lamiaceae) [root]	CYP – CYP2C9 (7) (CBZ, 12-LOX) [AI]
Plumbagin (naphthoquinone)	<i>Dionaea muscipula</i> , <i>Drosera</i> (Droseraceae), <i>Aristea</i> , <i>Sisyrinchium</i> , <i>Sparaxis</i> (Iridaceae), <i>Diospyros</i> (Ebenaceae), <i>Pera</i> (Euphorbiaceae) spp.; <i>Plumbago europaea</i> (Plumbaginaceae) [root]	CYP (CHS, ECMOX, MLCK, PKA, TOPII)
Proanthocyanidins (condensed tannins)	<i>Vitis vinifera</i> (grape seed) (Vitaceae)	CYP
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Oenothera</i> <i>biennis</i> (Onagraceae), <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice]	CYP IIIA4 – AROM (at 0.5) (LOX, PK) [AI, feeding stimulant]
2',5,6',7-Tetrahydroxy- flavone (flavone)	<i>Scutellaria baicalensis</i> (Lamiaceae) [root]	CYP – CYP3A4 (8)
Other		13.8Ko
Isothiocyanates block (R–N=C=S)	Indolyl-, alkyl- & indolyl isothiocyanates from glucosinolates via myrosinase (thioglucosidase)	CYP [anti-genotoxic, block xenobiotic conversion to genotoxics]
Non-plant reference		13.8Kn
[Norharman] (indole, β-carboline)	Animals	CYP11, CYP17 [endogenous modulator of steroidogenesis]

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Deacetylpecoside synthase (DAL5)		13.8L
Alangimakin (phenanthridine)	<i>Alangium lamarckii</i> (Alangiaceae)	DALS (10)
Dehydroalangimakin (phenanthridine)	<i>Alangium lamarckii</i> (Alangiaceae)	DALS (10)
Farnesyl-protein transferase (FPTase)		13.8M
Phenolic		13.8Mp
2-Hydroxycinnamaldehyde (<i>O</i> -Hydroxy-cinnamaldehyde) (phenolic)	<i>Cinnamomum cassia</i> (cinnamon-like) (Lauraceae) [stem oil]	FPTase (149) [cinnamon aroma, sweet taste]
Terpene		13.8Mt
Arteminolide (sesquiterpene lactone)	<i>Artemisia sylvatica</i> (Asteraceae) [leaf]	FPTase (0.4)
Costunolide (germacranolide sesquiterpene lactone)	<i>Artemisia dracuncululus</i> , <i>Saussurea lappa</i> (costus root oil) (Asteraceae), <i>Laurus nobilis</i> (bay laurel) (Lauraceae)	FPTase (20) (\downarrow iNOS) [anti-schistosomal, antitumour, dermatitic]
Lupeol (= Fagasterol; Monogynol B; β -Viscol) (lupane triterpene)	<i>Alstonia boonei</i> (Apocynaceae) [bark, seed], Asteraceae [flower], <i>Phyllanthus emblica</i> (Euphorbiaceae), <i>Lupinus luteus</i> (Fabaceae) [seed]	FPTase (152) (CAB Pase, CHY, PKA, PKC, TOPII, TRY) [anti-arthritic, AI, antitumour]
Ochraceolides A & B (lupane triterpenes)	<i>Lophopetalum wallichii</i> (Celastraceae) [stem, stem bark]	FPTase (2)
Rhombenone (dammarane triterpene)	<i>Hedera rhombea</i> (Japanese ivy) (Araliaceae)	FPTase
Fatty acid desaturase (FAD)		13.8N
18 β -Glycyrrhetic acid (= Glycyrrhetic acid) (triterpene)	<i>Glycyrrhiza glabra</i> (licorice) (Fabaceae) [rhizome, root]	FAD(at 10nM) (ALDO-R, CBG, CORT-R, FAD, EST-R, 11 β HSDH, SBG) [elevated cortisol, hypermineral-ocorticoidism]
Glycyrrhizic acid (= Glycyrrhinic acid; Glycyrrhizin; Glycyrrhizinic acid) (triterpene glycoside saponin)	<i>Glycyrrhiza glabra</i> (licorice) (Fabaceae) [rhizome, root]	FAD (ALDO-R, CBG, CORT-R, EST-R, SBG) [anti-ulcerogenic, expectorant, sweet]
Malvalic acid (= 7-(2-octylcyclopropenyl)-heptanoic acid) (cyclopropenic FA)	<i>Gossypium hirsutum</i> (cotton seed oil), <i>Hibiscus syriacus</i> (seed oil) (Malvaceae)	FAD
Sterculic acid (= 8-(2-Octylcyclopropenyl)-octanoic acid) (cyclopropenic FA)	<i>Gossypium hirsutum</i> (cotton seed oil) (Malvaceae), <i>Sterculia foetida</i> (Sterculiaceae) [seed oil]	FAD

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
L-Galactono-γ-lactone dehydrogenase (GALLDH)		13.8O
(-)-Lycorine (= Narcissine; Galanthidine) (galanthan alkaloid)	<i>Lycoris radiata</i> , <i>Narcissus</i> spp. (Amaryllidaceae); also as glycoside, FA ester, acetic acid ester	GALLDH (< 10) (PS) [antiviral, cytotoxic, highly toxic]
Gluconeogenesis	Discovered by Claude Bernard (nineteenth century)	13.8P
Ethanol (= Ethyl alcohol; Alcohol) (aliphatic alcohol); desire for fermentation-derived ethanol may have driven start of cereal agriculture-based civilization	From fermentation of plant-derived starch; writers Brendan Behan, Scott Fitzgerald, Henry Lawson, Edgar Allan Poe, Dylan Thomas and Tennessee Williams drank to excess	Inhibits gluconeogenesis
Tremetone (benzofuran)	<i>Ageratina</i> , <i>Brickellia</i> , <i>Eupatorium</i> , <i>Grindelia</i> , <i>Haplopappus</i> , <i>Liatris</i> , <i>Ligularia</i> (Asteraceae) spp.; milk from cow foraging on <i>Eupatorium rugosum</i> (white snakeroot) killed Abraham Lincoln's mother Nancy Hanks Lincoln	Microsomal oxidation yields hypoglycaemic toxin (Dehydrotremetone inactive) [toxin blocks gluconeogenesis from lactate \rightarrow plasma acidosis, sweating, tremor, death]
Glutathione-S-transferase (GST)		13.8Q
Alkaloid		13.8Qa
Quinidine (= β -Quinine) (quinoline)	<i>Cinchona</i> spp., <i>Remijia pedunculata</i> (Rubiaceae)	GST (1) [antimalarial]
Quinine (quinoline)	<i>Cinchona</i> spp., <i>Remijia pedunculata</i> (Rubiaceae)	GST (4) [antimalarial]
Phenolic		13.8Qp
Butein (= 2',4',3,4-Tetrahydroxy-chalcone) (chalcone)	<i>Dalbergia odorifera</i> , <i>Vicia faba</i> ; (Fabaceae); glycosides in <i>Coreopsis</i> , <i>Bidens</i> (Asteraceae), <i>Butea</i> (Fabaceae) spp.	GST (9) (EGF-RTK, F ₁ -ATPase, p60 ^{c-src} TK, 5 α R) [antioxidant]
Eugenol (= Allylguaiacol, Caryophyllic acid, Eugenig acid; 2-Methoxy-4-(2-propenyl)phenol) (phenylpropanoid)	<i>Achillea</i> , <i>Artemisia</i> (Asteraceae), <i>Cinnamomum</i> , <i>Sassafras</i> (Lauraceae), <i>Ocimum</i> , <i>Origanum</i> (Lamiaceae), <i>Sassafras</i> (Lauraceae), <i>Illicium</i> (Magnoliaceae), <i>Musa</i> (Musaceae), <i>Myristica</i> (Myristicaceae), <i>Eugenia</i> , <i>Pimentum</i> , <i>Syzygium</i> (Myrtaceae), <i>Piper</i> (Piperaceae), <i>Vitis</i> (Vitaceae), <i>Rosa</i> (Rosaceae), <i>Camellia</i> (Theaceae) spp.	Irreversible inhibitor of GST (COX-1, COX-2, OD-R) [anticonvulsant, antioxidant, anaesthetic, antiseptic, AI, PAI]
2'-Hydroxychalcone (chalcone)	Plant	GST (7) (MLCK)
4'-Hydroxychalcone (chalcone)	<i>Glycyrrhiza echinata</i> (Fabaceae)	GST (47)
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> , <i>Chlorophora tinctoria</i> , <i>Morus alba</i> (mulberry), <i>M.</i> spp., (Moraceae)	GST (14) (AR, DNAL, 5-LOX, ITDI, PK) [antibacterial, antiviral, allergenic, silkworm feeding attractant]

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Oenothera biennis</i> (Onagraceae), <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice]	GST (19) (LOX, PK) [AI, feeding stimulant]
Tannic acid (hydrolysable tannin)	Widespread, fruit & bark; e.g. <i>Quercus</i> spp. (Fagaceae)	GST (1; 50)
Terpene		13.8Qt
Artemisinin (= Quinghaosu) (sesquiterpene lactone peroxide)	<i>Artemisia annua</i> (qing hao) (Asteraceae); important post-Vietnam War antimalarial source	GST (2) [antimalarial] 500 million have malaria, 3 million die yearly
11 α ,13-Dihydrohelenalin (= Plenolin) (pseudoguaianolide sesquiterpenoid lactone)	Helenin <i>ex Anaphalis, Balduina, Gaillardia, Helenium</i> spp. (Asteraceae)	GST
Helenin-GSH adduct (pseudoguaianolide sesquiterpenoid lactone)	Helenin <i>ex Anaphalis, Balduina, Gaillardia, Helenium</i> spp. (Asteraceae)	GST
Other		13.8Qo
Glutathione (= γ -Glutamylcysteinylglycine; GSH) (tripeptide)	Universal; discovered by Sir Frederick Gowland Hopkins (UK, shared Nobel Prize, Medicine, 1929, growth stimulating vitamins); enzymatic synthesis studied by Konrad Bloch (Germany/USA, Nobel Prize, Physiology/Medicine, 1964, cholesterol biosynthesis)	GST substrate; GSH oxidized \rightarrow G-S-S-G dimer
Non-plant reference		13.8Qn
[Pyrimethamine] (chlorophenyl diaminopyrimidine)	Synthetic	GST (1) [antimalarial, antitoxoplasma]
[Tetracycline] (naphthacenicarboxamide)	<i>Streptomyces viridifaciens</i>	GST (1) (PS) [antibacterial, antimalarial]
Glycolysis		13.8R
Anaerobic glycolysis in yeast yields Ethanol (q.v.) – studied by Louis Pasteur; Edouard Buchner (Germany, Nobel Prize, Chemistry, 1907, cell-free fermentation); Sir Arthur Harden (UK) & Hans Von Euler-Chelpin (Germany/Sweden) (Nobel Prize, 1929, Chemistry, fermentation & “cozymase” = NAD)	Muscle anaerobic glycolysis yields lactate – Sir Frederick Gowland Hopkins (UK, shared Nobel Prize, Medicine, 1929, growth stimulating vitamins); Sir Archibald Hill (UK) & Otto Meyerhof (Germany) (Nobel Prize, Medicine, 1922, aerobic glycolysis processes); Otto Meyerhof (glycolytic intermediates) (Germany, Nobel Prize, Physiology/Medicine, 1922 with Archibald Hill (UK), metabolism)	Carl Cori & Gerty Cori (Austria/USA, glycogen metabolism), Bernardo Housay (Argentina, anterior pituitary & carbohydrate metabolism) (Nobel Prize, Physiology/Medicine, 1947); Luis Leloir (Argentina, Nobel Prize, Chemistry, 1970, sugar nucleotides & glycogen & starch synthesis)

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Arsenate (= HAsO_4^{2-}) (oxidized arsenic); drilling exposure of arsenic to oxygen has generated huge arsenite/arsenate-contaminated underground drinking water problem in Bangladesh & W. Bengal	Environmental; arsenic accumulator and hyper-accumulator plants e.g. <i>Pteris vittata</i> (ladder brake, fern), <i>Pityrogramma calomelanos</i> (silverback fern) (Pteridaceae); Arsenate toxic; inhibits glycolytic ATP production via phosphoglycerate kinase & 1,3-Bisphosphoglycerate; arsenite (AsO_3^{3-}) toxic due to reaction with thiols	GAPDH catalyses: Glyceraldehyde-3-P + NAD^+ + $\text{P}_i \rightarrow$ 1, 3-Bisphosphoglycerate + NADH ; HAsO_4^{2-} acts like P_i (HPO_4^{2-}) \rightarrow 3-Phosphoglyceroylarsenate \rightarrow 3-Phosphoglycerate + HAsO_4^{2-}
HydroxymethylglutarylCoA reductase (HMGCAR) [25-Hydroxycholesterol] (sterol)	Generated by cooking from cholesterol	13.8S HMGCAR (Na^+/H^+ TR)
Squalene (linear triterpene; cyclic triterpene precursor)	<i>Baccharis</i> spp. (Asteraceae), <i>Olea europaea</i> (Oleaceae), <i>Triticum aestivum</i> (Poaceae), <i>Tilia vulgaris</i> (Tiliaceae)	HMGCAR
4-Hydroxyphenylpyruvate dioxygenase (-)-Usnic acid (benzofuran)	<i>Cladonia</i> sp (lichen)	13.8T 4-Hydroxyphenylpyruvate dioxygenase (plant) (50 nM) [anti-mycobacterial]
Invertase (Sucrose hydrolase) (see also 13.1) <i>Beta</i> invertase inhibitor/lectin (19kDa protein)	<i>Beta vulgaris</i> (Chenopodiaceae)	13.8U Invertase; the plant-derived disaccharide sucrose a major source of catabolizable monosaccharides Glc & Fru
<i>Cyphomandra</i> invertase inhibitor/lectin (19kDa protein)	<i>Cyphomandra betacea</i> (Solanaceae) [fruit]	Invertase
<i>Ipomoea</i> invertase inhibitor/lectin (19kDa protein)	<i>Ipomoea batatas</i> (Convolvulaceae)	Invertase
<i>Lycopersicon</i> invertase inhibitor/lectin (19kDa protein)	<i>Lycopersicon esculentum</i> (tomato) (Solanaceae)	Invertase
Myosin ATPase	Myosin isolated from muscle by John Edsall & Alexander von Muralt (1930s)	13.8V
6-Tridecylresorcylic acid (= 6-Tridecyl-2,4-dihydroxybenzoic acid) (benzoic acid, phenolic)	<i>Lysimachia japonica</i> (primula) (Primulaceae)	Myosin ATPase (4) [blocks skeletal muscle contraction]
NADH oxidase (plasma membrane) (PM NADH OX)		13.8W

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
[Atebrin (= Mepacrine; Quinacrine)] (acridine)	Synthetic	PM NADH OX [anthelmintic, antimalarial, antiprotozoal, teniacide]
1 α ,25-Dihydroxyvitamin D ₃ (= Calcitriol) (ring-opened sterol)	<i>Pinus nigra</i> , <i>P. sylvestris</i> (Pinaceae), <i>Nicotiana glauca</i> , <i>Lycopersicon esculentum</i> , <i>Solanum glaucophyllum</i> , <i>S. malacoxylon</i> (Solanaceae); animals	PM NADH OX (VITD-R) [antirachitic, promotes intestinal Ca ²⁺ transport; anti-estrogenic at DNA level]
Glauucarubolone (quassinoid nortriterpene)	<i>Castela nicholsoni</i> [wood], <i>Perriera madagascariensis</i> [fruit], <i>Quassia</i> spp. [seed] (Simaroubaaceae)	PM NADH oxidase (at 1 nM)
all <i>trans</i> -Retinoic acid (= Retinoic acid) (carotene)	Post-ingestion from α -, β - & γ -carotene & other carotenes	PM NADH OX (RA-R) [anti-estrogenic at estrogen response element level]
NADPH:quinone oxidoreductase (NQOR) (DT-diaphorase)		13.8X
Dicoumarol (= Dicumarol; Dicumol; Dicoumarin; Dufalone; Melitoxin) (coumarin)	<i>Melilotus</i> sp. (Fabaceae), <i>Anthoxanthum</i> sp. (Poaceae) [in decomposing hay from 4-Hydroxycoumarin] cf. Warfarin	NQOR [10 nM] [anticoagulant, inhibits Vitamin K-dependent protein glutamate carboxylation]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae, <i>Oenothera biennis</i> (Onagraceae), <i>Koelerutera henryi</i> (Sapindaceae); widespread as glycosides	NQOR (AR, cAMP PDE, CFTR, DNAP, F ₁ -ATPase, HIV-1 RT, 11 β HSDH, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, Nase, NEP, PK, PS-EF-1 α , RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
Nucleotidase (Nase); Cyclic nucleotide-binding Nase (CABNase)		13. 8Y
Phenolic		13. 8Yp
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	Lamiaceae, ferns [leaf surface]; <i>Apium graveolens</i> (Apiaceae), <i>Digitalia exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]; as glycoside in <i>Apium</i> (celery), <i>Petroselinum</i> (parsley) (Apiaceae), <i>Cosmos</i> , <i>Erigeron</i> , <i>Dahlia</i> (Asteraceae), <i>Amorpha</i> (Fabaceae) spp.	Nase (BZ-R-like R, EST-R, F ₁ -ATPase, Na ⁺ /K ⁺ /Cl ⁻ TR, PK) [antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
Chrysin (= 5,7-Dihydroxyflavone) (flavone)	<i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (poplar) (Salicaceae) [leaf bud], <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	Nase AR (AR, cAMP PDE, ECMOX, 17 β HSOR, ITD) [antibacterial, AI, anxiolytic, inhibits histamine release]
Diosmetin (= Luteolin 4'-methyl ether) (flavone)	<i>Arnica</i> sp. (Asteraceae), <i>Salvia tomentosa</i> (Lamiaceae), <i>Stemodia viscosa</i> (Scrophulariaceae)	Nase
Diosmin (= Diosmetin 7-O-rutinoside) (flavone O-glycoside)	<i>Rosmarinus officinalis</i> (Lamiaceae), <i>Diosma crenulata</i> (Rutaceae) [leaf]	Nase [AI, decreases capillary fragility]

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread in leaves; <i>Ammi majus</i> (Apiaceae); widespread as glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]	Nase (ACE, AR, AROM, HIV-1 PR, ITD, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, succinate DH, TOPII, TPO) [antibacterial, AI, apoptotic, nodulation signal]
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> , <i>Chlorophora tinctoria</i> , <i>Morus alba</i> (mulberry), <i>M.</i> spp., (Moraceae)	Nase (AR, DNAL, GST, 5-LOX, ITDI, PK) [antibacterial, antiviral, allergenic, silkworm feeding attractant]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplophappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	Nase (1) [2] (DNAL, DNAP, F1 ATPase, HIV-1 RT, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, NEP, PK, 5 α R, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic, apoptotic]
Naringenin (= 5,7,4'-Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia</i> spp. (Asteraceae), <i>Citrus paradisi</i> , <i>C. sinensis</i> (Rutaceae) [grapefruit juice]	Nase (AR, cAMP PDE, CYP, EST-R) [antibacterial, antifungal]
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae, <i>Oenothera biennis</i> (Onagraceae), <i>Koeleruteria henryi</i> (Sapindaceae); widespread as glycosides	Nase (1) [0.6] (AR, cAMP PDE, CFTR, DNAP, F ₁ -ATPase, HIV-1 RT, 11 β HSDH, LOX, MDR-TR, Na ⁺ , K ⁺ -ATPase, NEP, PK, PS-EF-1 α , RTK, TOPII) [allergenic, antibacterial, AI, antiviral]
Terpene		
α -Amyrin (= α -Amyrenol; Viminalol) (ursane triterpene)	<i>Alstonia boonei</i> (Apocynaceae) [root], <i>Ficus variegata</i> (Moraceae), <i>Hevea brasiliensis</i> (rubber) (Euphorbiaceae) [latex], <i>Erythroxylum coca</i> (Erythroxylaceae), <i>Balanophora elongata</i> (Balanophoraceae)	13. 8Yt CABNase (25) (CHY, CDPK, collagenase, HIV-1 PR, PKA, PKC, TRY) [anti-arthritic, AI, anti-insect]
α -Amyrin linoleate (= α -Amyrin <i>cis</i> -9, <i>cis</i> -12-octadecadienoic acid acid ester) (ursane triterpene FA ester)	Semi-synthetic from α -Amyrin	CABNase (> 100) (CHY, collagenase, 5-LOX, MLCK, PKA, PKC, TRY) [AI]
α -Amyrin palmitate (= α -Amyrin hexadecanoic acid ester) (ursane triterpene FA ester)	Semi-synthetic from α -Amyrin	CABNase (13) (CHY, collagenase, PKA, PKC) [AI]
Lupeol (= Fagasterol; Monogynol B; β -Viscol) (lupane triterpene)	<i>Alstonia boonei</i> (Apocynaceae) [bark, seed], Compositae [flower], <i>Phyllanthus emblica</i> (Euphorbiaceae), <i>Lupinus luteus</i> (Fabaceae) [seed]	CABNase (38) (CHY, PKA, PKC, TOPII, TRY) [anti-arthritic, AI, antitumour]

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
[Lupeol linoleate (= Lupeol – 9, <i>cis</i> -12-octadecadienoic acid acid ester)] (lupane triterpene FA ester)	Semi-synthetic from Lupeol	CABNase (> 100) (CHY, PKA, PKC, TRY) [AI]
[Lupeol palmitate (= Lupeol hexadecanoic acid ester)] (lupane triterpene FA ester)	Semi-synthetic from Lupeol	CABNase (6; 33) [10] (CHY, PKA, TRY)[AI]
Ornithine trans-carbamoylase (OTCase)		13.8Z
1.-Canaline (= 2-Amino-4-(aminoxy)butyric acid) (amino acid)	<i>Canavalia ensiformis</i> (jackbean) (Fabaceae) [seed]	OTCase [0.5] [blocks pyridoxal pyrophosphate-dependent enzymes by forming oxime with the coenzyme; lysine antimetabolite]
2,4-Diaminobutyric acid (diaminoalkane carboxylic acid)	<i>Acacia</i> , <i>Lathyrus</i> spp. (Fabaceae), <i>Polygonatum multiflorum</i> (Solomon's seal) (Liliaceae)	OTCase (GABA TR) [anticonvulsant]
Phenolsulphotransferase (PSTase)		13.8ZA
(+)-Catechin (= Catechinic acid; Catechuic acid) (flavan-3-ol)	Widespread; <i>Agrimonia eupatoria</i> (Rosaceae), <i>Salix caprea</i> (willow) (Salicaceae) [flower]	PSTase (< 5) (AR, COX-1, COX-2, MLCK, PKA) [antioxidant, bitter]
Cyanidin 3-rutinoside (anthocyanin)	<i>Arum maculatum</i> (Araceae) <i>Potentilla atrosanguinea</i> (Rosaceae), <i>Litchi chinensis</i> (litchi) (Sapindaceae), <i>Antirrhinum majus</i> (Scrophulariaceae)	PSTase (< 5)
3-Phosphoglycerate kinase (PGK)		13.8ZB
Ellagic acid (= Benzoic acid; Lagistase) (phenolic acid lactone)	Widespread [leaf], ellagitannin product; <i>Fragaria</i> spp (Rosaceae)	PGK (0.7) (HIV-1 INT, ITD, PK, TK) [anti-mutagen, haemostatic]
Flavellagic acid (polyhydroxyphenolic)	Oxidation product of widespread phenolic Gallic acid	PGK (0.3)
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplopappus canescens</i> (Asteraceae) [aerial]; glycosides in <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Primula sinensis</i> (Primulaceae) [petal], <i>Camellia sinensis</i> (Theaceae) [leaf]	PGK (1) (DNAL, DNAP, F1 ATPase, HIV-1 RT, iNOS, 5-LOX, NADH DH, Na ⁺ , K ⁺ -ATPase, Nase, NEP, PK, 5 α R, succinate DH, TOPII, TPO) [antibacterial, antigonadotropic, apoptotic]
Purpurogallin (bicyclic phenolic)	<i>Dryophanta divisa</i> gall on <i>Quercus pedunculata</i> (Fagaceae)	PGK (1) (EGF-RTK, HIV-1 INT, PEP, XO) [antioxidant, red pigment]
[Rufigallol (= 1,2,3,5,6,7-hexahydroxyanthraquinone) (anthraquinone)]	Synthetic	PGK (0.8)

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Phospholipase A₂ (PLA₂)		
Bilobetin (biflavonoid)	<i>Ginkgo biloba</i> (Ginkgoaceae)	13.8ZC PLA ₂ [inhibits LPS-induced COX-2, iNOS & TNF α production]
Ginkgetin (biflavonoid)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [fruit, leaf]	PLA ₂ [inhibits LPS-induced COX-2, iNOS & TNF α production]
18- β -Glycyrrhetic acid (Glycyrrhetic acid; Glycyrrhetin) (triterpene saponin)	<i>Glycyrrhiza glabra</i> (licorice) (Fabaceae) [root, rhizome]	Binds PLA ₂ (ALDO-R, CBG, CORT-R, ELA, EST-R, β HSDH, PKA, PKC, SBG) [AI, anti-ulcerogenic, anti-diuretic]
Glycyrrhizic acid (= Glycyrrhizin; Glycyrrhinic acid; Glycyrrhizinic acid) (triterpene glycoside saponin)	<i>Glycyrrhiza glabra</i> (licorice) (Fabaceae) [root, rhizome]	Binds PLA ₂ (ALDO-R, CBG, CORT-R, EST-R, PKA, SBG) [AI, anti-ulcerogenic, sweet taste]
[Manoalide] (polyalicyclic)	Sponge	PLA ₂
Morelloflavone (flavanonylflavone, biflavonoid)	<i>Garcinia morello</i> , <i>G. multiflora</i> (Guttiferae)	PLA ₂ (0.6; 0.9) (AO/FRS, HIV-1 RT)
[Petrosaspongiolide] (polyalicyclic)	Sponge	PLA ₂
Phospholipase Cγ (PLCγ)		
Amentoflavone (flavone)	<i>Selaginella tamariscina</i> (Selaginellaceae)	13.8ZD PLC γ 1 (29)
Uncarinic acid A (triterpene ester)	<i>Uncaria rhynchophylla</i> (Rubiaceae)	PLC γ 1 (36)
Uncarinic acid B (triterpene ester)	<i>Uncaria rhynchophylla</i> (Rubiaceae)	PLC γ 1 (45)
Poly(ADP-ribose) glycohydrolase (PADPRH)		
Ellagitannins & Gallotannins (hydrolysable tannins)	Widespread	13.8ZE PADPRH (tetrameric > trimeric > dimeric > monomeric ellagitannins & gallotannins i.e. more complex more potent)
Oenothlein B (macrocircular dimeric ellagitannin)	<i>Cuphea hyssopifolia</i> (Lythraceae), <i>Eucalyptus consideriana</i> , <i>E. viminalis</i> (Myrtaceae), <i>Epilobium</i> spp., <i>Oenothera laciniata</i> (Onagraceae)	PADPRH (AROM, 5 α R) [antitumour, inhibits glucocorticoid-induced depolyADPribosylation]
Prolyl hydroxylase (ProH)		
Lithospermic acid (Lithospermate, Mg ²⁺ salt) (phenylpropanoid, benzofuran)	<i>Anchusa officinale</i> , <i>Echium vulgare</i> , <i>Lycopus europaeus</i> , <i>L. virginicus</i> , <i>Lithospermum officinale</i> , <i>L. ruderalis</i> (Boraginaceae), <i>Mentha piperita</i> , <i>Salvia deserta</i> (Lamiaceae) [root, rhizome]	13.8ZF ProH (AO/FRS, AR)

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Protein glycosylation		13.8ZG
Nerolidol (sesquiterpene)	<i>Virola surinamensis</i> (Myristicaceae)	Glycoprotein biosynthesis
[Corynetoxins] (glycolipid)	<i>Lolium rigidum</i> (annual rye grass) infected successively with a nematode & thence with <i>Corynebacterium</i> gall	Effects resemble those of Tunicamycin [toxic; annual ryegrass toxicosis]
[Tunicamycins] (uridine glycosides)	<i>Streptomyces</i> spp. (fungi)	N-linked protein glycosylation (apoptotic) [antibiotic, toxic]
Protoporphyrinogen oxidase		13.8ZH
(-)-Usnic acid (benzofuran)	<i>Cladonia</i> sp. (lichen)	Protoporphyrinogen oxidase (plant) (3) [anti- mycobacterial]
Sialyltransferase (SialylT)		13.8ZI
Soyasaponin I (triterpene saponin)	<i>Cicer arietinum</i> (chickpea), <i>Glycine max</i> (soya bean), <i>Lens culinaris</i> (lentil), <i>Phaseolus vulgaris</i> (bean) (Fabaceae)	SialylT [2]; hypersialylation found in oncogenic transformation & tumour metastasis & invasion
Squalene epoxidase (SEP)		13.8ZJ
1,6-Di- <i>O</i> -galloyl-2- <i>O</i> - cinnamoyl- β -D-glucose (gallotannin)	<i>Rheum palmatum</i> (rhubarb) (Polygonaceae) [rhizome]	SEP (0.6)
Ellagic acid (phenolic bis lactone)	Widespread; from ellagitannins; <i>Fragaria</i> spp. (Rosaceae)	SEP (2)
(-)-Epicatechin-3- <i>O</i> -gallate (= ECG) (flavan-3-ol galloyl ester)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	SEP (1)
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol galloyl ester)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	SEP (0.7) (EST-R, PK, proteosome, 5 α R, RTK, XO) [oxidation products give tea taste]
Eugenin (ellagitannin)	<i>Coriaria</i> (Coriariaceae), <i>Quercus</i> (Fagaceae), <i>Syzygium</i> (Myrtaceae), <i>Fuchsia</i> (Onagraceae), <i>Rosa</i> (Rosaceae), <i>Tellima</i> (Saxifragaceae) spp.	SEP (2)
(-)-Galocatechin-3- <i>O</i> -gallate (= GCG) (flavan-3-ol galloyl ester)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	SEP (0.7)
Pedunculagin (ellagitannin)	<i>Punica granatum</i> (Punicaceae) [pericarp]	SEP (2) (CA)
Procyanidin B-2 3,3'-di- <i>O</i> - gallate (condensed tannin)	<i>Rheum palmatum</i> (rhubarb) (Polygonaceae) [rhizome]	SEP (0.5)
Procyanidin B-5 3,3'-di- <i>O</i> - gallate (condensed tannin)	<i>Rheum palmatum</i> (rhubarb) (Polygonaceae) [rhizome]	SEP (0.6)

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects/
Theasinensin A (= 6',6''-Bis(5,7,3',4',5'-pentahydroxyflavan 3-O-galloyl ester)) (biflavanol)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	SEP (0.1)
1,2,6-Tri-O-galloyl- β -D-glucose (gallotannin)	<i>Rheum palmatum</i> (rhubarb) (Polygonaceae) [rhizome]	SEP (0.6)
Thiamine pyrophosphate (TPP)-dependent reactions		13.8ZK
Thiamine (= Vitamin B ₁) (pyrimidinylmethyl thiazole); dietary deficiency yields beriberi involving oedema, pain, neuritis, paralysis & death; detected by Christiaan Eijkman as polyneuritis in hens fed polished rice; isolated from polishings by Jansen & Donath	Vegetables, legumes, fruit, grain; Christiaan Eijkman (Netherlands, Nobel Prize, Medicine, 1929, anti-neuritic Vitamin B₁ in rice hull); Gerrit Grijns resolved anti-neuritic factor; Sir Frederick Gowland Hopkins (UK, shared Nobel Prize, Medicine, 1929, growth stimulating vitamins); nardoo (<i>Marsilea drumondii</i>) flour thiaminase caused thiamine deficiency afflicting Burke and Wills expedition return journey (R.O. Burke, W.J. Wills & C. Gray dying but J. King surviving with permanent peripheral neuropathy)	TPP involved in reactions catalysed by pyruvate decarboxylase (alcoholic fermentation), pyruvate dehydrogenase & α -ketoglutarate dehydrogenase (TCA cycle), transketolase (photosynthesis Calvin cycle) & acetolactate synthetase (Val, Leu biosynthesis)
Transaminase (TRA)		13.8ZL
L-Canaline (= 2-Amino-4-(aminoxyl)butyric acid (amino acid))	<i>Canavalia ensiformis</i> (jackbean) (Fabaceae) [seed]	TRA – blocks pyridoxal pyrophosphate-dependent enzymes by forming oxime with the coenzyme (OTCase) [lysine antimetabolite]
Trimethylamine oxidase (TMAOX)		13.8ZM
Sinapine (= Sinapic acid choline ester) (phenolic acid ester)	<i>Brassica nigra</i> (black mustard) (Brassicaceae) [seed]	TMAOX [but not in vivo & hence hen TMA “egg taint” due to another cause]
Tyrosinase (TYRase)		13.8ZN
Barbarin (= (<i>R</i>)-5-Phenyl-2-oxazolidinethione) (oxazolidine)	<i>Barbarea orthoceras</i> (Brassicaceae)	TYRase (42; 48) [33; 36]
[Kojic acid (= 2-Hydroxymethyl-5-hydroxy- γ -pyrone) (γ -pyrone)]	<i>Aspergillus oryzae</i> (fungus)	TYRase (34; 60) [23; 80]

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) part	Target (other targets) / in vivo effects
Norartocarpetin (flavone)	<i>Artocarpus gomezianus</i> (Moraceae) [root]	TYRase
Resveratrol (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum grandiflorum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis vinifera</i> (Vitaceae) spp.	TYRase (EST-R, F ₁ -ATPase, p56 ^{lck} TK, XO)
Xanthine oxidase (XO)		13.8ZO
Phenolic		13.8ZO_p
Axillarin (= 5,7,3',4'- Tetrahydroxy-3,6- dimethoxyflavone; Quercetagenin 3,6-dimethyl ether) (flavanol)	<i>Achillea</i> spp., <i>Ajania fruticulosa</i> , <i>Artemisia</i> spp., <i>Matricaria chamomilla</i> (chamomile), <i>M. recutita</i> (Asteraceae) [flower], <i>Didierea</i> spp. (Didieraceae)	XO (AHR, AR)
Caffeic acid (= 3,4- Dihydroxycinnamic acid) (phenylpropanoid)	Widespread; <i>Conium maculatum</i> (Apiaceae), <i>Achillea millefolium</i> , <i>Anthemis nobilis</i> , <i>Artemisia rubripes</i> , <i>Taraxacum officinale</i> (Asteraceae), <i>Ipomoea purga</i> (Convolvulaceae), <i>Alsophila spinulosa</i> (Cyatheaceae), <i>Olea europaea</i> (Oleaceae), <i>Papaver somniferum</i> (Papaveraceae), <i>Coffea arabica</i> , <i>Cinchona cuprea</i> (Rubiaceae), <i>Digitalis purpurea</i> (Scrophulariaceae)	XO (39) [28] (eEF-2, 5-LOX, 12-LOX) [AI, PAI, 5-LOX & LTB ₄ generation inhibited (weak)]
(-)-Epigallocatechin 3-gallate (= EGCG) (flavan-3-ol galloyl ester)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea) (Theaceae)	XO (at 10) (AO/FRS, EST-R, GlcTR, PK, proteasome, 5 α R, RTK, SEP, XO) [oxidation products give tea taste]
Esculetin (= 6,7- Dihydroxycoumarin) (coumarin)	Widespread; <i>Euphorbia lathyris</i> (Euphorbiaceae) [seed], <i>Aesculus hippocastanum</i> , <i>A. turbinata</i> (Hippocastanaceae) [wood], <i>Fraxinus</i> spp. (Oleaceae) [bark]	XO [2]
Isorhapontin (stilbene)	<i>Veratrum taliense</i> (Liliaceae) [rhizome, root]	XO (70) [19]
Mulberroside E (stilbene)	<i>Veratrum taliense</i> (Liliaceae) [rhizome, root]	XO (78) [14; 33]
Pentagalloylglucose (tannin)	<i>Acer</i> (Aceraceae), <i>Rhus</i> , <i>Cotinus</i> , <i>Schinus</i> (Anacardiaceae), <i>Terminalia</i> (Combretaceae), <i>Quercus</i> (Fagaceae), <i>Geranium</i> (Geraniaceae), <i>Nuphar</i> (Nymphaeaceae), <i>Epilobium</i> , <i>Fuchsia</i> (Onagraceae), <i>Paeollia</i> , <i>Paeonia</i> (Paeonaceae), <i>Rosa</i> (Rosaceae), <i>Camellia</i> (Theaceae)	XO (NADH DH (H ⁺ , K ⁺ - ATPase, NADH DH, Na ⁺ , K ⁺ -ATPase, XO) [anti-gastritis, anti-peptic ulcer]

(continued)

Table 13.8 (Continued)

Compound (class)	Plant (family) [part]	Target (other targets) / in vivo effects/
Piceid (stilbene)	<i>Veratrum taliense</i> (Liliaceae) [rhizome, root]	XO (66) [14]
Propylgallate (phenolic ester)	<i>Camellia</i> spp. (tea) (Theaceae) [leaf]	XO (at 10) (AO/FRS)
Purpurogallin (bicyclic phenolic)	<i>Dryophanta divisa</i> gall on <i>Quercus pedunculata</i> (Fagaceae)	XO (EGF-RTK, PEP) [antioxidant, red pigment]
Resveratrol (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum grandiflorum</i> , <i>V. taliense</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis vinifera</i> (Vitaceae) spp.	XO (97) [10] (EST-R, F ₁ -ATPase, p56 ^{lck} TK)
Santin (flavonol)	<i>Ajania fruticulosa</i> (Asteraceae) [aerial]	XO
Syringic acid (= 3,5-Dimethoxy-4-hydroxybenzoic acid) (phenolic)	<i>Conzya bonariensis</i> (Asteraceae), <i>Arachis hypogaea</i> , <i>Glycine max</i> (Fabaceae), <i>Impatiens</i> (Balsaminaceae), <i>Catalpa</i> (Bignoniaceae), <i>Ceanothus</i> (Rhamnaceae), <i>Citrus</i> (Rutaceae) spp.	XO (500)
Takakin 8-O-glucuronide (flavone glucuronide)	<i>Conzya bonariensis</i> (Asteraceae)	XO (170)
Theaflavin (polyphenol)	<i>Camellia</i> spp. (tea) (Theaceae) [leaf]	XO (at 50) (AO/FRS)
Theaflavin-3,3'-digallate (polyphenol)	<i>Camellia</i> spp. (tea) (Theaceae) [leaf]	XO (at 10) (AO/FRS)
Theaflavin-3-gallate (polyphenol)	<i>Camellia</i> spp. (tea) (Theaceae) [leaf]	XO (at 50) (AO/FRS)
Veraphenol (stilbene)	<i>Veratrum taliense</i> (Liliaceae) [rhizome, root]	XO (11) [33, 239]
Non-plant reference [Allopurinol] (allopurine)	Synthetic	13.8ZO XO [hyperuricemia & chronic gout treatment]
Protein adducts Aucubin (iridoid monoterpene glucoside)	<i>Aucuba japonica</i> (Cornaceae), <i>Rhinanthus</i> spp. (Scrophulariaceae)	13.8ZP Forms reactive aglycone Aucubiginin that yields imine protein adduct [protein denaturant; diuretic, laxative]
Alkyl- and aryl-isothiocyanates (= R=N=C=S) (isothiocyanates)	Generated from glucosinolates from Brassicaceae & some other families e.g. Caricaceae, Limnathaceae & Tropaeolaceae	R=N=C=S reacts with amino (NH ₂) & thiol (-SH) groups of proteins
Plenolin (= 11 α ,13-Dihydrohelenalin) (pseudoguaianolide)	<i>Baileya pleniradiata</i> , <i>Helenium autumnale</i> (Asteraceae)	Forms GST adduct
Oleuropein (seco-iridoid monoterpene glucoside)	<i>Ligustrum obtusifolium</i> (privet), <i>Olea europaea</i> (olive) (Oleaceae)	Forms reactive aglycone \rightarrow protein adduct [protein denaturant; spasmolytic]

(continued)

Table 13.8 (Continued)

<i>Compound (class)</i>	<i>Plant (family) part </i>	<i>Target (other targets) / in vivo effects/</i>
Thiocyanate ($=S=C=N^-$) (thiocyanate ion); from cyanogenic glycosides & glucosinolates	Generated (together with isothiocyanates & nitriles) from glucosinolates e.g. Vicianin, Prunasin, β -Cyanoalanine from <i>Vicia</i> spp. (vetch) (Fabaceae)	Nucleophilic & reactive [toxic; neurotoxic by promoting glutamate- AMPA GLU-R binding]
Warburganal (dialdehyde sesquiterpene)	<i>Warburgia salutaris</i> (Canellaceae)	Forms adduct with cysteine thiol (antifeedant) [antifungal]

14 Anti-inflammatory, antioxidant and antidiabetic plant compounds

14.1 Introduction

Inflammation (the “inflammatory response”) is triggered by tissue injury from bacterial infection, immune activation, wounding and other sources of damage. White blood cells (leucocytes) and antibodies access damaged tissue through vascular dilation and an increase in vascular permeability. Leucocytes (notably neutrophils) migrate to damaged tissue through the successive processes of adherence to vascular endothelium, “rolling” and transmigration into the extravascular space (diapedesis and extravasation). Leucocytes such as neutrophils and monocyte-derived macrophages phagocytose bacteria, damaged cells and cell debris to allow for tissue repair. The overall process involves kinins and the kinin-generating proteases, chemoattractant chemokines (CHs), pro- and anti-inflammatory (AI) cytokines, cell surface proteins involved in cell–cell interactions (selectins and integrins), small bioactive molecules (such as platelet activating factor (PAF), eicosanoids and histamine), cell surface receptors for the foregoing and the downstream signal transduction components described in Chapters 5–8.

Tissue damage gives rise to activation of blood clotting factor XII (a protease), this in turn leading to activation of a further specific protease (kallikrein) and formation of kinins (e.g. bradykinin) from proteolysis of the kininogen precursor. Kinin generation causes vasodilation, increased vascular permeability to proteins and increased access to damaged tissue of blood proteins and phagocytic leucocytes. Kinins are also chemotactic for neutrophils which are involved in debris removal through phagocytosis and protease release. CH leucocyte chemoattractants are also involved in leucocyte attraction. Kallikrein from neutrophils generates more kinins which, together with CH production from other cells, produce a “positive feedback loop” of more vasodilation, vascular permeability increase and neutrophil attraction.

Histamine is produced by various cells, including mast cells, basophils and platelets, and its release is stimulated by cell disruption and neutrophil-derived factors. Histamine (see Chapter 5) complements kinins in causing vasodilation, increased vascular permeability and the consequent introduction of neutrophils from the capillaries into the extravascular spaces of the tissue. The process of successive neutrophil adhesion, arrest, spreading and extravasation is called “diapedesis”. CHs enable the accumulation of leucocytes and cytokines (such as interferons and interleukins) are required for phagocytosis, B cell antibody production and production of bacteriocidal nitric oxide (NO) and reactive oxygen species (ROS). Neutrophils and monocyte-derived macrophages phagocytose bacteria and cell debris. Removal of bacterial and cell debris permits subsequent tissue repair. This overall process gives rise to the familiar redness (due to vascular dilation), swelling (increased blood vessel permeability) and pain (from kinin interaction with afferent nerve terminals).

While the inflammatory process operates for the protection and repair of tissues, it is also associated with diseases such as Alzheimer's disease and asthma and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and ulcerative colitis. Such diseases require AI treatment to deal with tissue damage and pain and many AI herbal remedies have been elaborated in various societies. The action of various AI plant-derived compounds have been considered previously, for example, PAF receptor antagonists (Chapter 5). This chapter deals with compounds variously inhibiting enzymes such as cyclooxygenase (COX), lipoxygenase (LOX) and aldose reductase (AR) and a large number of antioxidant plant compounds that scavenge free radicals. Before detailing such interactions it is useful to briefly outline the nature of the inflammatory response as well as pro-oxidant and anti-oxidant processes.

14.2 Adhesion and movement of inflammatory leucocytes

After infection and immune cell activation, endothelial cells are variously activated to bind peripheral blood leucocytes. Bacterial toxins such as lipopolysaccharide (LPS), inflammatory cytokines such as tumour necrosis factors α and β (TNF α and TNF β) and interleukin-1 β (IL-1 β) increase the synthesis of cell surface E- and P-selectins in endothelial cells. Histamine and thrombin increase PM P-selectins in endothelial cells and platelets. L-selectins are constitutively expressed in monocytes and lymphocytes. The selectins are involved in the initial adhesion of leucocytes with endothelial cells via selectin-selectin receptor interactions, for example, monocyte L-selectin-endothelial L-selectin ligand binding and T-lymphocyte-endothelial selectin-integrin interactions. This initial phase of leucocyte-endothelial adhesion enables an early stage of leucocyte "rolling" through successive formation and breakage of adhesive interactions.

A subsequent phase is the "arrest" and "spreading" of leucocytes. This process involves tighter interaction of monocyte or T-lymphocyte cell surface integrins with the endothelial cell surface intercellular cell adhesive molecules (ICAMs). The ICAMs belong to the immunoglobulin family and are of various kinds, namely ICAM-1 (on endothelium and certain leucocytes), ICAM-2 (endothelium and platelets) and ICAM-3 (leucocytes). Related cell surface immunoglobulins include vascular cell adhesion molecule-1 (VCAM-1, endothelium and smooth muscle) and platelet-endothelial cell adhesion molecule-1 (PECAM-1, endothelium and platelets).

Integrins are heterodimeric ($\alpha\beta$) complexes expressed on leucocytes. Monocytes and lymphocytes express $\beta 1$ integrins and all leucocytes express integrins having a common $\beta 2$ chain but different α chains. Integrins are involved in cell-matrix as well as cell-cell interactions. The synthesis of $\beta 1$ and $\beta 2$ integrins is stimulated by endothelium-derived leucocyte chemoattractants such as monocyte chemoattractant protein-1 (MCP-1). The endothelium ICAM-1 is subject to upregulation by leucocyte-derived cytokines.

The interaction of the various $\alpha\beta$ integrin complexes with ICAMs results in firm attachment and spreading. Subsequent VCAM-1-integrin and PECAM-1-integrin interactions are involved in leucocyte transmigration through endothelial cell junctions into the extravascular space. Leucocytes can thence proceed to interact with target cells and initiate inflammatory processes.

14.3 Chemokines

The CHs (pro-inflammatory leucocyte chemoattractants) are single polypeptide chains of about 70–100 amino acids in length and can be subdivided into four families based on

conserved cysteine (C) residue number and spacing (namely C, CC, CXC and CX₃C groups). The CH receptors are G protein-coupled receptors (GPCRs) that act via Gi-type G proteins. The CH signalling successively involves: CH binding to a Gi-linked receptor (R); the CH-R complex interacting with a trimeric Gi protein complex (Gi α -GDP-G β -G γ) with release of Gi α -GTP; inhibition of adenylyl cyclase; decreased cytosolic cAMP concentration; cAMP-dependent protein kinase (PKA) inactivation and cAMP-gated Na⁺ channel closure; cell membrane hyperpolarization, Ca²⁺ channel closure and decreased cytosolic Ca²⁺ concentration.

Chemokines are typically upregulated by pro-inflammatory cytokines such as TNFs and interleukin-1 (IL-1), upregulated by interferon- γ (IFN- γ) and downregulated by the AI cytokine IL-10. CH receptors are variously found on T cells, B cells, monocytes, eosinophils, basophils, T helper cells type 2 (Th2 cells), haematopoietic progenitor cells, erythrocytes and neutrophils. Leucocytes adhere and “roll” across the endothelium in a selectin-dependent process followed by arrest and transmigration involving CH-dependent β 2 integrin activation, tight integrin-mediated binding to endothelial ICAMs and subsequent transmigration into extravascular spaces. Leucocytes interact with CHs that are immobilized by proteoglycans (this providing a gradient in the extracellular matrix (EM) for leucocytes to follow to the zone of inflammation).

Chemokine accumulation occurs in autoimmune degenerative disease such as multiple sclerosis and in allergic inflammatory diseases such as asthma. Various viruses produce CH antagonists that interfere with the CH-mediated defence system and HIV-1 infects cells via the CCR5 receptor.

14.4 Phagocytosis

Phagocytosis by neutrophils or monocyte macrophages typically involves the cellular uptake of large particles in a process mediated by receptors. Such receptors include Fc receptors (FcRs) (that bind the Fc portion of antibodies distal to the antigen-binding region), complement receptors (CRs) and mannose receptors (MRs) on the macrophages. FcR- and MR-mediated phagocytosis involves activation of the pro-inflammatory responses of the macrophages (variously causing secretion of pro-inflammatory cytokines IL-1 β , IL-6, granulocyte macrophage-colony stimulating factor (GM-CSF), TNF- α and IL-12, the chemoattractants IL-8 and MCP-1 and pro-inflammatory metabolic products such as PAF, arachidonic acid, ROS, prostaglandins and leucotrienes). In CR-mediated phagocytosis and the phagocytosis of apoptotic cells such pro-inflammatory responses are not switched on.

Fc receptor-mediated phagocytosis involves recognition of IgG (immunoglobulin G) opsonized particles by the extracellular domain of these receptors. The consequence of this binding is transmitted via the transmembrane domain to the cytoplasmic tail of the receptor that contains “immunoglobulin gene family tyrosine activation motif” (ITAM) elements. FcR tyrosine phosphorylation on ITAMs successively yields phospholipase C γ (PLC γ) activation, PLC γ -catalysed formation of diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP₃), IP₃-mediated Ca²⁺ release from the endoplasmic reticulum (ER), Rho family GTPase activation, protein kinase C (PKC) activation by DAG and Ca²⁺ yielding MARCKS protein phosphorylation, actin polymerization, particle internalization into phagosomes and particle digestion. MR-mediated phagocytosis involves recognition of branched mannose and fucose oligosaccharides on the surface of the target body, formation of phagosomes and proteolytic digestion of the endocytosed material.

Complement proteins opsonize bacteria for phagocytosis via integrin family, $\alpha\beta$ heterodimeric CRs on the macrophages. Unlike the FcR-mediated process, CR-mediated

phagocytosis requires additional stimuli such as TNF- α , GM-CSF, attachment to a laminin- or fibronectin-coated substratum and PKC activation. Euphorbiaceae-derived phorbol esters such as TPE (tetradecanoylphorbol ester) are potent PKC activators (Chapter 8) and are consequently highly inflammatory (Chapter 8). Phagocytosis of apoptotic cells (unlike FcR- and MR-mediated phagocytosis) involves decreased production of pro-inflammatory cytokines.

14.5 Kinins, cytokines, platelet activating factor and eicosanoids

Tissue damage and neutrophil activation and migration yields production of kinins such as bradykinin from kininogens by various proteases including calpains, kallikrein and cathepsin. Bradykinin acts via G protein-linked B2 receptors to activate phospholipase A₂ (PLA₂) and PLC and ultimately elevate Ca²⁺. PLA₂ activation yields arachidonic acid and lysolecithin and thence PAF, 1-alkyl-2(*R*)-acetyl-*sn*-glycero-3-phosphocholine. Elevated Ca²⁺ promotes PLA₂ activity (and hence PAF and arachidonic acid levels) and constitutive nitric oxide synthase (cNOS) (and hence an increase in vasodilatory NO). Septic shock occurs when there is excessive hypotension causing severe organ stress exacerbated by pro-inflammatory cytokine production.

The cytokines TNF- α and TNF- β are inflammatory mediators produced by macrophages and other cells in response to invasive stimuli such as bacterial LPS and endotoxins, antigen-antibody complexes, products of complement activation and cytokines. TNF activates leucocytes, increases neutrophil and monocyte adherence and migration and stimulates the synthesis of other pro-inflammatory cytokines. TNF- α is membrane-located and interacts with a PM-located receptor (CD120) leading to activation of caspases (cysteine proteases critically involved in cell death) and activation of PLA₂.

A major signalling pathway involves activation of a protein kinase that phosphorylates inhibitor κ B proteins (I κ Bs) that normally inhibit the function of the nuclear transcription factor NF κ B. Phosphorylation of I κ B by the serine/threonine-specific I κ B kinases (IKKs) leads to NF κ B de-inhibition, nuclear translocation and expression of pro-inflammatory proteins such as inducible cyclooxygenase (iCOX) (which generates prostaglandins), inducible nitric oxide synthase (iNOS) (which generates vasodilatory and toxic free radical-generating NO) and pro-inflammatory cytokines.

Cytokines act via the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, binding to PM receptors and successively causing binding to the receptor by JAKs, reciprocal JAK tyrosine phosphorylation, STAT binding and tyrosine phosphorylation by JAKs and finally STAT nuclear translocation as tyrosine-phosphorylated and activated heterodimers to induce specific gene expression (Chapter 8).

Kinins (acting via G-linked receptors) or TNF (acting via PM receptors) initiate signalling pathways leading to activation of phospholipase A₂ (PLA₂). The PLA₂s include secretory PLA₂ (sPLA₂), cytosolic Ca²⁺-dependent PLA₂ (cPLA₂), intracellular Ca²⁺-independent PLA₂ (iPLA₂) and PAF acetylhydrolases. PLA₂ cleaves 1,2-diacylphospholipids such as phosphatidylcholine to yield a free fatty acid from position 2 (notably arachidonic acid) and a 2-lysophospholipid, which is thence acetylated in position 2 to yield PAF. PAF is a key inflammation mediator that acts via PM PAF receptors (e.g. on platelets). PAF increases vascular permeability and platelet aggregation.

Prostaglandins, thromboxanes and leucotrienes are eicosanoids deriving from oxidation of arachidonic acid. Arachidonic acid (deriving from PLA₂ action on phospholipids) is cyclized by constitutive cyclooxygenase (COX-1) or inducible cyclooxygenase (COX-2) to yield

prostaglandin (PG) H_2 (PGH₂). PGH₂ is converted to PGI₂ (prostacyclin) via prostacyclin synthase and thence to 6-keto-PGF_{1 α} . Alternatively, PGH₂ is converted (via PG synthase) to PGD₂, PGE₂ and PGF_{2 α} or (via thromboxane synthase) to thromboxane A₂, thromboxane B₂ and 2,3-di-nor-thromboxane B₂. Arachidonic acid can also be oxidized to the hydroperoxyacid 15-HPETE (15-hydroperoxyeicosatetraenoic acid) by 15-lipoxygenase (15-LOX) and thence to the epoxyacid 15-HETE (15-hydroxyeicosatetraenoic acid) or to 12-HPETE (by 12-LOX) and thence to 12-HETE. Arachidonic acid can be oxidized to 5-HPETE (by 5-LOX) and thence to 5-HETE. 5-HETE can be further converted to leukotrienes (LTs) LTA₄, LTB₄, LTC₄, LTD₄, LTE₄ and LTF₄.

Eicosanoids have pro-inflammatory effects including vasodilation and increased vascular permeability, platelet aggregation, granulocyte chemotaxis, B- and T-lymphocyte proliferation, natural killer cell cytotoxicity and degradation of extracellular matrix cartilage and bone. The major AI drugs are non-steroidal AI drugs (NSAIDs) that inhibit PG synthesis (e.g. aspirin (acetylsalicylic acid), ibuprofen, indomethacin and the COX-2-specific drug celebrex), corticosteroids such as cortisol (which causes global inhibition of the arachidonic acid cascade, inhibits the synthesis of pro-inflammatory proteins such as iNOS and of pro-inflammatory cytokines and inhibits the immune response) and methotrexate (a folic acid antagonist that inhibits dihydrofolate reductase and thence nucleotide synthesis, cell proliferation and the immune response).

14.6 Plant-derived anti-inflammatory compounds

A variety of plant-derived compounds are AI by inhibiting the formation of pro-inflammatory signalling molecules such as prostaglandins (made via cyclooxygenases) or leukotrienes (made via lipoxygenases) (Table 14.1). Many plant substances (notably phenolics) are antioxidants by scavenging ROS (free radicals) such as OH and superoxide (O₂⁻) free radicals (Table 14.2). Conversely, some plant-derived compounds are pro-oxidants in themselves, generate free radicals or inhibit hydrogen peroxide removal (Table 14.3). As seen previously, various plant compounds inhibit the action of pro-inflammatory agents such as PAF (Chapter 5, Table 5.3). Many plant compounds inhibit the NF κ B-mediated signalling pathway in immune cells that leads to the production of iNOS (Chapter 7, Table 7.3; 14.4), pro-inflammatory cytokines (Chapter 8) and inducible cyclooxygenase (COX2) (Table 14.1). Various plant compounds inhibit I κ B kinase (IKK), thus preventing NF κ B activation and the expression of pro-inflammatory proteins such as cytokines, COX2 and iNOS (Table 8.1). Further compounds interfering with NF κ B activation are listed in Table 7.3.

14.7 Diabetes mellitus and plant antidiabetic compounds

Diabetes mellitus (“sweet urine”) involves relative over-production of glucose by the liver and under-utilization by other organs. Diabetes is the most serious metabolic disease in terms of its social impact. Obesity and the indulgent “Western” diet correlates with mature age diabetes. Type 1 diabetes (juvenile diabetes) typically manifests at less than 20 years from autoimmune destruction of the insulin-producing pancreatic β cells. Type 1 diabetes is insulin-dependent diabetes mellitus (IDDM) and is fatal without exogenous insulin. Type 2 diabetes mellitus (mature age diabetes) occurs later in life and typically involves both deficient insulin production and “insulin resistance”, that is, the target cells are less responsive to insulin. Type 2 diabetes is initially non-insulin-dependent diabetes (NIDDM) but insulin therapy (in addition to oral antidiabetics) may eventually be required. Hyperglycaemia due

to lack of “blood glucose control” results in protein glycation, advanced glycation endproducts (AGEs), progressive damage to microvasculature and other tissue and ultimately complications of retinopathy, neuropathy, nephropathy and atherosclerosis.

The management of diabetes mellitus involves injection of appropriate insulin preparations where required, careful monitoring of blood glucose levels, exercise and diet. Various oral medications are directed at reducing glucose intake in the small intestine, increasing insulin production by the pancreas and increasing insulin effectiveness at the target cell level (see Chapter 8).

Consequences and complications of diabetes include hyperglycaemia and diabetic ketoacidosis (requiring emergency treatment with rehydration and insulin) and hypoglycaemia from too little food while on medication or from too much insulin being injected. Hypoglycaemia is treated with readily absorbed glucose to prevent possible “insulin shock” from the brain being starved of glucose. Damage due to sustained hyperglycaemia derives successively from protein glycosylation, Schiff base (R–C = N–Y) rearrangement, oxidation of glycated proteins yielding AGEs, thickening of the basement membrane in blood vessels, microvascular damage and further complications.

Retinal capillaries become leaky and vessels clog resulting successively in local ischaemia (blocked blood supply), local hypoxia, vascular endothelial growth factor (VEGF) expression, RTK- and PKC-mediated signalling, angiogenesis (blood vessel development), proliferative retinopathy (neovascularization) plus neuron death and ultimately blindness. Further complications include kidney damage (nephropathy), nerve damage (neuropathy), atherosclerosis, stroke/heart attack and peripheral circulatory damage (with gangrene, progressive amputation and septicaemia as potential consequences). Major therapeutic targets for the increased cellular oxidative state in diabetes are aldose reductase and aldehyde reductase and many plant compounds inhibit these enzymes (Table 14.5). Antioxidants may ameliorate this state and vitamin E is therapeutic for diabetic retinopathy. A wide range of plant compounds, notably phenolics, are scavengers of ROS (Table 14.2).

Table 14.6 summarizes the reported effects of a variety of hypoglycaemic (blood glucose lowering) and insulin-release promoting (insulinotropic) plant-derived compounds. These effects were observed in various mammalian situations (normal, alloxan- or streptozotocin-induced diabetes and “knockout” mice lacking the diet-modulating leptin receptor). The “non-plant reference” section (Table 14.6n) shows that major oral antidiabetic therapies include insulinotropic drugs that close ATP-sensitive K^+ channels, inhibit α -glycosidase (and hence glucose absorption) or decrease insulin resistance. A variety of plant defensive compounds close ATP-sensitive K^+ channels (Table 4.3) or otherwise promote insulin secretion (Table 8.3), inhibit α -glycosidases and other digestive glycohydrolases (Table 13.1) or interact with insulin signalling pathway components downstream from the insulin receptor kinase (Table 8.3). The latest therapies for diabetic complications include angiotensin converting enzyme (ACE) inhibitors, the antioxidant and PKC β inhibitor vitamin E and the aldehyde scavenging compound aminoguanidine (Table 14.6).

A wide range of other systems described in the previous chapters impact on insulin-regulated glucose homeostasis. Thus, a ligand-modulated ion channel (Chapter 3) regulates insulin secretion signalled by elevated blood glucose; Na^+ gradient-driven intestinal glucose uptake (Chapter 4) ultimately signals synthesis of the insulin secretagogue GLP-1; GLP-1 acts via a GPCR (Chapter 5) to stimulate insulin secretion and to exert its anorexigenic effect via cAMP as a second messenger (Chapter 7); the second messengers cAMP and Ca^{2+} (Chapter 7) act via second messenger-regulated PKs to regulate catabolic/anabolic balance together with the insulin signalling system (Chapter 8) and hormones such as thyroxine and corticosteroids operating through cytosolic hormone receptors (Chapter 11) regulate

metabolism (Chapter 13); gene expression (Chapter 9) and proteolysis (Chapter 13) modulate levels of key catabolic/anabolic enzymes, and apoptosis and cell division determine the complement of hormone-producing cells; diet is regulated by elements such as anorexigenic/orexigenic hormones (Chapters 5 and 8), taste and odour (Chapter 10) and other perceptions integrated by neurotransmission (Chapters 3–8); autoimmune damage in diabetes involves a variety of signalling molecules variously involving GPCRs (Chapter 5) or RTKs (Chapter 8).

The example of insulin-dependent glucose homeostasis illustrates the connectedness of the signalling systems involved. Further, nearly all of the plant defensive compounds described here interact with these signalling systems. Accordingly many such compounds may have synergistic effects on physiological processes such as blood glucose balance. Accordingly, the warning on herbal medicinal use presented in the Foreword, must certainly be repeated with diabetes as an example. Diabetes requires careful medical management involving continuous monitoring, exercise, diet and thoroughly validated medications and accordingly herbal medicines should only be used by diabetics on the advice of specialist doctors.

14.8 Summary

In general, the information summarized in this book indicates a basis for further research and development to establish safe and effective pharmaceuticals based on the bioactivities of plant defensive compounds. Knowledge of biochemical sites of interaction of bioactive medicinal plant constituents provides a basis for understanding herbal medicinal efficacy and for quality control of such herbal preparations. However, the overwhelming targeting of signal-responsive systems by plant defensive compounds, multiple sites of action and the connectedness of signalling pathways indicate the likelihood of pleiotropic effects (or multiple consequences) of administration of such agents. Any plant will contain a multiplicity of defensive compounds and the present analysis clearly indicates a basis for synergistic effects in herbal medicine action.

This book summarizes current knowledge of the molecular basis of our interaction with plant defensive components that represents a major aspect of our dance with nature. However, knowledge must be used responsibly and has intrinsic dangers as illustrated in the ancient Greek myth of Pandora's box and as more recently explored in *The Magic Mountain* by Thomas Mann. Herbal medicine still represents a major therapeutic resort for a large part of humanity but the potential for deleterious effects of plant bioactive compounds means that expert medical advice should be sought before use of herbal extracts for medical conditions.

Table 14.1 Plant lipoxygenase and cyclooxygenase inhibitors

<i>Compound (class)</i>	<i>Plant source (family)</i>	<i>Targets (other targets) / in vivo effects/</i>
Alkaloids		14.1Aa
Berberine (protoberberine isoquinoline)	<i>Berberis vulgaris</i> , <i>Mahonia aquifolium</i> (Berberidaceae), <i>Coptis chinensis</i> , <i>C. spp.</i> (Ranunculaceae)	5-LOX
Budmunchiamine X1 (macrocyclic pithecolobine alkaloid)	<i>Albizia amara</i> (Fabaceae)	COX [cytotoxic, PAI]
Chelerythrine (benzophenanthridine)	<i>Bocconia arborea</i> , <i>Chelidonium majus</i> (Papaveraceae) [root]	5-LOX, 12-LOX (V-R ligand, CaMPK, PKA, PKC, TPK)

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Columbamine (protoberberine isoquinoline)	<i>Berberis vulgaris</i> , <i>Mahonia aquifolium</i> (Berberidaceae)	5-LOX
Corytuberine (aporphine isoquinoline)	<i>Mahonia aquifolium</i> (Berberidaceae), <i>Corydalis</i> spp. (Papaveraceae)	5-LOX
Cryogenine (alkaloid)	<i>Decodon verticillatus</i> , <i>Heimia salicifolia</i> , <i>H. myrtifolia</i> , <i>Lagerstroemia fauriei</i> (Lythraceae)	COX (PGS) [AI]
Girinimbine (carbazole indole alkaloid)	<i>Murraya euchrestifolia</i> (Rutaceae) [leaf]	COX (PGS) [PGS I i.e. TxB2, PGD2, PGE2 synthesis; ↑ cAMP, PAI]
Magnoflorine (aporphine isoquinoline)	<i>Berberis vulgaris</i> , <i>Mahonia aquifolium</i> (Berberidaceae)	5-LOX
[4-(Methylnitrosamino)-1-(3-pyridyl-1-butanone)] [nicotine-derived pyridine alkaloid in tobacco smoke]	<i>Nicotiana tabacum</i> (Solanaceae) [tobacco leaf smoke nicotine derivative]	[Induces COX-1 & activates NFκB; tumorigenic]
Nesodine (alkaloid)	<i>Heimia salicifolia</i> (Lythraceae)	COX (PGS)
Oxyberberine (protoberberine isoquinoline)	<i>Mahonia aquifolium</i> (Berberidaceae), <i>Coptis</i> spp. (Ranunculaceae)	5-LOX
Rutaecarpine [= Rutecarpine; Rhetine] (indole alkaloid)	<i>Evodia rutaecarpa</i> , <i>Hortia arborea</i> (Rutaceae) [fruit]	COX-2 [AI]
Sanguinarine (= Pseudochelerythrine) (benzophenanthridine)	<i>Papaver somniferum</i> , <i>Dicentra spectabilis</i> , <i>D. peregrina</i> , <i>Chelidonium majus</i> , <i>Sanguinaria canadensis</i> (Papaveraceae), <i>Fumaria officinalis</i> (Fumariaceae), <i>Zanthoxylum</i> spp. (Rutaceae), <i>Pteridophyllum</i> spp. (Sapindaceae)	5-LOX, 12-LOX (V-R, ATPase, Diamine oxidase CDPK, MLCK, PKA, PKC) [antibacterial, AI]
Tryptanthrine (= Couroupitine A) (quinazoline)	<i>Strobilanthes cusia</i> (Acanthaceae), <i>Isatis tinctoria</i> (woad) (Brassicaceae), <i>Couroupita guaianensis</i> (Lecithidaceae), <i>Polygonum tinctorum</i> (Polygonaceae); woad yielded the blue dye and body paint of the ancient Britons such as Boadicea (Boudicca)	COX-2 (2) (ARH-R) [↓ iNOS expression; inhibits NO & PGE2 production]
Phenolics		14.1Ap
Acacetin (= Apigenin 4'-methyl ether) (flavone)	<i>Buddleja officinalis</i> , <i>B.</i> spp. (Buddlejaceae)[flower], some Betulaceae [leaf bud surface], some Asteraceae [leaf surface], <i>Agastache foeniculum</i> (Lamiaceae)	COX [inhibits histamine release, AI, allergen]
1-(3'-Acetoxy-4'-methoxyphenyl)-7-phenyl-3-heptanone) (phenyl propanoid, aryl heptanoid)	<i>Alpinia oxyphylla</i> (Zingiberaceae) [rhizome]	COX (0.5), 5-LOX (0.4)

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
[6]-Acetylgingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (2)
Acteoside (= Verbascoside; Kusagin)in (phenylpropanoid glycoside)	<i>Stachys sieboldii</i> (Lamiaceae), <i>Buddleja globosa</i> , <i>B. officinalis</i> , <i>Forsythia</i> sp. (Oleraceae), <i>Monochasma savatieri</i> , <i>Verbascum sinuatum</i> (Scrophulariaceae), <i>Lippia dulcis</i> (Verbenaceae); Gesneriaceae, Oronbranchaccae, Acanthaceae, Bignonaceae, Plantaginaceae	5-LOX (AR) [AI, antihepatotoxic, bitter]
Alphitol (= 3,5-Dihydroxy-4- methoxyphenethyl alcohol) (phenolic)	<i>Alphitonia zizyphoides</i> (Rhamnaceae) [bark]	COX
Amentoflavone (= 3',8"- Biapigenin) (biflavone)	<i>Rhus succedanea</i> (Anacardiaceae), <i>Viburnum prunifolium</i> (Caprifoliaceae), <i>Cycas</i> <i>revoluta</i> (Cycadaceae), <i>Ginkgo biloba</i> (Ginkgoaceae), <i>Podocarpus montanus</i> (Podocarpaceae)	COX
Anacardic acids (6-alkyl phenols)	<i>Anacardium occidentale</i> (cashew) (Anacardiaceae) [nut], <i>Ginkgo</i> <i>biloba</i> (Ginkgoaceae)	COX (PGS) [antitumour, dermatitic]
C22-Anacardic acid (6-alkyl phenol)	<i>Pelargonium xhortorum</i> (Geraniaceae) [trichome]	COX (PGS), potato LOX
C22:0-Anacardic acid (6-alkyl phenol)	<i>Pelargonium xhortorum</i> (geranium) (Geraniaceae) [trichome]	COX (PGS), potato LOX
C22:1 ω 5-Anacardic acid (6-alkyl phenol)	<i>Pelargonium xhortorum</i> (Geraniaceae) [trichome]	COX (PGS) (27), potato LOX (6)
Apigenin (= 5,7,4'- Trihydroxyflavone) (flavone)	<i>Apium graveolens</i> (Apiaceae), <i>Ocimum sanctum</i> (basil), Lamiaceae, ferns [leaf surface]; glycosides widespread e.g. <i>Apium</i> <i>graveolens</i> , <i>Petroselinum</i> (Apiaceae), <i>Cosmos bipinnatus</i> , <i>Erigeron annuus</i> <i>Dahlia variabilis</i> (Asteraceae), <i>Amorpha fruticosa</i> (Fabaceae)	COX-1 (< 1000), COX-2 (ADH, HIV-1 PR, PGP TR, PK, RTK) [blocks COX-2 & iNOS induction per I κ B kinase inhibition; antibacterial, AI, diuretic, hypotensive, <i>Rhizobium</i> nodulation stimulant]
Ardisiaquinone A (quinone)	<i>Ardisia sieboldii</i> (Myrsinaceae) [wood]	5-LOX
Atractylochromene (chromene)	<i>Atractylodes lancea</i> (Asteraceae) [rhizome]	COX-1, 5-LOX
Astringenin (stilbene)	<i>Picea abies</i> , <i>P. sylvestris</i> (Pinaceae)	COX (PGS)
Baicalein (= 5,6,7- Trihydroxyflavone) (flavone)	<i>Scutellaria baicalensis</i> , <i>S.</i> spp. (Lamiaceae), <i>Plantago major</i> (Plantaginaceae); glycosides in <i>S. galericulata</i> (Lamiaceae), <i>Oroxylum indicum</i> (Bignonaceae) [leaf]	12-LOX (BZ-R, CK-R, glyoxalase I, PAR) [AI]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Brevifolin (= Phloracetophenone 4, 6-dimethyl ether; Xanthoxylin) (phenolic ketone)	<i>Pancreatium biflorum</i> (Amaryllidaceae), <i>Artemisia brevifolia</i> (Asteraceae), <i>Hippomane mancinella</i> , <i>Sebastiana schottiana</i> , <i>Sapium sebiferum</i> (Euphorbiaceae), <i>Geranium thunbergii</i> (Geraniaceae), <i>Xanthoxylum piperitum</i> , <i>X. alatum</i> (Rutaceae)	COX (PGS), 5-LOX
Brousoaurone A (aurone)	<i>Broussonetia papyrifera</i> (Moraceae)	COX [PAI (AA induced PA)]
Brousochalcone (chalcone)	<i>Broussonetia papyrifera</i> (Moraceae)	COX [PAI (AA induced PA)]
Brousoflavonol F (flavonol)	<i>Broussonetia papyrifera</i> (Moraceae)	COX [PAI (AA induced PA)]
Caffeic acid (3,4-Dihydroxycinnamic acid) (phenylpropanoid)	<i>Conium</i> (Apiaceae), <i>Artemisia</i> , <i>Taraxacum</i> , <i>Anthemis</i> , <i>Achillea</i> (Asteraceae), <i>Ipomoea purga</i> (Convolvulaceae), <i>Olea</i> (Oleaceae), <i>Papaver</i> (Papaveraceae), <i>Coffea</i> , <i>Cinchona</i> (Rubiaceae), <i>Digitalis</i> (Scrophulariaceae) spp.	5-LOX, 12-LOX (eEF-2, XO)[AI, PAI, 5-LOX & LTB ₄ generation inhibited (weak)]
Caffeic acid phenethyl ester (phenylpropanoid)	<i>Populus</i> sp. (Salicaceae), bee propolis	5-LOX (AO/FRS, HIV-1 INT) [antioxidant]
3-Caffeoyl-4-sinapoylquinic acid (phenylpropanoid)	<i>Gardenia fructus</i> (Rubiaceae)	LOX
(+)-Catechin (flavan-3-ol)	Widespread; <i>Agrimonia eupatoria</i> (Rosaceae), <i>Salix cuprea</i> (Salicaceae) [flower]	COX-1, COX-2
Centaureidin (flavonoid)	<i>Tanacetum microphyllum</i> (Asteraceae)	SLOX, COX
Cirsilineol (flavone)	<i>Artemisia dracunculus</i> (Asteraceae), Asteraceae; <i>Ocimum sanctum</i> (basil) [leaf, stem], <i>Thymus vulgaris</i> (thyme), <i>Salvia tomentosa</i> , <i>Sideritis</i> spp. (Lamiaceae) [leaf surface]	COX-1, COX-2 [AI]
Cirsiliol (= 5,3',4'-Trihydroxy-6,7-dimethoxyflavone) (flavone)	<i>Cirsium lineare</i> , other spp. (Asteraceae), <i>Salvia officinalis</i> (sage), <i>Sideritis</i> spp. (Lamiaceae) [aerial]	5-LOX, 12-LOX (AR)
Cirsimaritin (flavone)	<i>Ocimum sanctum</i> (Lamiaceae) [leaf, stem]	COX-1, COX-2 [AI]
Coniferyl aldehyde (= Ferulaldehyde) (phenylpropanoid)	<i>Acer saccharum</i> (Aceraceae), <i>Eleutherococcus senticosus</i> (Araliaceae), <i>Senra incana</i> (Bombacaceae), <i>Quercus</i> spp. (Fagaceae), <i>Juglans cinerea</i> (Juglandaceae)	COX (PGS)

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Curcumin (phenylpropanoid)	<i>Curcuma longa</i> , <i>C. aromatica</i> , <i>C. xanthorrhiza</i> (turmeric), <i>Zingiber officinale</i> (Zingiberaceae) [root]	COX, LOX [AI, cytotoxic, inhibits Ca ²⁺ , PAF- & AA- but not PMA-induced PA; inhibits AA-induced oedema]
Cycloheterophyllin (prenylflavone)	<i>Artocarpus heterophyllus</i> (Moraceae)	COX [APA (AA-induced), PKC]
Daidzein (isoflavone)	<i>Glycine max</i> , <i>Trifolium repens</i> (clover), <i>Ulex europaeus</i> (gorse) (Fabaceae) [leaf]	COX [antifungal]
4'-Demethyleupatilin (flavone)	<i>Artemisia rubripes</i> (Asteraceae)	5-LOX
[6]-Dehydrogingerdione (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (1)
[10]-Dehydrogingerdione (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (1)
Dehydroperiloxin (prenyl 3-benzoxepin)	<i>Perilla frutescens</i> (Lamiaceae)	COX-1
[6]-Diacetylgingerol (phenylpropanol diester)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (3)
[2',5'-Dihydroxychalcone] (chalcone)	Semi-synthetic	COX [AI]
5,3'-Dihydroxy-4'-methoxy- 7-carbomethoxyflavonol (flavonol)	<i>Tanacetum microphyllum</i> (Asteraceae)	SLOX, COX
[5,7-Dihydroxy-4- methylcoumarin] (coumarin)	Semi-synthetic	COX [free radical scavenger]
2-(3,4-Dihydroxyphenyl)- ethanol (phenolic)	<i>Olea europaea</i> (olive) (Oleaceae)	5-LOX (13), 12-LOX (4)
2',6'-Dimethoxy-4'- hydroxyacetophenone (phenolic ketone)	<i>Pancreatum biflorum</i> (Amaryllidaceae) [bulb]	COX (PGS), 5-LOX
2,6-Dimethoxyphenol (phenol)	<i>Mucuna birdwoodiana</i> (Fabaceae)	COX (PGS) [PAI]
1-(3',4'-Dimethoxyphenyl)- 7-phenyl-3-heptanone) (phenyl propanoid, aryl heptanoid)	<i>Alpinia oxyphylla</i> (Zingiberaceae) [rhizome]	COX (> 100)
(-)-Epiafzelechin (flavan-3-ol)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial], <i>Camellia sinensis</i> (Theaceae) [leaf]	COX-1 (ATP K ⁺ CH, α 1A-R, α 2A-R, β A-R, D2-R, O-R) [AI with carrageenin-induced paw oedema]
(-)-Epigallocatechin-3- gallate (= EGCG) (flavan-3-ol)	<i>Davidsonia pruriens</i> (Davidsoniaceae), <i>Hamamelis virginiana</i> (Hamamelidaceae), <i>Camellia sinensis</i> (Theaceae)	[AI, blocks COX-2 & iNOS induction]
Esculetin (= 6,7- Dihydroxycoumarin; Aesculetin; Cichorigenin; Esculetol) (coumarin)	<i>Euphorbia lathyris</i> (Euphorbiaceae) [seed], <i>Arachis hypogaea</i> (Fabaceae), <i>Aesculus turbinate</i> (Hippocastanaceae) [wood], <i>Fraxinus</i> spp. (Oleaceae) [bark]	LOX [antibacterial, antifungal]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
[Esculin (= Esculetin glycoside; Aesculin; Crataegin; Polychrom; Esculoside; Bicolorin) (coumarin glycoside)]	Glycoside of Esculetin <i>ex</i> <i>Euphorbia lathyris</i> (Euphorbiaceae), <i>Aesculus hippocastanum</i> (Hippocastanaceae), <i>Fraxinus</i> spp. (Oleaceae), <i>Crataegus oxyacantha</i> (Rosaceae), <i>Bursaria spinosa</i> (Pittosporaceae)	Aglycone esculetin inhibits LOX [antibacterial]
Eugenol (= Allylguaiacol; Caryophyllic acid; Eugenenic acid) (phenylpropanoid)	<i>Achillea</i> , <i>Artemisia</i> (Asteraceae), <i>Ocimum</i> , <i>Origanum</i> (Lamiaceae), <i>Cinnamomum</i> , <i>Sassafras</i> (Lauraceae), <i>Myristica</i> (Myristicaceae), <i>Eugenia</i> , <i>Pimentum</i> , <i>Syzygium</i> (Myrtaceae), <i>Piper</i> (Piperaceae), <i>Rosa</i> (Rosaceae), <i>Camellia</i> (Theaceae) spp.	COX-1 (9), COX-2 (OD-R, TYR) [antioxidant, AI, PAI]
Eupatilin (flavone)	<i>Artemisia rubripes</i> , <i>Eupatorium semiserratum</i> , <i>Tanacetum vulgare</i> (Asteraceae), <i>Citrus reticulata</i> (Rutaceae), <i>Sideritis tomentosa</i> (Lamiaceae)	5-LOX
<i>N-cis</i> -Feruloyltyramine (phenolic acid amide)	<i>Ipomoeae aquatica</i> (Convolvulaceae)	COX
<i>N-trans</i> -Feruloyltyramine (phenolic acid amide)	<i>Ipomoeae aquatica</i> (Convolvulaceae)	COX
Fisetin (flavonol)	<i>Acacia catechu</i> , <i>Trigonella</i> spp., many spp. (Fabaceae)	5-LOX [blocks basophil histamine release]
Flavone (= 2-Phenyl-1,4-benzopyrone) (flavone)	<i>Ammi visnaga</i> , <i>Anethum graveolens</i> (Apiaceae), <i>Dionysia</i> spp., <i>Primula malacoides</i> , <i>P. pulverulenta</i> (Primulaceae) [leaf], <i>Pimelea decora</i> , <i>P. simplex</i> (Thymelaeaceae)	COX, 5-LOX, ECMOX (AD-R) [AI, PAI, inhibits basophil histamine release]
Forsythiaside (= Forsythoside A) (phenylpropanoid)	<i>Forsythia suspensa</i> , <i>F. koreana</i> (Oleraceae) [fruit]	5-LOX
Fraxetin (= 7,8-Dihydroxy-6-methoxycoumarin) (coumarin)	<i>Aesculus turbinata</i> , <i>A. hippocastanum</i> (Hippocastanaceae), <i>Lawsonia inermis</i> (Lythraceae), <i>Fraxinus</i> spp. (Oleaceae), <i>Vestia lycioides</i> (Solanaceae)	5-LOX
Galangin (= 3,5,7-Trihydroxyflavone) (flavonol)	Betulaceae, Salicaceae, ferns, Lamiaceae, <i>Datisca cannabina</i> (Datisceae), <i>Escallonia</i> spp. (Saxifragaceae), <i>Alpinia officinarum</i> (Zingiberaceae)	COX (ADH, cAMP PDE) [antibacterial]
(+)-Galocatechin (hydrolysable tannin)	<i>Gossypium</i> sp. (Malvaceae), <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	COX-1, COX-2
Genistein (= Genisteol; Prunetol; Sophoricol) (isoflavone)	<i>Genista</i> spp. (broom), <i>Trifolium brachycalycinum</i> , T. spp. (clover) (Fabaceae), <i>Prunus</i> spp. (plum) (Rosaceae) [wood]	COX-1 [blocks COX-2 & iNOS induction; antifungal, oestrogenic]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
[6]-Gingerdiacetate (phenylpropanol diester)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (2)
[6]-Gingerdione (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (2)
[10]-Gingerdione (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (2)
[2]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	5-LOX (> 10) (OD-R)
[4]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (> 100), 5-LOX (> 10) (OD-R)
[6]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (5–6), 5-LOX (3) (OD-R, VAN-R)
[8]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (5), 5-LOX (OD-R) (0.4)
[10]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (2–3), 5-LOX (OD-R) (53 nM)
[12]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (4), 5-LOX (OD-R) (46 nM)
[14]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (6), 5-LOX (OD-R) (42 nM)
[16]-Gingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (9), 5-LOX (OD-R) (55 nM)
Ginkgetin (Amentoflavone 7,4'-dimethyl ether) (biflavone)	<i>Zamia angustifolia</i> (cycad) (Cycadaceae), <i>Ginkgo biloba</i> (ginkgo) (Ginkgoaceae), <i>Taxus</i> spp. (yew) (Taxaceae)	COX (weak)
Ginkgol (= (15:1)-Cardanol; 3-(Pentadec-8-enyl) phenol) (phenol)	<i>Schinus terebinthifolius</i> (pink pepper) (Anacardiaceae), <i>Ginkgo</i> <i>biloba</i> (Ginkgoaceae)	COX, 5-LOX
Ginkgoic acid (= 2-Hydroxy- 5-pentadec-8-enyl) benzoic acid) (phenol)	<i>Anacardium occidentale</i> (Anacardiaceae), <i>Ginkgo biloba</i> (ginkgo) (Ginkgoaceae)	COX
Glabridin (isoflavan)	<i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root]	COX
Gossypetin (= 8- Hydroxyquercetin) (flavonol)	<i>Gossypium indicum</i> (cotton), <i>Hibiscus</i> spp. (Malvaceae) [flower]	12-LOX [antibacterial]
Gossypin (= Gossypetin 8- O-glucoside (flavonol O-glycoside)	<i>Gossypium indicum</i> (cotton), <i>Hibiscus vitifolius</i> (Malvaceae) [flower]	12-LOX [AI]
Grevillol (= 1,3-Dihydroxy- 5-tridecylbenzene) (phenol)	<i>Grevillea robusta</i> , <i>G.</i> spp. (Proteaceae)	5-LOX [irritant]
Guaiacol (= 2- Methoxyphenol) phenol)	<i>Apium graveolens</i> (celery) (Apiaceae), <i>Betula</i> sp. (beech) (Betulaceae) [resin], <i>Micromeria</i> <i>juliana</i> (Lamiaceae), <i>Guaicum</i> sp. (Zygophyllaceae)	COX (PGS), SLOX [inhibits AA-induced PA]
Hellicoside (phenylpropanoid glycoside)	<i>Plantago asiatica</i> (Plantaginaceae)	5-LOX (cAMP PDE) [AI, anti-asthmatic]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Hexahydrocurcumin (dimeric phenylpropanoid)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (23), 5-LOX (OD-R) (3)
Hibifolin (flavonoid)	Medicinal herbs	12-LOX
Hirsutanolol (= 5 <i>S</i> -1,7-Bis-(3,4-dihydroxyphenyl)-5-hydroxyheptane-3-one (diarylheptanoid)	<i>Alnus hirsuta</i> (alder) (Betulaceae) [bark]	[inhibits TPA-induced COX-2 expression]
2'-Hydroxychalcone (chalcone)	<i>Dracaena cinnabari</i> (Agavaceae)	COX (CYP)
3-Hydroxy-1-phenyl-7-(3''-methoxy-4''-hydroxyphenyl)heptane (phenylpropane ketone)	<i>Alpinia officinarum</i> (Zingiberaceae) [rhizome]	5-LOX (0.2)
5-Hydroxy-1-(3',4'-dihydroxyphenyl)-7-phenyl-3-heptanone (phenylpropane ketone)	<i>Alpinia officinarum</i> (Zingiberaceae) [rhizome]	5-LOX (18 nM)
6-Hydroxy-2-(2-hydroxy-4-methoxyphenyl)benzofuran (isoflavone)	<i>Dalbergia odorifera</i> (Fabaceae) [wood]	5-LOX
5-Hydroxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenyl-3,5-heptadione (phenylpropane ketone)	<i>Alpinia officinarum</i> (Zingiberaceae) [rhizome]	COX (PGS) (2)
5-Hydroxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenyl-3-heptanone (phenylpropane ketone)	<i>Alpinia officinarum</i> (Zingiberaceae) [rhizome]	COX (PGS) (4), 5-LOX (2)
5-Hydroxy-7-(4''-hydroxyphenyl)-1-(3',4'-dihydroxyphenyl)-3-heptanone (phenylpropane ketone)	<i>Alpinia officinarum</i> (Zingiberaceae) [rhizome]	5-LOX (0.3)
5-Hydroxy-7-(4''-hydroxyphenyl)-1-phenyl-3-heptanone (phenylpropane ketone)	<i>Alpinia officinarum</i> (Zingiberaceae) [rhizome]	COX (PGS) (19)
1-[8-Hydroxy-2-methyl, 2-(4-methylpent-3-enyl) chromene], 3-[2,4-dihydroxyphenyl]-propane-3-one (= AC-3-1) (chromene)	<i>Artocarpus communis</i> (breadfruit) (Moraceae) [flower]	5-LOX [AI (AA-induced ear oedema)]
Hydroxyobtustystyrene (cinnamylphenol)	<i>Dalbergia odorifera</i> (Fabaceae)	COX (PGS)
3-Hydroxy-1-phenyl-7-(3''-methoxy-4''-hydroxyphenyl)heptane (phenylpropane ketone)	<i>Alpinia officinarum</i> (Zingiberaceae) [rhizome]	5-LOX (0.2)
2-Hydroxy-4,4,7-trimethylnaphthaleneone (naphthalene phenolic)	<i>Ipomoea pes-caprae</i> (Convolvulaceae)	COX (PGS) (230)

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Hydroxytyrosol (= 2-(3,4-Dihydroxyphenyl)-ethanol (catechol))	<i>Olea europaea</i> (Oleaceae) [olive oil]	5-LOX (13), 12-LOX (4) (AO/FRS) [5-LOX & LTB ₄ generation inhibited]
Hypolaetin (= 8-Hydroxyluteolin) (flavone)	<i>Sideritis</i> sp. (Lamiaceae), <i>Hypolaena fastigiata</i> (Restionaceae)	COX, 5-LOX, 12-LOX [AI]
Hypolaetin-8-O-β-D-glucoside (flavone glycoside)	<i>Sideritis</i> spp. (Lamiaceae)	COX, 5-LOX (weak), 12-LOX (aglycone more potent) [AI]
(+)-Isoduartin (isoflavan)	<i>Dalbergia odorifera</i> (Fabaceae)	COX (PGS)
Isoliquiritigenin (= 2',4',4-Trihydroxychalcone) (chalcone)	<i>Glycyrrhiza glabra</i> (Fabaceae); as glycoside in <i>Dahlia variabilis</i> (Asteraceae) [flower], <i>Glycyrrhiza glabra</i> (Fabaceae) [root, rhizome]	COX, 5-LOX (AROM, uncoupler) [PAI, yellow]
[Isoliquiritigenin 4-glucoside (chalcone glycoside)]	Precursor of Isoliquiritigenin in <i>Glycyrrhiza glabra</i> (Fabaceae) [root, rhizome]	[Isoliquiritigenin inhibits COX, 5-LOX, PA]
[Isoliquiritigenin 4'-glucoside (chalcone glycoside)]	Precursor of Isoliquiritigenin in <i>Dahlia variabilis</i> (Asteraceae)	[Isoliquiritigenin inhibits COX, 5-LOX, PA]
[Isoliquiritigenin 4'-diglucoside] (chalcone glycoside)	Precursor of Isoliquiritigenin in <i>Dahlia variabilis</i> (Asteraceae)	[Isoliquiritigenin inhibits COX, 5-LOX, PA]
Isomucronostyrene (cinnamylphenol)	<i>Dalbergia odorifera</i> (Fabaceae)	COX (PGS)
Isorhapontigenin (stilbene)	<i>Picea abies</i> , <i>P. sylvestris</i> (Pinaceae)	COX (PGS)
Isothymonin (flavone)	<i>Ocimum sanctum</i> (basil), <i>Thymus vulgaris</i> (Lamiaceae) [leaf, stem]	COX-1, COX-2 [AI]
Isothymusin (flavone)	<i>Ocimum sanctum</i> (basil) (Lamiaceae) [leaf, stem]	[AI]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread; <i>Azadirachta indica</i> (Meliaceae), Hippocastanaceae [aerial], Fabaceae [wood, leaf]; <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice]	COX-1, 5-LOX (CYP; 17βHSD) [blocks COX-2 & iNOS induction; AI, antibacterial, mutagenic, radical scavenger]
(+)-Kavain (= Kawain; Gonosan) (4-methoxy-α-pyrone)	<i>Piper methysticum</i> (kava) (Piperaceae) [rhizome, root]	COX [AI, inhibits AA-induced PA, anaesthetic]
Kazinol B (phenolic extract)	<i>Broussonetia kazinoki</i> , <i>B. papyrifera</i> (paper mulberry) (Moraceae)	COX [PA (AA-induced)]
Kuwanon G (flavone)	<i>Morus alba</i> (mulberry) (Moraceae) [root bark]	COX (at 100–1000) [hypotensive]
Kuwanon H (flavone)	<i>Morus alba</i> (mulberry) (Moraceae) [root bark]	COX (at 100–1000) [hypotensive]
Leucocyanidol (flavone)	<i>Euphorbia hirta</i> (Euphorbiaceae), <i>Gossypium</i> spp. (cotton) (Malvaceae)	12-LOX [AI]
Magnolol (lignan)	<i>Magnolia officinalis</i> (Magnoliaceae) [bark], <i>Sassafras randaianse</i> (Lauraceae) [root]	COX, LOX [AI]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Marchantin H (macrocyclic bis(benzyl) phenolic)	<i>Marchantia</i> sp. (liverwort) (Marchantiaceae)	5-LOX (AO/FRS)
(-)-Medicarpin (= Demethylhomopterocarpin) (pterocarpan)	<i>Dalbergia odorifera</i> , <i>D. variabilis</i> , <i>Andira inermis</i> [wood], <i>Lathyrus</i> spp., <i>Medicago</i> spp., <i>Trifolium</i> <i>pratense</i> , <i>T.</i> spp., <i>Trigonella</i> spp., <i>Vicia faba</i> (Fabaceae)	5-LOX [antifungal]
(-)-Mellein (phenolic lactone)	<i>Ipomoea pes-caprae</i> (Convolvulaceae)	COX (PGS) (340)
5-Methoxy-7-(4''-hydroxy-3''-methoxyphenyl)-1-phenyl-3-heptanone (phenylpropane ketone)	<i>Alpinia officinarum</i> (Zingiberaceae) [rhizome]	COX (PGS) (2)
(2 <i>S</i>)-5-Methoxy-6-methylflavan-7-ol (flavanol)	<i>Draconis resina</i> (Palmaceae)	COX
(<i>S</i>)-(+)-7-Methoxy- α -methyl-2-naphthaleneacetic acid (= 7-methoxy isomer of Naproxene) (phenolic)	<i>Musa acuminata</i> (Musaceae)	COX-2
4-Methyl-daphnetin (= 7,8-Dihydroxy-4-methyl-coumarin) (coumarin)	Thymelaeaceae	5-LOX [free radical scavenger]
4'- <i>O</i> -Methyl- <i>ent</i> -gallo catechin (tannin flavanol)	<i>Panda oleosa</i> (Pandaceae)	COX-1, COX-2
[6]-Methylgingerol (phenylpropane ketone)	<i>Zingiber officinale</i> (ginger) (Zingiberaceae) [root]	COX (PGS) (110)
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Morus alba</i> , <i>M.</i> spp., <i>Chlorophora tinctoria</i> , <i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> (Moraceae)	5-LOX (HIV-1 PR) [antiviral, antibacterial, allergenic, feeding attractant]
Mulberrofuran G (benzofuran)	<i>Morus alba</i> (mulberry) (Moraceae) [root bark]	LOX (at 10) [hypotensive]
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soyimida febrifuga</i> (Meliaceae) [wood], <i>Haplopappus canescens</i> (Asteraceae) [aerial]	5-LOX [antibacterial, AI]
Myrigalone A (dihydrochalcone)	<i>Myrica gale</i> (Myricaceae) [fruit]	SLOX
Myrigalone B (dihydrochalcone)	<i>Myrica gale</i> (Myricaceae) [fruit]	SLOX
Naproxene (= (<i>S</i>)-(+)-6-Methoxy- α -methyl-2-naphthaleneacetic acid) (naphthalene)	<i>Musa acuminata</i> (banana) (Musaceae)	COX-1, COX-2 [AI]
Nobiletin (= 5,6,7,8,3',4'-Hexamethoxyflavone) (flavone)	<i>Citrus aurantium</i> , <i>C. depressa</i> , <i>C. unshiu</i> (Rutaceae)	[inhibits COX-2, iNOS & proMMP- 1, 3 & 9 induction, AI]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Nordihydroguaiaretic acid (= Masoprocol) (lignan)	<i>Larrea tridentata</i> , <i>L.</i> spp., <i>Guaiacum sanctum</i> , <i>G. officinale</i> (Zygophyllaceae) [resin]	5-LOX (2), 12-LOX, SLOX [antitumour, antibacterial, antifungal, source resin anti- rheumatic] [inhibits AA-induced PA]
Ocobullenone (neolignan)	<i>Ocotea bullata</i> (Lauraceae) [stem bark]	5-LOX
(-)-Odoricarpan (pterocarpan)	<i>Dalbergia odorifera</i> (Fabaceae)	COX (PGS)
Odoriflavene (isoflavene)	<i>Dalbergia odorifera</i> (Fabaceae)	COX (PGS)
Oleuropein (phenolic)	<i>Ligustrum japonicum</i> , <i>Olea europaea</i> (Oleaceae) [olive oil]	[5-LOX, AO/FRS]
Oligomeric proanthocyanidin complexes (condensed tannins)	Widespread (fruit, vegetables, nuts, seeds)	COX, LOX [AI, antioxidant]
Oregonin = (5 <i>S</i>)-1,7-Bis- (3,4-Dihydroxyphenyl)- heptane-3-one-5- <i>O</i> -β-D- xylopyranoside (diarylheptanoid glycoside)	<i>Alnus hirsuta</i> (alder) (Betulaceae) [bark]	[inhibits TPA-induced COX-2 expression]
Oroxylin A (flavone)	<i>Scutellaria baicalensis</i> (Lamiaceae) [root]	12-LOX (CBZ-R, CYP) [AI]
Osthol (= 8-(3-Methyl-2- butenyl) herniarin; 7- Methoxy-8-[3-methyl- pent-2-enyl] coumarin)) (methylated prenyl coumarin)	<i>Atractylodes lancea</i> (Asteraceae), <i>Peucedanum ostruthium</i> , <i>Angelica</i> <i>archangelica</i> , <i>A. pubescens</i> , <i>Prangos pabularia</i> (Apiaceae) [root, rhizome], <i>Flindersia</i> <i>bennettiana</i> , <i>F.</i> spp., <i>Citrus</i> , <i>Clausenia</i> , <i>Cneoridium</i> , <i>Haplophyllum</i> spp. (Rutaceae) [aerial]	5-LOX
Osthenol (coumarin)	<i>Angelica pubescens</i> [root], <i>A. sinensis</i> (Dong Gui) [root], <i>Apium graveolens</i> (celery) [seed], <i>Foeniculum vulgare</i> (Apiaceae)	5-LOX, COX-1
Ouratea-catechin (flavanol)	<i>Syzygium</i> spp. (Myrtaceae)	COX-1, COX-2
Ouratea-proanthocyanidin A (flavanol)	<i>Syzygium</i> spp. (Myrtaceae)	COX-1, COX-2
[8]-Paradol (vanilloid phenolic)	<i>Zingiber officinale</i> (ginger) [rhizome] (Zingiberaceae)	COX-2 [apoptotic, chemopreventive]
Pedalitin (flavone)	<i>Sullivantia</i> spp. (Saxifragaceae), <i>Frullania</i> spp. (Hepaticae), <i>Sesamum indicum</i> (Pedaliaceae) [leaf]	5-LOX
Perilloxin (prenyl 3-benzoxepin)	<i>Perilla frutescens</i> (Lamiaceae)	COX-1
Phenethyl ferulate (phenylpropanoid)	<i>Notopterygium incisum</i> (root = Qianghuo) (Apiaceae)	COX
1-Phenyl-7-(3'-methoxy- 4"-hydroxyphenyl)-3- heptanone) (phenyl propanoid, aryl heptanoid)	<i>Alpinia oxyphylla</i> (Zingiberaceae) [rhizome]	5-LOX (0.2)

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Piceid (= 3,4',5-Trihydroxystilbene-3-O-glucoside) (stilbene)	<i>Polygonum cuspidatum</i> (Polygonaceae) [root]	COX, LOX
Pinosylvin (stilbene)	<i>Alnus sieboldiana</i> (Betulaceae), <i>Dalbergia sisso</i> (Fabaceae), <i>Nothofagus</i> spp. (Fagaceae), <i>Picea abies</i> , <i>Pinus sylvestris</i> , <i>P.</i> spp. (Pinaceae)	COX (PGS)
Pinosylvin-monomethylether (stilbene)	<i>Picea abies</i> , <i>P. sylvestris</i> (Pinaceae)	COX (PGS)
Plantamajoside (phenolic glycoside)	<i>Plantago major</i> , <i>P. asiatica</i> (Plantaginaceae) [leaf], <i>Rehmannia glutinosa</i> (Scrophulariaceae) [callus]	5-LOX [AI]
Propyl gallate (phenolic acid ester)	<i>Camellia</i> spp. (tea) (Theaceae) [leaf]	COX (PGS), SLOX (AO/FRS) [inhibits AA-induced PA]
Quercetagenin-7-O- β -D-glucoside (6-Hydroxyquercetin-7-O- β -D-glycoside) (flavonol glycoside)	<i>Tagetes erecta</i> (marigold) (Asteraceae) [flower]	12-LOX
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Oenothera biennis</i> (Onagraceae), <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice]	LOX (GST, PI3K, PK, RTK) [AI, feeding stimulant]
Quercetrin (= Quercetin 3-O-rhamnoside) (flavonol-O-glycoside)	<i>Quercus tinctoria</i> (oak) (Fagaceae), <i>Eucalyptus globulus</i> (Myrtaceae), <i>Polygonum</i> spp. (Polygonaceae)	Yields aglycone Quercetin (LOX inhibition, AI) [feeding attractant, feeding deterrent, antibacterial, antiviral]
Quercimeritrin (= Quercetin 7-O-glucoside) (flavonol O-glycoside)	<i>Gossypium hirsutum</i> , <i>G.</i> spp. (cotton) (Malvaceae), <i>Camellia sinensis</i> (Theaceae)	Yields aglycone Quercetin (LOX inhibition, AI) [feeding stimulant]
Quercetin 3'-O-glucoside (flavonol 3-O-glycoside)	<i>Gossypium hirsutum</i> , <i>G.</i> spp. (cotton) (Malvaceae)	Yields aglycone Quercetin (LOX inhibition, AI) [feeding stimulant]
Resveratrol (= 3,5,4'-Trihydroxystilbene) (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis vinifera</i> (Vitaceae) spp.	COX (PGH ₂ S), LOX
Rosmarinic acid (phenylpropanoid)	<i>Anethum</i> , <i>Levisticum</i> , <i>Sanicula</i> , <i>Astrantia</i> (Apiaceae), <i>Symphytum</i> (Boraginaceae), <i>Melissa</i> , <i>Mentha</i> , <i>Prunella</i> , <i>Ocimum</i> , <i>Oreganum</i> , <i>Rosmarinus</i> , <i>Salvia</i> , <i>Teucrium</i> (Lamiaceae) spp.	COX-1 (< 1000), COX-2 (C5 convertase, HIV-1 INT, ITD) [AI]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Rutin (= Quercetin 3-rutinoside; Rutoside) (flavonol O-glycoside)	Widespread; <i>Sophora japonica</i> (Fabaceae), <i>Polygonum</i> spp., (Polygonaceae), <i>Ruta graveolens</i> (Rutaceae), <i>Viola tricolor</i> (Violaceae)	5-LOX, yields aglycone Quercetin [AO, AR, feeding attractant, feeding deterrent, ovipositing stimulant, antiviral, antibacterial]
(Salicylic acid) (phenolic acid)	Widespread (induced in plant defence signalling), <i>Sauromatum guttatum</i> (Araceae) (& as methyl ester in <i>Gaultheria procumbens</i> (wintergreen) (Ericaceae) [leaf], <i>Betula lenta</i> (birch) (Betulaceae) [bark])	[analgesic synthetic acetylsalicylic acid inhibits COX-1 & COX-2 by Serine acetylation]
Sanggenon C	<i>Morus alba</i> (mulberry) (Moraceae) [root bark]	COX (at 100–1000) [hypotensive]
[6]-Shogaol (phenylpropanoid)	<i>Zingiber officinale</i> (ginger) [rhizome], <i>Amomum melegueta</i> [seed] (Zingiberaceae)	COX (2), 5-LOX (VAN-R) [AI (carrageenin-induced paw oedema), PAI (AA induced PA)]
Sibyllenone (neolignan)	<i>Ocotea bullata</i> (Lauraceae) [stem bark]	5-LOX
Sideritoflavone (flavone)	<i>Hyptis verticillata</i> , <i>Mentha piperita</i> , <i>Sideritis</i> spp. (Lamiaceae)	COX (PGS), 12-LOX
Silybin (flavanolignan)	<i>Silybum marianum</i> (Asteraceae) [fruit]	SLOX (NC)
Silychristin (flavanolignan)	<i>Silybum marianum</i> (Asteraceae) [fruit]	SLOX (NC)
Silydianin (flavanolignan)	<i>Silybum marianum</i> (Asteraceae) [fruit]	SLOX (NC)
Sinapaldehyde (phenol)	<i>Acer saccharinum</i> (Aceraceae), <i>Juglans nigra</i> (Juglandaceae), <i>Quercus rubra</i> (Fagaceae) [wood], <i>Senra incana</i> (Bombacaceae)	COX (PGS)
Suspensaside (phenylpropanoid glycoside)	<i>Forsythia suspensa</i> (Oleaceae) [fruit]	5-LOX (cAMP PDE, AO/FRS) [AI, anti-asthmatic]
Tannic acid (hydrolysable gallotannin)	Widespread	SLOX, COX
Taxifolin (= Dihydroquercetin, Distylin, 3,5,7,3',4'-Pentahydroxyflavanone) (dihydroflavonol)	Many Coniferae; <i>Acacia catechu</i> , <i>Robinia pseudoacacia</i> (Fabaceae), <i>Engelhardtia chrysolepis</i> (Juglandaceae), <i>Polygonum nodosum</i> (Polygonaceae), <i>Salix capraea</i> (Salicaceae),	5-LOX (AR, NADH DH, succinate DH)
Tectorigenin (isoflavone)	<i>Centrosema</i> spp. (phytoalexin), <i>Baptisia</i> spp., <i>Dalbergia</i> spp., <i>Ononis spinosa</i> (Fabaceae) [leaf], <i>Belamcanda chinensis</i> , <i>Iris germanica</i> (iris) (Iridaceae) [rhizome]	COX [antifungal phytoalexin]
[Δ^6 -Tetrahydrocannabinol-7-oic acid] (phenolic)	Major metabolite in humans of Δ^9 -Tetrahydrocannabinol	COX, 5-LOX (PAF-R) [antinociceptive (probably responsible for activity of parent Δ^9 -Tetrahydrocannabinol)]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
2',3,4,5'-Tetrahydroxychalcone (chalcone)	Semi-synthetic	COX
Thymoquinone (quinone)	<i>Satureja montana</i> (Lamiaceae), <i>Nigella sativa</i> (Ranunculaceae) [seed]	[Ca ²⁺ ionophore A23187-induced 5-LOX- & COX-mediated AA metabolism]
7,3',4'-Trihydroxy-2'-geranylflavanone (= AC-5-2) (flavanone)	<i>Artocarpus communis</i> (breadfruit) (Moraceae) [flower]	5-LOX [AI (AA-induced ear oedema)]
3,4,2',4'-Tetrahydroxy-2'-geranyldihydrochalcone (= AC-5-1) (chalcone)	<i>Artocarpus communis</i> (breadfruit) (Moraceae) [flower]	5-LOX, COX (PGS) [AI (AA-induced ear oedema)]
5,7,4'-Trihydroxy-8'-geranylflavanone (= AC-3-3) (flavanone)	<i>Artocarpus communis</i> (breadfruit) (Moraceae) [flower]	5-LOX [AI (AA-induced ear oedema)]
4,2',4'-Trihydroxy-5'-geranyldihydrochalcone (= AC-3-2) (chalcone)	<i>Artocarpus communis</i> (breadfruit) (Moraceae) [flower]	5-LOX [AI (AA-induced ear oedema)]
Tyrosol (= 4-Hydroxyphenylethanol) (phenol)	<i>Olea europaea</i> (olive) (Oleaceae) [leaf, bark, fruit, olive oil], <i>Plantago major</i> (Plantaginaceae)	[AO/FRS, 5-LOX & LTB ₄ generation inhibited (weak)]
Urushiol (alkyl catechol)	<i>Rhus toxicodendron</i> , <i>Toxicodendron radicans</i> (Anacardiaceae)	COX, LOX [causes allergic reactions]
Vavain (= 5,3'-Dihydroxy-7,4',5'-trimethoxyisoflavone) (isoflavone)	<i>Ceiba pentandra</i> (kapok tree) (Bombacaceae) [bark]	COX-1
Vavain 3'-O-β-D-glucoside (= 5,3'-Dihydroxy-7,4',5'-trimethoxyisoflavone 3'-O-β-D-glucoside) (isoflavone glycoside)	<i>Ceiba pentandra</i> (kapok tree) (Bombacaceae) [bark]	COX-1
Verbascoside (= Acteoside; Kusagin) (phenyl propanoid glycoside)	<i>Echinacea</i> spp. (Asteraceae), <i>Buddleja</i> spp., <i>Forsythia suspensa</i> (Oleraceae), <i>Plantago media</i> (Plantaginaceae), <i>Verbascum sinuatum</i> (Scrophulariaceae), <i>Ballota nigra</i> (Lamiaceae)	5-LOX (EGF-RTK, AR) [AI, antiproliferative]
(+)-α-Viniferin (oligomeric stilbene)	<i>Carex humilis</i> (Cyperaceae) [root], <i>Caragana chamlagu</i> (Fabaceae), <i>Vitis vinifera</i> (Vitaceae)	COX (PGH ₂ S)
4-Vinylguaicol (= 2-Methoxy-4-vinylphenol) (phenol)	<i>Ipomoea pes-caprae</i> (Convolvulaceae), <i>Coffea</i> spp. (coffee seed) (Rubiaceae), <i>Citrus sinensis</i> (orange juice) (Rutaceae)	COX (PGS) (18) [orange juice "off" odour]
Vitamin E (= α-Tocopherol) (chromanol)	Widespread	SLOX, 5-LOX, COX [antioxidant; AI]
Wedelolactone (coumestan)	<i>Echlipta alba</i> , <i>E. alba</i> , <i>Wedelia calendulacea</i> (Asteraceae) [leaf], <i>Ougeinia dalbergioides</i> (Fabaceae) [wood]	5-LOX (1-10)

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Wogonin (= Norwogonin 8-methyl ether) (flavone)	<i>Anodendron affine</i> (Apocynaceae) [stem], <i>Scutellaria baicalensis</i> , <i>S. spp.</i> (Lamiaceae) [root]	COX-2 (46), 12-LOX [↓ iNOS & COX-2 expression; inhibits PGE2 formation (0.8); oestrogenic, anti-implantation]
Xanthomicrol (flavone)	<i>Mentha piperita</i> , <i>Ocimum basilicum</i> , <i>Sideritis spp.</i> (Lamiaceae)	COX
Yakuchinone A (= 1-(4'-Hydroxy-3'-methoxyphenyl)-7-phenyl-3-heptanone) (phenyl propanoid, aryl heptanoid)	<i>Alpinia oxyphylla</i> (Zingiberaceae) [rhizome]	COX (0.5), 5-LOX (0.4) (TYR) [anti-tumour potential: ↓ TPA-induced AP-1 activation & ODC, TNF-α & O ₂ ⁻ production]
Yakuchinone B (= 1-(4'-Hydroxy-3'-methoxyphenyl)-7-phenylhept-1-en-3-one) (phenyl propanoid, aryl heptenoid)	<i>Alpinia oxyphylla</i> , <i>A. officinarum</i> (Zingiberaceae) [rhizome]	COX (2), (ACAT, TYR) [anti-tumour potential: ↓ TPA-induced AP-1 activation & ODC, TNF-α & O ₂ ⁻ production]
Terpenes		
Abietic acid (abietane diterpene)	<i>Pinus kesiya</i> , <i>P. insularis</i> , <i>P. spp.</i> (Pinaceae) [resin]	5-LOX (17βHSOR)
14-Acetoxycedrol (= 14-Acetyl 8,14-cedranediol) (sesquiterpene)	<i>Juniperus squamata</i> (Cupressaceae)	COX-1 [platelet TBX2 formation] (V-gated Ca ²⁺ channel) [vasorelaxant]
Acetyl-11-keto-β-boswellic acid (pentacyclic triterpene)	<i>Boswellia serrata</i> (Bursaceae) [gum resin]	5-LOX (2-16) (TOPI, TOPII) [LTB ₄ , LTC ₄ release inhibitor; AI in EAE]
Achillin (guaianolide sesquiterpene lactone)	<i>Achillea millefolium</i> , <i>Achillea spp.</i> , <i>Artemisia spp.</i> (Asteraceae)	Precursor of Chamazulene (AO/ROS, COX & 5-LOX inhibitor) [AI]
[α-Amyrin linoleate (= α-Amyrin <i>cis</i> -9, <i>cis</i> -12-octadecadienoic acid ester)] (ursane triterpene FA ester)	Semi-synthetic from α-Amyrin	(MLCK, PKA, PKC, CABPase, collagenase) [AI, 5-LOX (24-70)]
Artabsin (guaianolide sesquiterpene lactone)	<i>Artemisia absinthium</i> , <i>A. sieversiana</i> (Asteraceae)	Precursor of Chamazulene (AO/ROS, COX & 5-LOX inhibitor) [AI]
Attractylon (sesquiterpene)	<i>Atractylodes lancea</i> (Asteraceae) [rhizome]	5-LOX
Betulinic acid (triterpene)	<i>Psophocarpus tetragonolobus</i> (Fabaceae), <i>Alphitonia zizyphoides</i> (Rhamnaceae); "soapy" leaves	COX
Buddledin A (sesquiterpenoid)	<i>Buddleja davidii</i> , <i>B. globosa</i> (Buddlejaceae) [root]	5-LOX, COX [piscicidal]
Capsidiol (sesquiterpene)	<i>Nicotiana sylvestris</i> [elicited cultured cells], <i>N. tabacum</i> [TMV- infected leaf], <i>Capsicum annuum</i> , <i>C. frutescens</i> [fungus-infected fruit] (Solanaceae)	COX (PGS) [phytoalexin, antifungal]
Carnosol (abietane diterpenoid)	<i>Salvia officinalis</i> (sage), <i>Rosmarinus officinalis</i> (rosemary) (Lamiaceae) [leaf]	5-LOX, COX

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
α -Cembrane diol (diterpenoid)	<i>Nicotiana tabacum</i> (Solanaceae)	COX (PGS)
β -Cembrane diol (diterpenoid)	<i>Nicotiana tabacum</i> (Solanaceae)	COX (PGS)
[Chamazulene] (sesquiterpene)	Steam distillation product of achillin, artabsin & matricin, sesquiterpene lactones from various Asteraceae species	5-LOX (2) [inhibits LTB ₄ synthesis; AI]
Chrysanthenyl acetate (monoterpene)	<i>Tanacetum parthenium</i> (<i>Chrysanthemum parthenium</i>) (Asteraceae) [herb]	COX (14) (PGS \rightarrow PGE ₂)
Croctin monogentiobiosyl ester (carotenoid sugar ester)	<i>Buddleja officinalis</i> (Buddlejaceae), <i>Crocus</i> spp. (Iridaceae)[flower]	COX
2-[(2E)-3,7-Dimethyl-2,6-octadienyl]-6-methyl-2,5-cyclohexadiene-1,4-dione (sesquiterpene)	<i>Atractylodes lancea</i> (Asteraceae) [rhizome]	5-LOX, COX-1
Gossypol (phenolic dimeric sesquiterpene)	<i>Gossypium</i> spp., <i>Montezuma speciosissima</i> , <i>Thespesia populnea</i> (Malvaceae) [seed]	COX, LOX [antifungal, antitumour, blocks spermatogenesis]
Hydroxyachillin (sesquiterpene lactone)	<i>Achillea millefolium</i> , <i>Tanacetum microphyllum</i> (Asteraceae) [aerial]	COX, SLOX [AI]
Labdane F2 (diterpenoid)	<i>Sideritis javalambrensis</i> (Lamiaceae)	COX [blocks COX-2 & iNOS induction]
Matricin (guaianolide sesquiterpene lactone)	<i>Matricaria chamomilla</i> , <i>M. recutita</i> , <i>Achillea</i> spp., <i>Artemisia caruthii</i> , <i>Jurinea maxima</i> (Asteraceae)	Precursor of chamazulene (AO/ROS, COX & 5-LOX inhibitor)
Michefuscalide (sesquiterpene lactone)	<i>Tanacetum parthenium</i> (<i>Chrysanthemum parthenium</i>) (feverfew) (Asteraceae) [herb]	COX (12) (PGS, AA \rightarrow PGE ₂)
Oleanolic acid (triterpene)	<i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae), <i>Syzygium aromaticum</i> (Myrtaceae)	COX-1, COX-2 [AI]
Oleanolic acid 3-O-GlcA (terpene glycoside)	<i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae)	[Yields Oleanolic acid, molluscicidal]
Oleuropein (catechol, monoterpene, seco-iridoid glucoside)	<i>Ligustrum japonicum</i> , <i>Olea europaea</i> (olive) (Oleaceae) [leaf, bark, fruit, olive oil]	5-LOX, 12-LOX [5-LOX & LTB ₄ generation inhibited; aglycone & elenolic acid hydrolysis products antibacterial]
Parthenolide (sesquiterpene lactone)	<i>Tanacetum parthenium</i> (<i>Chrysanthemum parthenium</i> , <i>Ambrosia</i> spp., <i>Arctotis</i> spp., <i>Tanacetum vulgare</i>) (Asteraceae), <i>Michelia champaca</i> , <i>M. lanuginosa</i> (Magnoliaceae) [herb, leaf surface]	COX (11) (PGS \rightarrow PGE ₂) [cytotoxic, antitumour, antibacterial, antifungal]
Pristamerin (friedelane triterpene)	<i>Catha edulis</i> , <i>Maytenus</i> spp., <i>Pristimera indica</i> , <i>Schaefferia cuneifolia</i> (Celastraceae) [root]	[Inhibits NF κ B activation & thence iNOS induction; antitumour, anti-bacterial, toxic, germination inhibitor]

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
β -Thujaplicin (= Hinokitiol); 4-Isopropyltropolone) (tropolone monoterpene)	<i>Thuja plicata</i> , <i>Cupressus sargentii</i> , <i>C. abramsiana</i> , <i>C. macrocarpa</i> (Cupressaceae) [wood]	5-LOX, 12-LOX, SLOX, 15-LOX [anti-bacterial, allergen]
Ursolic acid (= Malol; Malolic acid; Micromerol; Prunol; Urson) (ursane triterpene)	<i>Calluna vulgaris</i> , <i>Arctostaphylos</i> <i>uva-ursi</i> , <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Plantago major</i> (Plantaginaceae), <i>Prunella</i> <i>vulgaris</i> , <i>Salvia triloba</i> (Lamiaceae), <i>Malus</i> sp., <i>Pyrus</i> sp. (Rosaceae) [fruit waxy coat]	COX-1, COX-2, 5-LOX (1), potato 5-LOX (300), soya bean 15-LOX (300) [AI, cytotoxic, antileukaemic]
Other compounds		14.1Aa
Ajoene (= <i>E</i> & <i>Z</i>)-4,5,9- Trithiadodeca-1,6,11- triene-9-oxide mixture) (alkene sulfide)	<i>Allium cepa</i> (onion), <i>A. sativum</i> (garlic) (Liliaceae) [bulb]	COX (5), 5-LOX (2), SLOX (mixed inhibition)
Allyl methyl trisulfide (alkene sulfide)	<i>Allium cepa</i> (onion), <i>A. sativum</i> (garlic) (Liliaceae) [bulb]	SLOX (competitive)
2-Amino-5-(<i>N</i> -ethylcarbox- amido)-pentanoic acid (aliphatic carboxylic acid)	<i>Camellia sinensis</i> (tea) (Theaceae) [unprocessed leaf]	[Inhibits formation of Thromboxane]
Arachidonic acid (unsaturated FA)	<i>Mnium</i> spp. (moss) (Mniaceae), <i>Scolopendrium vulgare</i> (fern) (Aspleniaceae), <i>Brassica oleracea</i> (Brassicaceae)	SLOX (inactivated), 5-LOX (barley; competitive with linoleic acid) (PPA-R)
Calendulic acid (unsaturated FA)	<i>Calendula officinalis</i> (marigold) (Asteraceae)	COX (31)
Canatoxin (protein)	<i>Canavalia ensiformis</i> (Fabaceae) [seed]	[Activates LOX pathway (stimulates exocytosis, serotonin & insulin secretion); toxic IP, cathepsin-activated]
Cerebrosides (phosphosphingosine glycolipids)	<i>Phytolacca</i> sp. (Phytolaccaceae) [root]	COX-2 (10)
Columbinic acid (= 18:3, $\Delta^{5,9,12}$ -FA) (unsaturated FA)	<i>Aquilegia vulgaris</i> (Ranunculaceae)	COX (40)
Crepenynic acid (= Octadec- <i>cis</i> -9-en- 12-ynoic acid) (acetylenic FA)	<i>Crepis foetida</i> , <i>Ixiolaena</i> <i>brevicompta</i> (Asteraceae), <i>Afzelia</i> <i>cuanzensis</i> (Fabaceae) [seed oil]	COX (<10, 40), 5-LOX (85) [sheep mortality]
Diallyl disulfide (alkene sulfide)	<i>Allium cepa</i> (onion), <i>A. sativum</i> (garlic) (Liliaceae) [bulb]	SLOX (competitive)
Diallyl trisulfide (alkene sulfide)	<i>Allium cepa</i> (onion), <i>A. sativum</i> (garlic) (Liliaceae) [bulb]	SLOX (competitive)
Dicranin (= ζ, ζ, ζ - Octadeca-6-yne-9,12,15- trienoic acid) (acetylene)	<i>Dicranum scoparium</i> (moss) (Dicranaceae) [aerial]	SLOX [antibacterial]
11(<i>S</i>),16(<i>R</i>)-Dihydroxy- octadeca-9 <i>Z</i> ,17-diene- 12,14-diyn-1-yl acetate (polyacetylene alcohol acetic acid ester)	<i>Angelica pubescens</i> (Apiaceae) [root = Du Huo]	COX-1, 5-LOX

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Di-(1-propenyl) sulfide (alkene sulfide)	<i>Allium cepa</i> (onion), <i>A. sativum</i> (garlic) (Liliaceae) [bulb]	SLOX (mixed inhibition)
Eicosapentaenoic acid (= <i>cis</i> -5,8,11,14,17-C20:5) (unsaturated FA)	After ingestion α -Linolenic acid precursor from <i>Linum usitatissimum</i> (Linaceae) [seed oil, linseed oil]; fish oil	5-LOX (PPA-R) [anti-hyperlipoprotein-emic]
Elaidic acid (unsaturated FA)	Widespread	5-LOX
Falcarindiol (long chain polyacetylene alcohol)	<i>Notopterygium incisum</i> (root = Qianguo) <i>Angelica pubescens</i> [root = Du Huo], <i>Apium graveolens</i> , <i>Daucus carota</i> (carrot) (Apiaceae) [root], <i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [fungal-infected leaf]	COX-1, 5-LOX [antifungal, phytoalexin]
Falcarinol (polyacetylene alcohol)	<i>Angelica furcijuga</i> , <i>Daucus carota</i> , <i>Falcaria vulgaris</i> , <i>Oenanthe crocata</i> (Apiaceae) [root], <i>Hedera helix</i> , <i>Schefflera arboricola</i> (Araliaceae)	5-LOX (↓ iNOS expression) [blocks LPS-induced macrophage iNOS expression, dermatitic]
Fumaric acid (unsaturated C4 dicarboxylic acid)	Universal – a tricarboxylic acid (TCA) cycle intermediate; <i>Helianthus annuus</i> (Asteraceae), <i>Pisum sativum</i> (Fabaceae), <i>Averrhoa carambola</i> (Oxalidaceae), <i>Glaucium flavum</i> (Papaveraceae), <i>Malus domestica</i> (Rosaceae)	LOX (wheat germ; competitive)
Heptadeca-2 <i>E</i> , 8 <i>E</i> , 10 <i>E</i> , 16-tetraene-4,6-diyne (long chain polyacetylene)	<i>Bidens campylothea</i> (Asteraceae) [herb]	COX, 5-LOX
Heptadeca-2 <i>E</i> , 8 <i>Z</i> , 10 <i>E</i> , 16-tetraene-4,6-diyne (long chain polyacetylene)	<i>Bidens campylothea</i> (Asteraceae) [herb]	COX, 5-LOX
Heptadeca-2 <i>E</i> , 8 <i>E</i> , 16-triene-4,6-diyne-10-ol (long chain polyacetylene alcohol)	<i>Bidens campylothea</i> (Asteraceae) [herb]	COX, 5-LOX
<i>cis</i> -Hexadec-11-en-7,9-diynoic acid (polyacetylene)	<i>Heisteria acuminata</i> (Olacaceae) [bark]	COX, 5-LOX
[15-Hydroperoxy-6,8,11,14-eicosatetraenoic acid (hydroperoxy unsaturated FA)]	Hydroperoxy product of Arachidonic acid from <i>Mnium</i> spp. (moss) (Mniaceae), <i>Scolopendrium vulgare</i> (fern) (Aspleniaceae)	SLOX (inactivated), 5-LOX (barley)
8(<i>R</i>)-Hydroxylinoleic acid (unsaturated FA)	Widespread	5-LOX
Linoleic acid (= <i>cis</i> -9, <i>cis</i> -12-Octadecenoic acid; Linolic acid) (unsaturated FA)	Widespread; <i>Helianthus annuum</i> (Asteraceae), <i>Cucumis melo</i> (Cucurbitaceae), <i>Arachis hypogaea</i> , <i>Glycine max</i> (Fabaceae), <i>Linum usitatissimum</i> (Linaceae), <i>Gossypium hirsutum</i> (Malvaceae)	5-LOX (PPA-R)

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
α -Linolenic acid (= <i>cis</i> -9,12,15-C18:3) (unsaturated FA)	Widespread; <i>Cucumis sativus</i> (Cucurbitaceae), <i>Linum usitatissimum</i> (Linaceae) [seed]	COX, 5-LOX
Jacarandic acid (= 8 ζ ,10 E ,12 ζ -Octadecatrienoic acid)	<i>Jacaranda mimosifolia</i> (Bignoniaceae)	COX (2)
Octadeca-8,10,12-triynoic acid (polyacetylene acid)	<i>Heisteria acuminata</i> (Olacaceae) [bark]	COX
<i>cis</i> -Octadec-12-en-7,9-diynoic acid (polyacetylene acid)	<i>Heisteria acuminata</i> (Olacaceae) [bark]	COX, 5-LOX
Oleic acid (= <i>cis</i> -9-Octadecenoic acid) (unsaturated C ₁₈ FA)	Widespread; olive, sunflower, peanut [seed oil]; <i>Persea americana</i> (avocado) (Lauraceae)	SLOX, 15-LOX
Paraffinic polysulfides (long chain alkyl polysulfides)	<i>Allium sativum</i> (garlic), <i>A. cepa</i> (onion) (Alliaceae) [bulb]	COX, LOX [PAI]
Panaxynol (polyacetylene ketone)	<i>Panax ginseng</i> , <i>P. quinquefolium</i> (Araliaceae)	5-LOX (HPGDH) (↓ iNOS expression) [blocks LPS- & IFN- γ - induced macrophage iNOS expression]
Pentadeca-6,8,10-triynoic acid (polyacetylene acid)	<i>Heisteria acuminata</i> (Olacaceae) [bark]	COX
<i>trans</i> -Pentadec-10-en -6,8-diynoic acid (polyacetylene)	<i>Heisteria acuminata</i> (Olacaceae) [bark]	COX
Persenone A (long chain aliphatic ester)	<i>Persea americana</i> (avocado) (Lauraceae)	Blocks LPS- & IFN- γ -induced COX-2 (& iNOS) expression (at 20) [AI]
Polyunsaturated alkylamides (unsaturated FA amides)	<i>Echinacea angustifolia</i> , <i>Achillea</i> spp., <i>Anacyclus pyrethrum</i> , <i>Aaronsohnia pubescens</i> (Asteraceae)	COX, 5-LOX
1-Propenylpropyl sulfide (alkene sulfide)	<i>Allium cepa</i> (onion), <i>A. sativum</i> (garlic) (Liliaceae) [bulb]	SLOX
Ricinoleic acid (unsaturated FA)	<i>Ricinus communis</i> (Euphorbiaceae) [seed], <i>Argemone mexicana</i> (Papaveraceae)	5-LOX
Safynol (long chain polyacetylene alcohol)	<i>Bidens camphylothea</i> [herb], <i>Carthamus tinctorius</i> [fungal-infected], <i>Centaurea</i> spp. [herb] (Asteraceae)	COX, 5-LOX [phytoalexin, antifungal]
Safynol-2- <i>O</i> -isobutyrate (long chain polyacetylene alcohol isobutyric acid ester)	<i>Bidens camphylothea</i> (Asteraceae) [herb]	COX, 5-LOX
Ximenynic acid (= Octadec- <i>trans</i> -11-en-9-ynoic acid) (acetylenic FA)	<i>Ixiolaena brevicompta</i> (Asteraceae)	COX (39), LOX (60)

(continued)

Table 14.1 (Continued)

Compound (class)	Plant source (family)	Targets (other targets) / in vivo effects/
Non-plant reference		14.1An
[Aspirin (= Acetylsalicylic acid; Salicylic acid acetate)] (phenol)	Synthetic; acetate ester of Salicylic acid; first marketed by Bayer 1899; aspirin named & prior research led by Arthur Eichengrün who later survived Holocaust & disputed sole credit given to subordinate Felix Hoffmann by Nazis	COX (PGH ₂ synthase) [analgesic, antipyretic, AI]; “the greatest drug in history” because of its analgesic & anti-platelet activity; Sir John Vane (UK, Nobel Prize, Medicine, 1982, PG synthesis & aspirin inhibition of COX)
[Celecoxib (= Celebrex)] (NSAID)	Synthetic	COX-2 specific [AI, anti-arthritis]; inhibits production of vasodilator/PAI PGI ₂ but not of vasoconstrictor/PA TXA ₂ production → ↑ thrombosis risk concerns]
[N-Linoleoyldopamine] (fatty acyl catechol)	Synthetic	5-LOX (2 nM)
[8Z,10E,12E-Octadecatrienoic acid] (long chain FA)	Synthetic	COX (1)
[Timnodonic acid (= cis-Δ ^{5,8,11,14,17} -Eicosapentaenoic acid; 20:5-Δ ^{5,8,11,14,17} -FA)] (unsaturated FA)	Fish oil	COX (43)
15-Hydroxyprostaglandin dehydrogenase (HPGDH)		14.1B
Panaxynol (polyacetylene ketone)	<i>Panax ginseng</i> , <i>P. quinquefolium</i> (Araliaceae)	HPGDH (25) (5-LOX, ↓ iNOS expression) [blocks LPS- & IFN-γ-induced macrophage iNOS expression]

Table 14.2 Antioxidant free radical scavengers

Compound (class)	Plant (family) part/	Effect (other targets) / in vivo effects/
Alkaloid		14.2a
Boldine (aporphine alkaloid)	<i>Sassafras albidum</i> (Lauraceae), <i>Peumus boldus</i> (boldo) (Monimiaceae) [bark, leaf]	AO/FRS
Bismurrayafoline E (carbazole)	<i>Murraya koenigii</i> (curry leaf) Rutaceae [leaf]	AO/FRS – scavenges DPPH
Euchristine B (carbazole)	<i>Murraya koenigii</i> (curry leaf) Rutaceae [leaf]	AO/FRS – scavenges DPPH
Mahanimbicine (carbazole)	<i>Murraya koenigii</i> (curry leaf) Rutaceae [leaf]	AO/FRS – scavenges DPPH

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
Mahanimbine (carbazole)	<i>Murraya koenigii</i> (curry leaf) Rutaceae) [leaf]	AO/FRS – scavenges DPPH (TOPI, TOPII) [antimicrobial, mosquitocidal]
Mahanine (carbazole)	<i>Murraya koenigii</i> (curry leaf) (Rutaceae) [leaf]	AO/FRS – scavenges DPPH (TOPI, TOPII) [antimicrobial, mosquitocidal]
Melanin (indole-containing polymer)	<i>Camellia sinensis</i> (Theaceae), <i>Vitis vinifera</i> (grape) (Vitaceae); polymer <i>ex tyrosine</i> via tyrosinase	AO/FRS
Melatonin (= <i>N</i> -Acetyl-5-methoxytryptamine) (indole)	<i>Pharbitis</i> sp. (morning glory) (Convolvulaceae), <i>Lycopersicon esculentum</i> (tomato) (Solanaceae) [fruit]; <i>ex vertebrate pineal gland</i> ; synchronizes circadian & circannual rhythms	AO/FRS – scavenges OH, H ₂ O ₂ , NO, ONOO ⁻ , ONOOH, HOCl, peroxy radical (ROO), superoxide anion (O ₂ ⁻) [reverses MSH (melanotropin) darkening effect; circadian regulation]
Phenolic		14.2p
2'- <i>O</i> -Acetylaceoside (phenylethanoid)	<i>Cistanche deserticola</i> (Orobanchaceae) [stem]	AO/FRS – scavenges NO radical (↓ NO ₂ ⁻) [AI]
Aceteoside (phenylethanoid)	<i>Stachys sieboldii</i> (Lamiaceae), <i>Cistanche deserticola</i> (Orobanchaceae) [stem]	AO/FRS – scavenges NO radical (↓ NO ₂ ⁻) [AI]
Anthocyanins (anthocyanins); anthocyanin studies by Sir Robert Robinson (UK, Nobel Prize, 1947, Chemistry, alkaloids)	Widespread; e.g. <i>Vitis vinifera</i> (Vitaceae) (wine); anthocyanins studied by Richard Willstätter (Nobel Prize, Chemistry, 1915, plant pigments & chlorophyll; fled Nazis)	AO/FRS
Apigenin (flavone)	<i>Apium graveolens</i> (Apiaceae), <i>Mezoneuron cucullatum</i> (Fabaceae), <i>Ballota nigra</i> (black horehound) (Lamiaceae)	AO/FRS – scavenge DPPH
Arenarioside (phenyl propanoid glycoside)	<i>Ballota nigra</i> (black horehound) (Lamiaceae)	AO/FRS – scavenges OH, O ₂ ⁻ , H ₂ O ₂ , HOCl [AI, neurosedative]
Artonins A & B (prenylflavone)	<i>Artocarpus heterophyllus</i> (Moraceae)	AO/FRS – scavenge DPPH, peroxy & OH radicals, inhibit Cu(II)-mediated LDL oxidation
Astringin (stilbene)	<i>Vitis vinifera</i> (grape) (Vitaceae)	AO/FRS – scavenges DPPH, ↓ Fe(III)- & Cu(II)-induced lipid peroxidation
Ballotetroside (phenyl propanoid glycoside)	<i>Ballota nigra</i> (black horehound) (Lamiaceae)	AO/FRS – scavenges H ₂ O ₂ , HOCl [AI, neurosedative]
Caffeic acid (= 3,4-Dihydroxycinnamic acid) (phenylpropanoid)	<i>Conium</i> (Apiaceae), <i>Artemisia</i> , <i>Taraxacum</i> , <i>Anthemis</i> , <i>Achillea</i> (Asteraceae), <i>Ipomoea purga</i> (Convolvulaceae), <i>Olea</i> (Oleaceae), <i>Papaver</i> (Papaveraceae), <i>Coffea</i> , <i>Cinchona</i> (Rubiaceae), <i>Digitalis</i> (Scrophulariaceae) spp.	AO/FRS – scavenges DPPH (5-LOX, 12-LOX, eEF-2)[AI, PAI, 5-LOX & LTB ₄ generation inhibited (weak)]

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
Caffeic acid phenethyl ester (phenylpropanoid)	<i>Populus</i> sp. (Salicaceae); bee propolis	AO/FRS – scavenges ROS (in neutrophils & XO-generated) (< 10) (HIV-1 INT, 5-LOX) [antioxidant]
Caffeoyl malic acid (phenyl propanoid glycoside)	<i>Ballota nigra</i> (black horehound) (Lamiaceae)	AO/FRS – scavenges OH, O ₂ ⁻ , H ₂ O ₂ , HOCl [AI, neurosedative]
Caffeoyltartaric acid (= Caftaric acid) (phenylpropanoid)	<i>Lapsana communis</i> (Asteraceae)	AO/FRS
(-)-Carinol (phenolic lignan)	<i>Cerbera manghas</i> (Apocynaceae)	AO/FRS – scavenges DPPH
(+)-Catechin (flavan-3-ol)	Widespread; <i>Prosopis flexuosa</i> (Fabaceae) [aerial], <i>Agrimonia eupatoria</i> (Rosaceae), <i>Salix cuprea</i> (Salicaceae) [flower]	AO/FRS – scavenges DPPH, OH, H ₂ O ₂ , O ₂ ⁻ (COX-1, COX-2)
Chalcomoracin (isoprenylated flavonoid)	<i>Morus alba</i> (mulberry) (Moraceae) [UV-induced phytoalexin]	AO/FRS – scavenges superoxide anion (O ₂ ⁻), blocks lipid peroxidation
Chlorogenic acid (= 3-O-Caffeoylquinic acid) (phenylpropanoid)	Widespread; <i>Cynara scolymus</i> (artichoke), <i>Helianthus annuus</i> (Asteraceae) [leaf], <i>Coffea arabica</i> (coffee) (Rubiaceae), <i>Camellia sinensis</i> (tea) (Theaceae)	AO/FRS – ↓ LDL peroxidation, FRS
Cistanoside (phenylethanoid)	<i>Cistanche deserticola</i> (Orobanchaceae) [stem]	AO/FRS – scavenges NO radical (↓ NO ₂ ⁻) [AI]
Cycloheterophyllin (prenylflavone)	<i>Artocarpus heterophyllus</i> (Moraceae)	AO/FRS – scavenges DPPH, peroxy & OH radicals, ↓ Cu(II)-mediated LDL oxidation (COX, PKC)
(+)-Cyclooolivil (phenolic lignan)	<i>Cerbera manghas</i> (Apocynaceae)	AO/FRS – scavenges DPPH
[5,7-Dihydroxy-4-methylcoumarin] (coumarin)	Semi-synthetic	AO/FRS – scavenges OH, O ₂ ⁻ , HOCl; ↓ Fe(III)-ascorbate- induced lipid peroxidation (<20)
6,7-Dimethoxy-5,8,4'-trihydroxyflavone (flavone)	<i>Prunus cerasus</i> (tart cherry) (Rosaceae)	AO/FRS – inhibits Fe ²⁺ - induced lipid peroxidation
Echinacoside (phenylethanoid)	<i>Echinacea</i> spp. (Asteraceae), <i>Cistanche deserticola</i> (Orobanchaceae) [stem]	AO/FRS – scavenges NO radical (↓ NO ₂ ⁻) [AI]
Epicatechin (flavan-3-ol)	<i>Mitragyna speciosa</i> (Rubiaceae), <i>Camellia sinensis</i> (tea) (Theaceae)	AO/FRS – scavenges NO
(-)-Epicatechin 3-O-gallate (= ECG) (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae); East India Company Chinese tea & bullion for Bengali opium trade – led to China Opium Wars (1839–1842, 1856–1860) & thence to Tai Ping rebellion (1850–1864; 20–100 million deaths from war & associated famine)	AO/FRS – scavenges DPPH, OH [•] , NO & O ₂ ⁻ , chelates Fe (II) ions, ↓ lipid peroxidation (collagenase, EST-R, 5αR) [apoptotic, asbestos-induced macrophage injury protectant (10)]

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
(-)-Epicatechin-3-benzoate (flavan-3-ol)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial]	AO/FRS – scavenges DPPH
(-)-Epicatechin-5- <i>O</i> - β -glucosyl-3-benzoate (flavan-3-ol glycoside)	<i>Celastrus orbiculatus</i> (Celastraceae) [aerial]	AO/FRS – scavenges DPPH
(-)-Epigallocatechin (= EGCG) (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae)	AO/FRS – scavenges NO, OH [*] , [antitumour, apoptotic, cytotoxic]
(-)-Epigallocatechin-3-gallate (= EGCG) (flavanone)	<i>Davidsonia pruriens</i> (Davidsoniaceae) [leaf], <i>Hamamelis virginiana</i> (Hamamelidaceae) [bark], <i>Camellia sinensis</i> (tea leaf) (Theaceae); green tea cancer chemopreventive	AO/FRS – scavenges DPPH, OH [*] , NO & O ₂ ⁻ , chelates Fe ions (XO) [asbestos-induced macrophage injury protectant (10), AI, apoptotic, blocks COX-2 & iNOS induction, cytotoxic, antitumour]
Eriocitrin (= Eriodictyol 7- <i>O</i> -rutinoside) (flavanone <i>O</i> -glycoside)	<i>Mentha piperita</i> (Lamiaceae), <i>Myoporum tenuifolium</i> (Myoporaceae), <i>Citrus limon</i> , <i>C.</i> spp. (Rutaceae); lemon juice flavonoids discovered by Albert Szent-Györgyi as “vitamin P”	Antioxidant <i>in vivo</i> (diabetic rat)
Evening primrose meal phenolics (phenolic mixture)	<i>Oenothera biennis</i> , <i>O.</i> spp. (evening primrose) (Onagraceae)	AO/FRS – scavenges OH, H ₂ O ₂ , O ₂ ⁻
Forsythiaside (= ForsythosideA) (phenylpropanoid glycoside)	<i>Forsythia suspensa</i> , <i>F. koreana</i> (Oleraceae) [fruit]	AO/FRS (cAMP PDE, 5-LOX)
Ferulic acid (= 3- <i>O</i> -Methylcaffeic acid) (phenylpropanoid)	Widespread; <i>Ferula foetida</i> (Apiaceae) [root sap], <i>Salvia</i> sp. (Lamiaceae)	AO/FRS – scavenges nitrite (NO ₂ ⁻) (TYR)
Flavonoids (flavones); moderate wine consumption protects against oxidative DNA damage	Widespread; notably <i>Vitis vinifera</i> (Vitaceae) [red wine], fruit; “Mediterranean diet” – notably olive oil & vegetables – vegetables rich in flavonoid antioxidants	AO/FRS (LDL oxidation protectant, scavenge ROS, chelate transition metal ions) [UV-B protection; colour, defensive compounds]
Forsythoside B (phenyl propanoid glycoside)	<i>Ballota nigra</i> (black horehound) (Lamiaceae), <i>Forsythia suspensa</i> (Oleaceae)	AO/FRS – scavenges OH, O ₂ ⁻ , H ₂ O ₂ , HOCl [AI, neurosedative]
Fraxetin (= 7,8-Dihydroxy-6-methoxycoumarin) (coumarin)	<i>Aesculus hippocastanum</i> (horse chestnut) (Hippocastanaceae), <i>Laesonia inermis</i> (Lythraceae), <i>Fraxinus ornus</i> , <i>F. rhynchophylla</i> (Oleaceae)	AO/FRS – scavenges superoxide anion (O ₂ ^{*-}), alkylperoxyl (ROO [*]); inhibits lipid peroxidation; pro-oxidant (+ Fe ³⁺) → hydroxyl radical (OH [*])
Galic acid (= 3,4,5-Trihydroxybenzoic acid) (phenolic)	Widespread; component of gallotannins (hydrolysable tannins); <i>Mangifera indica</i> (Anacardiaceae)	AO/FRS – scavenges DPPH, O ₂ ⁻
Gallocatechin 3- <i>O</i> -gallate (flavan-3-ol)	<i>Camellia sinensis</i> (tea) (Theaceae)	AO/FRS – scavenges DPPH, ↓ lipid peroxidation

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
Garcinol (polyisoprenylated benzophenone)	<i>Garcinia indica</i> (Clusiaceae) [fruit rind]	AO/FRS – scavenges OH, O ₂ ⁻ , CH ₃ ⁺ (H ₂ O ₂ / NaOH/DMSO system) & O ₂ ⁻ (hypoxanthine/XO system) [anti-ulcer]
Genistein (= Genisteol; Prunetol; Sophoricol; 4', 5,7-Trihydroxyisoflavone) (isoflavone)	<i>Prunus</i> spp. (plum) (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Trifolium brachycalycinum</i> , <i>T.</i> spp. (clover) (Fabaceae)	AO/FRS – scavenges ROS e.g. from H ₂ O ₂ /Cu(II) or hydroquinone/Cu(II) (COX-1) [blocks COX-2 & iNOS induction; antifungal, oestrogenic]
Gossypol (dimeric phenolic sesquiterpenoid)	<i>Gossypium</i> spp. (cotton), <i>Montezuma speciosissima</i> , <i>Thespesia populnea</i> (Malvaceae) [seed];	AO/FRS – scavenges O ₂ ⁻ , lipid peroxyl radicals; ↓ Fe(II)- induced lipid peroxidation (1) (Ca ²⁺ -ATPase, CAMA, CDPK, 11βHSDH, MLCK, PKA, PKC) [antifungal, antitumour, inhibits spermatogenesis, male contraceptive]
Hesperidin (= Hesperetin <i>O</i> -rutinoside) (flavanone <i>O</i> -glycoside)	<i>Hyssopus</i> , <i>Mentha</i> (Lamiaceae), <i>Citrus limon</i> , <i>C.</i> spp. (Rutaceae) spp.; lemon juice flavonoids discovered by Albert Szent-Györgyi as “vitamin P”	Antioxidant <i>in vivo</i> (diabetic rat); scavenges DPPH (weak) [↓ Dehydroascorbate, ↑ lysosomal stability]
Hydroxytyrosol (= 2- (3,4-Dihydroxyphenyl) ethanol) (phenolic)	<i>Olea europaea</i> (olive) (Oleaceae) [seed oil]	AO/FRS – scavenges ONOO ⁻ (5-LOX, 12-LOX) [apoptotic via cytochrome c release]
Hyperoside (flavonol glycoside)	<i>Ilex aquifolium</i> (Aquifoliaceae), <i>Tussilago farfara</i> (Asteraceae)	AO/FRS – ↓ LDL peroxidation, FRS
Isoacteoside (phenylethanoid)	<i>Cistanche deserticola</i> (Orabanchaceae) [stem]	AO/FRS – scavenges NO radical (↓ NO ₂ ⁻) [AI]
Isochlorogenic acid b (= Caffe-tannin; Quinic acid dicaffeoyl ester) (phenylpropanoid)	Asteraceae; <i>Arachis hypogaea</i> (Fabaceae), <i>Coffea</i> spp. (Rubiaceae)	AO/FRS
Isotorachryson (= 2-Acetyl-8-methoxy- 3-methyl-naphthalene 1, 6-diol) (naphthalene phenolic)	<i>Rhamnus nakaharai</i> (Rhamnaceae)	AO/FRS – ↓ Fe(II)- & Cu(II)- induced lipid & LDL peroxidation (2)
Kaempferol (= 3,5,7,4'- Tetrahydroxyflavone) (flavonol)	Widespread; Fabaceae [wood, leaf], Hippocastanaceae [aerial], <i>Azadirachta indica</i> (Meliaceae)	AO/FRS – scavenges O ₂ ⁻ (COX-1, 5-LOX, PK, RTK) [blocks COX-2 & iNOS induction; AI, antibacterial, mutagenic, radical scavenger]
Kaempferol-3-glucoside (flavone glycoside)	<i>Helichrysum italicum</i> (curry plant) (Asteraceae) [flower]	AO/FRS – scavenges OH, O ₂ ⁻ , lipid peroxyl radicals; ↓ Fe(II)-induced lipid peroxidation

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
Kaempferol 3-O-neohesperidoside (flavonol)	<i>Daphniphyllum calycinum</i> (Daphniphyllaceae)	AO/FRS – scavenges DPPH
Lithospermic acid (phenylpropanoid, caffeic acid trimer, benzofuran)	<i>Cnicus benedictus</i> (Asteraceae), <i>Salvia miltiorhiza</i> (Lamiaceae)	AO/FRS – scavenges DPPH (AC, ProH)
Marchantin H (macrocyclic bis(benzyl) phenolic)	<i>Marchantia</i> sp. (liverwort) (Marchantiaceae)	AO/FRS – scavenges DPPH, ↓ Fe(II)-induced lipid peroxidation, ↓ Cu(II)-induced LDL oxidation (5-LOX)
Marchantinquinone (macrocyclic bis(benzyl) phenolic, lignan)	<i>Reboulia hemisphaerica</i> (liverwort) (Aytoniaceae)	AO/FRS – scavenges DPPH, peroxy; ↓ LDL oxidation & Fe(II)-induced lipid peroxidation (15) (PAI)
4-Methylaphnetin (= 7,8-Dihydroxy-4-methylcoumarin) (coumarin)	Semi-synthetic	AO/FRS – scavenges superoxide anion ($O_2^{\bullet-}$), alkylperoxyl (ROO^{\bullet}); inhibits lipid peroxidation; pro-oxidant (+ Fe^{2+}) → hydroxyl radical (OH) [irritant]
7,8-Methylenedioxy-3 (4-hydroxybenzyl) chromane (homoisoflavonoid)	<i>Dracaena cinnabari</i> (Agavaceae)	AO/FRS
Moracin C (benzofuran)	<i>Morus alba</i> (mulberry) (Moraceae) [UV-induced phytoalexin]	AO/FRS – scavenges superoxide anion ($O_2^{\bullet-}$), blocks lipid peroxidation
Moracin N (benzofuran)	<i>Morus alba</i> (mulberry) (Moraceae) [UV-induced phytoalexin]	AO/FRS – scavenges superoxide anion ($O_2^{\bullet-}$), blocks lipid peroxidation
Morelloflavone (flavanonylflavone, biflavonoid)	<i>Garcinia morello</i> , <i>G. multiflora</i> (Guttiferae)	AO/FRS – scavenges superoxide anion ($O_2^{\bullet-}$) (HIV-1 RT, PLA2) [AI]
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Morus alba</i> (mulberry), <i>M.</i> spp., <i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> , <i>Chlorophora tinctoria</i> (Moraceae)	AO/FRS – scavenges ROS (AR, CDPK, 5-LOX, ITDI, MLCK, PKA) [antibacterial, antiviral, allergenic, hepatoprotectant, silkworm feeding attractant]
Naringenin 3-glucoside (flavone glycoside)	<i>Helichrysum italicum</i> (Asteraceae) [flower]	AO/FRS – scavenges OH, $O_2^{\bullet-}$, lipid peroxy radicals; ↓ Fe(II)-induced lipid peroxidation
Nasunin (= Delphinidin-3-(<i>p</i> -coumaroylrutinoside)-5-glucoside (anthocyanin))	<i>Solanum melongena</i> (eggplant) (Solanaceae)	AO/FRS – scavenges OH, $O_2^{\bullet-}$, lipid peroxy radicals; ↓ Fe(II)-induced lipid peroxidation
Oleuropein (phenolic)	<i>Ligustrum japonicum</i> , <i>Olea europaea</i> (Oleaceae) [olive oil]	[AO/FRS, 5-LOX]

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
Oligomeric proanthocyanidins (polyphenolic, condensed tannins)	Widespread (esp. vegetables) [bark, flower, fruit, nut, seed]	AO/FRS
Olivil (lignan)	<i>Cerbera manghas</i> (Apocynaceae)	AO/FRS – scavenges DPPH
<i>Oryza</i> polyphenols (polyphenolic)	<i>Oryza sativa</i> (rice) (Poaceae)	AO/FRS
γ -Oryzanol (ferulic esters of sterols & triterpene alcohols)	<i>Oryza sativa</i> (rice) (Poaceae)	AO/FRS [hypocholesterolaemic]
Piceatannol (= 3,3',4,5'-Tetrahydroxystilbene) (stilbene)	<i>Picea</i> spp., <i>Pinus</i> spp., <i>Tsuga canadensis</i> (Pinaceae), <i>Laburnum anagyroides</i> [wood], <i>Mezoneuron cucullatum</i> (Fabaceae)	AO/FRS – scavenges DPPH (CDPK, MLCK, PKA, PKC, p56 ^{lck} TK, p40 TK) [antifungal]
Procyanidin B-2 (condensed tannin)	<i>Malus</i> sp. (apple) (Rosaceae), <i>Uncaria sinsensis</i> (Rubiaceae)	AO/FRS – scavenges DPPH (PKC)
Propylgallate (phenolic ester)	<i>Camellia</i> spp. (tea) (Theaceae) [leaf]	AO/FRS (scavenges O ₂ ⁻) (XO)
Punicalagin (ellagitannin)	<i>Terminalia catappa</i> (Combretaceae), <i>Punica granatum</i> (Punicaceae) [pericarp]	AO/FRS – scavenges O ₂ ⁻ ; ↓ lipid peroxidation & O ₂ ⁻ formation (CA)
Punicalin (ellagitannin)	<i>Terminalia catappa</i> (Combretaceae), <i>Punica granatum</i> (Punicaceae) [pericarp]	AO/FRS – scavenges O ₂ ⁻ ; ↓ lipid peroxidation & O ₂ ⁻ formation (CA)
Pycnogenol (<i>Pinus</i>) (Proanthocyanidin polyphenolic, bioflavonoid & phenolic acid mixture) (phenolics)	<i>Pinus maritima</i> (Pinaceae) [bark]	AO/FRS – scavenges OH & NO
Pycnogenol (<i>Vitis</i>) (Proanthocyanidin polyphenolic, bioflavonoid & phenolic acid mixture) (phenolics)	<i>Vitis vinifera</i> (grape) (Vitaceae) [seed]	AO/FRS – scavenges O ₂ ⁻ , OH
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Oenothera biennis</i> (Onagraceae)	AO/FRS – scavenges O ₂ ⁻ , ONOO ⁻ (LOX, PK, RTK) [AI, feeding stimulant; ↓ Dehydroascorbate, ↑ lysosomal stability]
<i>trans</i> -Resveratrol (= 3,5,4'-Trihydroxystilbene) (stilbene)	<i>Cassia</i> , <i>Intsia</i> , <i>Trifolium</i> (Fabaceae), <i>Nothofagus</i> (Fagaceae), <i>Veratrum</i> (Liliaceae), <i>Artocarpus</i> , <i>Morus</i> (Moraceae), <i>Eucalyptus</i> (Myrtaceae), <i>Pinus</i> (Pinaceae), <i>Polygonum</i> (Polygonaceae), <i>Vitis vinifera</i> (Vitaceae) spp.	AO/FRS scavenges DPPH, inhibits lipid peroxidation) (COX, LOX) [apoptotic]
Rosmarinic acid (phenylpropanoid)	<i>Anethum</i> , <i>Levisticum</i> , <i>Sanicula</i> , <i>Astrantia</i> (Apiaceae), <i>Symphytum</i> (Boraginaceae), <i>Melissa</i> , <i>Mentha</i> , <i>Prunella</i> , <i>Ocimum</i> , <i>Origanum</i> , <i>Rosmarinus</i> , <i>Salvia</i> , <i>Teucrium</i> (Lamiaceae) spp.	AO/FRS – scavenges DPPH (AR, COX-1, COX-2, ITD) [AI]

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects/
Rutoside (= Quercetin 3-rutinoside; Rutin) (flavonol O-glycoside)	<i>Ilex aquifolium</i> (Aquifoliaceae), <i>Sambucus simpsonii</i> (Caprifoliaceae), <i>Polygonum</i> spp. (Polygonaceae), <i>Ruta graveolens</i> (Rutaceae)	AO/FRS – ↓ LDL peroxidation, FRS (AR, 5-LOX) [overcomes capillary fragility]
Scirpusin A (stilbene dimer)	<i>Mezoneuron cucullatum</i> (Fabaceae),	AO/FRS – scavenge DPPH
[Silibinin dihemiacetate] (flavonolignan)	Semi-synthetic from antihepatotoxic Silybin (Silymarin) from <i>Silybum marianum</i> (Asteraceae)	AO/FRS – scavenges OH, O ₂ ⁻ ; ↓ Fe(III)/ascorbate-induced lipid peroxidation
Suspensaside (phenylpropanoid glycoside)	<i>Forsythia suspensa</i> (Oleaceae) [fruit]	AO/FRS (cAMP PDE, 5-LOX) [AI, anti-asthmatic]
5,7,3',5'-Tetrahydroxy-8,4'-dimethoxyflavonol (flavonol)	<i>Chorizanthe diffusa</i> (Polygonaceae)	AO/FRS – scavenges DPPH
4,2',4',6'- Tetrahydroxychalcone-2'-glucoside (flavone glycoside)	<i>Helichrysum italicum</i> (Asteraceae) [flower]	AO/FRS – scavenges OH, O ₂ ⁻ , lipid peroxy radicals; ↓ Fe(II)-induced lipid peroxidation
5,7,3',4'- Tetrahydroxyflavonol-3-rhamnoside (flavonol glycoside)	<i>Prunus cerasus</i> (tart cherry) (Rosaceae)	AO/FRS – inhibits Fe ²⁺ -induced lipid peroxidation
5,6,7,4'-Tetrahydroxyflavonol-3-rutinoside (flavonol glycoside)	<i>Daphniphyllum calycinum</i> (Daphniphyllaceae)	AO/FRS – scavenges DPPH
Theaflavin (polyphenol)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	AO/FRS – scavenges NO, O ₂ ⁻ (XO)
Theaflavin-3,3'-digallate (polyphenol)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	AO/FRS – scavenges NO, O ₂ ⁻ (XO)
Theaflavin-3-gallate (polyphenol)	<i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	AO/FRS – scavenges NO, O ₂ ⁻ (XO)
Thearubigins (polyphenols)	<i>Camellia sinensis</i> (tea) (Theaceae)	AO/FRS – scavenge NO
5,8,4'-Trihydroxy-7,3'-dimethoxyflavonol (flavonol)	<i>Chorizanthe diffusa</i> (Polygonaceae)	AO/FRS – scavenges DPPH
5,7,4'-Trihydroxyflavanone (flavanone)	<i>Prunus cerasus</i> (tart cherry) (Rosaceae)	AO/FRS – inhibits Fe ²⁺ -induced lipid peroxidation
5,7,4'-Trihydroxyflavonol 3-rutinoside (flavonol glycoside)	<i>Prunus cerasus</i> (tart cherry) (Rosaceae)	AO/FRS – inhibits Fe ²⁺ -induced lipid peroxidation
5,7,4'-Trihydroxyisoflavone (isoflavone)	<i>Prunus cerasus</i> (tart cherry) (Rosaceae)	AO/FRS – inhibits Fe ²⁺ -induced lipid peroxidation
5,7,4'-Trihydroxyisoflavone 7-glucoside (isoflavone glycoside)	<i>Prunus cerasus</i> (tart cherry) (Rosaceae)	AO/FRS – inhibits Fe ²⁺ -induced lipid peroxidation
5,3',4'-Trihydroxy-7-methoxyflavonol (flavonol)	<i>Chorizanthe diffusa</i> (Polygonaceae)	AO/FRS – scavenges DPPH
6,3',4'-Trihydroxy-7-methoxyflavonol (flavonol)	<i>Chorizanthe diffusa</i> (Polygonaceae)	AO/FRS – scavenges DPPH

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects/
5,7,4'-Trihydroxy-3'-methoxyflavonol 3-rutinoside (flavonol glycoside)	<i>Prunus cerasus</i> (tart cherry) (Rosaceae)	AO/FRS – inhibits Fe ²⁺ -induced lipid peroxidation
2,10,11-Trihydroxy-8-methoxy-1,6,7,8-tetrahydro-2H-benzo[e]azecine-3,5-dione (cyclic phenyllactamide)	<i>Salvia miltiorrhiza</i> (Lamiaceae) [rhizome]	AO/FRS – scavenges DPPH
Tubuloside A (phenylethanoid)	<i>Cistanche deserticola</i> (Orobanchaceae) [stem]	AO/FRS – scavenges NO radical (↓ NO ₂ ⁻) [AI]
Tubuloside B (phenylethanoid)	<i>Cistanche deserticola</i> (Orobanchaceae) [stem]	AO/FRS – scavenges NO radical (↓ NO ₂ ⁻) [AI]
Tyrosol (= 4-Hydroxyphenylethanol) (phenol)	<i>Olea europaea</i> (olive) (Oleaceae) [leaf, bark, fruit, olive oil], <i>Plantago major</i> (Plantaginaceae)	[AO/FRS, 5-LOX & LTB ₄ generation inhibited (weak)]
Vanillin (= 3-Methoxy-4-hydroxy-benzaldehyde; Methylprotocatechuic aldehyde) (phenolic acid)	Widespread as aglycone & glucoside (Vanilloside); <i>Xylopiya aethiopica</i> (Annonaceae), <i>Dahlia</i> spp. (Asteraceae), <i>Beta vulgaris</i> (Chenopodiaceae), <i>Asparagus</i> spp. (Liliaceae), <i>Syzygium aromaticum</i> (Myrtaceae), <i>Gymmadenia</i> spp., <i>Vanilla planifolia</i> (Orchidaceae), <i>Hordeum vulgare</i> (Poaceae), <i>Coffea</i> spp. (Rubiaceae), <i>Citrus paradisi</i> , <i>Ruta</i> spp. (Rutaceae), <i>Litchi chinensis</i> , <i>Nephelium lappaceum</i> (Sapindaceae), <i>Vitis vinifera</i> (Vitaceae) (wine)	AO/FRS (OD-R (vanilla-like, candy) [antifungal]; non-fat dry milk aroma-active (elevated by higher heat-treatment)
Verbascoside (= Acteoside; Kusagin) (phenyl propanoid glycoside)	<i>Echinacea</i> spp. (Asteraceae), <i>Ballota nigra</i> (Lamiaceae), <i>Buddleja</i> spp., <i>Forsythia suspensa</i> (Oleraceae), <i>Plantago media</i> (Plantaginaceae), <i>Verbascum sinuatum</i> (Scrophulariaceae)	AO/FRS – scavenges OH, O ₂ ⁻ , H ₂ O ₂ , HOCl (AR, EGF-RTK, 5-LOX) [AI, antiproliferative]
<i>Vitis</i> polyphenols (polyphenols)	<i>Vitis vinifera</i> (Vitaceae) [red wine]; “French paradox” – moderate red wine consumption beneficial for health, protects against coronary heart disease	AO/FRS
Terpene		14.2t
1-Acetoxyarturin (sesquiterpene lactone)	<i>Podanthus</i> spp. (Asteraceae)	AO/FRS – scavenges DPPH
8-Acetoxyovatifolin (sesquiterpene lactone)	<i>Podanthus</i> spp. (Asteraceae)	AO/FRS – scavenges DPPH
Arturin (sesquiterpene lactone)	<i>Podanthus</i> spp. (Asteraceae)	AO/FRS – scavenges DPPH
Carnosic acid (abietane diterpenoid)	<i>Rosmarinus officinalis</i> (rosemary), <i>Salvia officinalis</i> (Lamiaceae) [leaf]	AO/FRS – scavenges OH

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) / part/	Effect (other targets) / in vivo effects/
Carnosol (abietane diterpenoid)	<i>Salvia officinalis</i> (sage), <i>Rosmarinus officinalis</i> (rosemary) (Lamiaceae) [leaf]	AO/FRS – scavenges OH (COX, 5-LOX)
β -Carotene (carotene)	Widespread	AO/FRS [pro-vitamin A, sunscreen agent, yellow]
Carotenoids – ~600 known (carotenes)	Widespread (PS light-harvesting assembly pigments; plastids)	AO/FRS
Coenzyme Q (= CoQ; Ubiquinone) (terpene)	Universal (mitochondrial electron transfer participant); e.g. CoQ ₁₀	AO/FRS – inhibits LDL oxidation [anti-ageing, antiatherosclerotic, membrane stabilizer, nutraceutical]
Deacetylovatifolin (germacranolide sesquiterpene lactone)	<i>Podanthus</i> spp. (Asteraceae)	AO/FRS – scavenges DPPH
11,13-Dihydroovatifolin (germacranolide sesquiterpene lactone)	<i>Podanthus</i> spp. (Asteraceae)	AO/FRS – scavenges DPPH
1,10-Epoxyovatifolin (germacranolide sesquiterpene lactone)	<i>Podanthus</i> spp. (Asteraceae)	AO/FRS – scavenges DPPH
<i>Ginkgo biloba</i> extract e.g. EGb-761) (triterpene saponins + flavonoids)	<i>Ginkgo biloba</i> (maidenhair tree) (Ginkgoaceae) [leaf]; anti- glaucoma & alleviates diabetic retinopathy (alloxan-treated rat) (esp. +Zn²⁺)	AO/FRS – ROS, NO; ↓ lipid peroxidation [AI, PAF antagonism; ↑ blood flow, blocks angiogenesis, ↓ metastasis, ↓ LDL oxidation]
Lutein (= Vegetable luteol; Xanthophyll) (carotene)	Widespread in green leaves & fruit e.g. <i>Brassica</i> spp. (Brassicaceae) [leaf], <i>Ananas cosmosus</i> (pineapple) (Bromeliaceae), <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Rheum rhabarbarum</i> (Polygonaceae), <i>Citrus</i> spp. (Rutaceae), <i>Malus</i> , <i>Prunus</i> (Rosaceae) sp.; deposited in retinal macula	AO/FRS [dietary vitamin; protects visual macula by absorbing blue light]; active against age-related macula degeneration (AMD) (leading cause of irreversible blindness)
Ovatifolin (germacranolide sesquiterpene lactone)	<i>Podanthus</i> spp. (Asteraceae)	AO/FRS – scavenges DPPH
Plastoquinone (carotene)	In chloroplasts/plastids of all photosynthetic organisms – cf. mitochondrial ETC Coenzyme Q (Ubiquinone)	AO/FRS – ↓ lipid peroxidation & pigment bleaching
Soyasaponin α (terpene saponin glycoside & DDMP ether)	<i>Christia obcordata</i> , <i>Desmodium heterophyllum</i> , <i>D. triflorum</i> , <i>D. uncinatum</i> , <i>Phaseolus coccineus</i> , <i>Vigna sinensis</i> (Fabaceae) [seed]	AO/FRS – scavenges OH, O ₂ ⁻
Soyasaponin α g (= Soyasapogenol 3-O-glycoside 22-O-DDMP (2,3-dihydro-2,5-dihydroxy-6-methyl-4H-pyran-4-one) ether) (terpene saponin glycoside & DDMP ether)	<i>Christia obcordata</i> , <i>Desmodium heterophyllum</i> , <i>D. triflorum</i> , <i>D. uncinatum</i> , <i>Glycine max</i> , <i>G. soja</i> , <i>Phaseolus coccineus</i> , <i>P. lunatus</i> , <i>P. vulgaris</i> , <i>Vigna sinensis</i> (Fabaceae) [seed]	AO/FRS – scavenges OH, O ₂ ⁻

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects/
Soyasaponin $\beta\alpha$ (terpene saponin glycoside & DDMP ether)	<i>Amorpha</i> , <i>Desmodium</i> , <i>Galactia</i> , <i>Glycine</i> , <i>Phaseolus</i> , <i>Vigna</i> (Fabaceae) spp. [seed]	AO/FRS – scavenges OH, O_2^-
Soyasaponin $\beta\gamma$ (terpene saponin glycoside & DDMP ether)	<i>Aeschynomene</i> , <i>Alisicarpus</i> , <i>Amorpha</i> , <i>Amphicarphaea</i> , <i>Apios</i> , <i>Arachis</i> , <i>Centrosema</i> , <i>Christia</i> , <i>Cicer</i> , <i>Desmodia</i> , <i>Dolichos</i> , <i>Dunbaria</i> , <i>Flemingia</i> , <i>Galactia</i> , <i>Glycine</i> , <i>Indigofera</i> , <i>Lens</i> , <i>Lotononis</i> , <i>Medicago</i> , <i>Phaseolus</i> , <i>Pisum</i> , <i>Rudua</i> , <i>Stylosanthes</i> , <i>Vicia</i> , <i>Vigna</i> , <i>Wisteria</i> spp. (Fabaceae) [seed]	AO/FRS – scavenges OH, O_2^-
Soyasaponin $\gamma\gamma$ (terpene saponin glycoside & DDMP ether)	<i>Amorpha fruticosa</i> , <i>Apios americana</i> , <i>Canavalia</i> spp., <i>Centrosema pubescens</i> , <i>Glycine</i> spp., <i>Phaseolus</i> spp., <i>Pisum</i> <i>sativum</i> , <i>Vigna sinensis</i> , <i>Wisteria</i> <i>floribunda</i> (Fabaceae) [seed]	AO/FRS – scavenges OH, O_2^-
[α -, β -, γ - & δ -Tocopherols (= Vitamin E)] (chromanol isoprenoid)	Green vegetables, palm, safflower, sunflower oil, wheat germ; discovered by Herbert M. Evans (Berkeley, USA, 1922)	AO/FRS – scavenges OH, O_2^- ; α -Tocopherol most bioactive (PKC) [anti- ageing nutraceutical, antioxidant]
α - & β -Tocotrienols (chromanol isoprenoids)	<i>Triticum aestivum</i> (wheat germ oil) (Poaceae)	AO/FRS – inhibit LDL oxidation [\downarrow HMGCoAR, antiproliferative, antiatherosclerotic, neuroprotective]
Tyrosol (phenolic)	<i>Olea europaea</i> (Oleaceae) [olive oil], <i>Plantago major</i> (Plantaginaceae)	5-LOX (AO/FRS)
Withaperuvin-E (phytosterol)	<i>Physalis peruviana</i> (Solanaceae)	AO/FRS
Zeaxanthin (= (3R, 3R')-3, 3-Dihydroxy- β -carotene; Zeaxanthol) (carotene)	Widespread in leaves; <i>Crocus sativus</i> (Iridaceae) [flower], <i>Lilium hansonii</i> (Liliaceae), <i>Zea mays</i> (corn) (Poaceae) [seed], <i>Citrus sinensis</i> , <i>C.</i> spp., (Rutaceae) [fruit peel], <i>Capsicum</i> <i>annuum</i> (red pepper), <i>Lycium</i> <i>barbarum</i> (Solanaceae) [fruit]	AO/FRS [dietary vitamin; protects visual macula by absorbing blue light]; active against age- related macula degeneration (leading cause of irreversible blindness)
Other		14.2o
N-Acetylcysteine (amino acid, thiol)	Glutathione (GSH) precursor	AO/FRS – scavenges O_2^- , NO_2^-
Aged garlic extract (= AGE) (thiols)	<i>Allium sativum</i> (garlic) (Liliaceae) [bulb]; garlic suppresses LDL oxidation & antiatherosclerotic	AO/FRS – scavenges ROS (e.g. OH), increases GSH [anti-ageing]
Allicin (= S-Oxo- diallyldisulfide) (allyl disulfide)	From crushed <i>Allium cepa</i> , <i>A. sativum</i> (garlic) (Liliaceae) bulbs via allinase from Allicin	AO/FRS – scavenges ROS
Alliin (allyl amino acid)	<i>Allium cepa</i> , <i>A. sativum</i> (garlic) (Liliaceae) [bulb]	AO/FRS – scavenges OH, \downarrow LDL oxidation [\downarrow atherogenic effects of oxidized LDL, PAI]

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects
L-Ascorbic acid (= Vitamin C) (sugar, lactone); oxidized form Dehydroascorbate; Vitamin C use against common cold popularized by Linus Pauling (USA, Nobel Prizes for Chemistry, 1954 [bonding & protein structure] & Peace, 1962 [against nuclear weapons]); synthesized by Tadeus Reichstein (Poland/ Switzerland, Nobel Prize, 1953, Physiology/Medicine, glucocorticoids)	Widespread; <i>Malus</i> (apple), <i>Rosa</i> (rose hip) (Rosaceae), <i>Citrus</i> (Rutaceae), <i>Capsicum</i> (Szgedi paprika) (Solanaceae) spp.; Vitamin C reaches 20–300 mM in chloroplasts; discovered by Albert Szent-Györgyi (Hungary/ USA, Nobel Prize, 1937 [vitamin C & biological oxidations]); structure & synthesis (Sir Walter Haworth (UK, Nobel Prize, Chemistry, 1937, [carbohydrates & vitamin C]); identified by W.A. Waugh & C.G. King (USA)	AO/FRS – scavenges DPPH, nitrite (NO ₂ ⁻), OH, O ₂ ⁻ ; O ₂ ⁻ , ONOO ⁻ ; regenerates α- Tocopherol from α- Tocopheryl radical; anti- ageing nutraceutical; vitamin C-deficiency disease scurvy cured by lime juice – found by Dr James Lind & promoted by Captain James Cook in British navy (18th century) – hence “limeys”; Dr Lind befriended poet Percy Shelley & was thence the “source” for <i>Frankenstein or The Modern Prometheus</i> by Mary Wollstonecraft Shelley
Bran (feruloylated & lignan cross-linked cellulose & hemicellulose)	<i>Triticum aestivum</i> (wheat) (Poaceae) [seed]	AO/FRS – scavenges nitrite (NO ₂ ⁻)
Citrulline (R group O for N-arginine analogue) (amino acid)	<i>Citrullus lunatus</i> , <i>C. vulgaris</i> (watermelon) [elevated in drought], <i>Sesamum indicum</i> (Pedaliaceae); animal urea cycle intermediate	AO/FRS – scavenges OH radical
Cysteine (thiol amino acid)	Universal; <i>Helianthus annuus</i> (Asteraceae)	AO/FRS – scavenges O ₂ ⁻ , NO ₂ ⁻
Dimethyldiselenide (= CH ₃ -Se-Se-CH ₃) (diselenide)	Selenium accumulator plants – <i>Astragalus</i> (Fabaceae), <i>Oenopsis</i> , <i>Xylorhiza</i> (Asteraceae), <i>Stanleya</i> (Brassicaceae) spp.	Reacts with thiols e.g. GSH → ROS (O ₂ ⁻ , OH) → selenium toxicity
Ergothioneine (thiol amino acid)	<i>Hevea brasiliensis</i> (rubber) (Euphorbiaceae)	AO/FRS – scavenges OH, HOCl; ↓ Fe(II)- & Cu(II)- dependent lipid OH generation from H ₂ O ₂ , FA oxidation & protein oxidation
Glucosinolates (sugar derivative)	Brassicaceae	AO (per glutathione-S- transferase induction)
Glutathione (= γ-Glutamyl- cysteinyl-glycine); GSH) (peptide); GSH biosynthesis studies by Konrad Bloch (Germany/USA, Nobel Prize, Physiology/ Medicine, 1964, cholesterol biosynthesis)	Universal cytosolic reductant; oxidized dimer G-S-S-G; polyGSH transition metal chelator in plants; crystalliza- tion & structure by Edward Kendall (USA) (Nobel Prize, Physiology/Medicine, 1950, glucocorticoids, with T. Reichstein & P. Hench)	AO/FRS – scavenges O ₂ ⁻ , NO ₂ ⁻ [keeps thiols reduced in cytosol]

(continued)

Table 14.2 (Continued)

Compound (class)	Plant (family) part	Effect (other targets) / in vivo effects/
Mannitol (sugar)	Widespread	AO/FRS – scavenges O_2^- , OH
Nitric oxide (= NO) (nitrogen oxide)	Universal	AO/FRS in some situations (e.g. after herbicide methylviologens Paraquat & Diquat application in plants)
Olive oil (unsaturated FAs, triterpenes)	<i>Olea europaea</i> (olive) (Oleaceae) [fruit & seed oil]; anti-atherogenic “Mediterranean diet” – notably olive oil, red wine & vegetables	AO/FRS – scavenges DPPH, ↓ Scavenger Receptor mRNA (i.e. ↓ Scavenger Receptor expression & hence oxidized LDL uptake & atherogenic lipid accumulation in intimal macrophages)
Plant oils (esp. unsaturated FAs)	Almond, corn, hazelnut, linseed, olive, peanut, rapeseed, safflower, sesame, soya bean, sunflower, walnut oil	AO/FRS – scavenges DPPH radical
Phytic acid (= Inositol hexaphosphate) (alicyclic polyphosphate)	Widespread e.g. Poaceae [seed]; <i>Triticum aestivum</i> (Poaceae)	AO
Selenite (= SO_3^-) (selenium oxide)	Selenium accumulator plants – <i>Oenopsis</i> , <i>Xylorrhiza</i> (Asteraceae), <i>Stanleya</i> (Brassicaceae), <i>Astragalus</i> (Fabaceae) spp.	Reacts with thiols e.g. GSH → ROS (O_2^- , OH) → selenium toxicity
Selenium dioxide (= SeO_2) (selenium oxide)	Selenium accumulator plants – <i>Oenopsis</i> , <i>Xylorrhiza</i> (Asteraceae), <i>Stanleya</i> (Brassicaceae), <i>Astragalus</i> (Fabaceae) spp.	Reacts with thiols e.g. GSH → ROS (O_2^- , OH) → selenium toxicity
Non-plant reference		14.2n
[Dimethylsulfoxide (= DMSO)] (alkyl sulfoxide)	Synthetic	AO/FRS – scavenges O_2^- , OH [broadly compatible solvent for polar & nonpolar compounds]
[Fish oil] (esp. unsaturated FAs)	Fish	↓ intercellular adhesion molecule 1 (ICAM-1) & Scavenger Receptor expression [anti-atherosclerosis per ↓ macrophage-induced plaque]
[Trolox] (carotene)	Analogue of α -Tocopherol	AO/FRS – scavenges OH

Table 14.3 Pro-oxidant compounds

Compound (class)	Plant (family) part	Enzyme inhibited/effect (other targets) / in vivo effects/
Ascorbate peroxidase (APX)		14.3A
[2,6-Dichloroisonicotinic acid] (chloro piperidine)	Synthetic	APX (→ elevates H_2O_2) [induces plant defence responses]

(continued)

Table 14.3 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited / effect (other targets) in vivo effects
Salicylic acid (= 2-Hydroxybenzoic acid) (phenolic)	Widespread – plant defence signalling molecule; <i>Sauromatum guttatum</i> (Araceae), <i>Betula lenta</i> (birch), <i>Gaultheria procumbens</i> (Ericaceae), <i>Glycyrrhiza glabra</i> (Fabaceae)	APX (→ elevates H ₂ O ₂) [induces plant defence responses & plant systemic acquired resistance (SAR)]
ROS generation		14.3B
Terpene		14.3Bt
Artemisinin (= Quinghaosu) (sesquiterpene lactone peroxide)	<i>Artemisia annua</i> (qing hao) (Asteraceae); important antimalarial source after post-Vietnam War rise of chloroquine-resistant malaria-causing <i>Plasmodium falciparum</i>	O ₂ ⁻ generation (after binding to haem from proteolytically degraded haemoglobin) [antimalarial] 500 million have malaria
Other		14.3Bo
Cu(II) (= Cupric ion)	Environmental	Lipid peroxidation
Fe(II) (= Ferrous ion)	Environmental	Lipid peroxidation
Dimethyldiselenide (= CH ₃ -Se-Se-CH ₃) (alkyl diselenide)	From methylated seleno-amino acids 1.-Selenomethionine & 1.-Se-methylselenocysteine	Generates O ₂ ⁻ [anticarcinogenic, apoptotic, chemopreventative]
Hydrogen peroxide (= H ₂ O ₂)	Universal	Oxidant
Se-Methylselenocysteine (seleno amino acid)	<i>Oenopsis condensata</i> (Asteraceae), <i>Astragalus bisulcatus</i> (Fabaceae) – selenium accumulating plants	Yields Dimethyldiselenide, Methylseleninic acid & Methylselenol → O ₂ ⁻ [animal blind staggers, anticarcinogenic chemopreventative, apoptotic, selenosis]
Methylseleninic acid (= CH ₃ -Se(=O)-OH) (selenium derivative)	From methylated seleno-amino acids 1.-Selenomethionine & 1.-Se-methylselenocysteine	Generates O ₂ ⁻ [anticarcinogenic, apoptotic, chemopreventative]
Methylselenol (= Methyl-SeH) (senenol)	From 1.-Selenomethionine, 1.-Se-Methylselenocysteine	Generates O ₂ ⁻ [apoptotic chemopreventative cytotoxic]
Mimosine (= Leucaenol) (pyridinone amino acid)	<i>Leucaena leucocephala</i> (jumbie bean), <i>Mimosa pudica</i> (sensitive plant) (Fabaceae) [leaf, seed]; <i>M. pudica</i> leaves close on mechanical stimulation	Mimosine-Fe(II) → DNA binding & oxidative breakage (DNA) [depilatory, goitrogenic, teratogenic]
Nitric oxide (NO)	Universal	Generates nitrogen oxide radicals
Nitrite (NO ₂ ⁻)	Universal	Generates peroxy nitrite radical
Peroxy nitrite (ONOO ⁻)	Universal; <i>ex</i> cigarette smoke – <i>Nicotiana tabacum</i> (Solanaceae)	Reactive FR
Ranunculin (aliphatic lactone glycoside)	<i>Actaea rubra</i> , <i>Anemone pulsatilla</i> , <i>Clematis</i> sp., <i>Ranunculus</i> sp. (buttercup) (Ranunculaceae)	FR generation – O ₂ ⁻ (bitter) [DNAS inhibition per FR; wounding plant yields vesicant dermatitic oil Protoanemonin]
1.-Selenocysteine (seleno amino acid)	Selenium accumulating plants growing on seleniferous soils	Yields Dimethyldiselenide, Methylseleninic acid & Methylselenol → O ₂ ⁻ [chemopreventative, selenium toxicity]

(continued)

Table 14.3 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited / effect (other targets) in vivo effects
L-Selenomethionine (seleno amino acid)	Selenium accumulating plants growing on seleniferous soils	Yields Dimethyldiselenide, Methylseleninic acid & Methylselenol → O ₂ ⁻ [chemopreventative, selenium toxicity]
Superoxide (O ₂ ⁻)	Universal	Reactive FR
Hydroxyl radical (OH [*])	Universal	Reactive FR
Non-plant reference		14.3Bn
[Cryptogein] (protein)	<i>Phytophthora cryptogaea</i> – fungal pathogen on <i>Nicotiana tabacum</i> (tobacco) (Solanaceae)	Fungal elicitor – elicits infected plant intracellular NO burst
[DMSO (= Dimethylsulfoxide)] (alkyl sulfoxide)	Synthetic	DMSO + H ₂ O ₂ & NaOH generates OH, O ₂ ⁻ & CH ₃ ⁺
DPPH (= 1,1-Diphenyl-2- picrylhydrazyl radical) (aromatic)	Synthetic	Stable free radical [used to detect & quantitate AO/FRSs]
Xanthine oxidase (= XO) (enzyme)	Universal	XO + Hypoxanthine generates OH, O ₂ ⁻ , & H ₂ O ₂

Table 14.4 Antioxidant enzyme induction and pro-inflammatory blockage

Compound	Plant source	Biochemical process / target(s) inhibited in vivo effects
Antioxidant enzyme induction		14.4A
6-Methylsulfinyl- hexylisothiocyanate (alkyl isothiocyanate, R–N=C=S)	From 6-Methylsulfinyl- hexylglucosinolate from <i>Wasabi japonica</i> (Japanese horseradish) (Brassicaceae)	Induces GST [indirect AO]
Sulforaphane (= 1- Isothiocyanato(methyl- sulfinyl)butane (alkyl isothiocyanate, R–N=C=S)	From Glucoraphanin (= 4- (Methylsulfinyl)-butylglucosinolate) from <i>Raphanus sativus</i> (radish), <i>Brassica oleracea</i> (broccoli) (Brassicaceae)	Induces GST, NADPH quinone reductase (phase 2 antioxidant enzymes) & γ-glutamylcysteine synthetase (GSH synthesis, ↑ GSH) [indirect AO]
Sulforaphane nitrile (R(CN)–N=C=S)	From Glucoraphanin	Induces GST, NADPH quinone reductase [indirect AO]
Pro-inflammatory protein synthesis blockage		14.4B
(For many inhibitors of NFκB-mediated iNOS & COX expression see Tables 7.3 & 8.1)		

Table 14.5 Aldose reductase and aldehyde reductase inhibitors

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) / in vivo effects
Aldose reductase (AR), Aldehyde reductase (AHR)		14.5
Alkaloid		14.5a
Dehydrocorydaline	<i>Corydalis turtchaninovi</i> (Papaveraceae) [tuber]	AR
Phenolic		14.5p
Acacetin (= Apigenin 4'-methylether; 5,7,4'-Trihydroxyflavone 4'-methyl ether) (flavone)	Fern [leaf exudate], Asteraceae [leaf], Betulaceae [leaf bud exudate]; <i>Agastache foeniculum</i> (Lamiaceae); glycosides in <i>Cirsium arvense</i> (Asteraceae), <i>Tilia japonica</i> (Tiliaceae), [leaf], <i>Linaria vulgaris</i> (Scrophulariaceae) [flower]	AR (rat lens) (1–10) (EGF-RTK, ITDI) [allergenic, inhibits histamine release]
Acacetin-7-O-rhamnosyl-glucoside (flavone O-glycoside)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower], <i>Buddleja officinalis</i> (Loganiaceae) [flower]	AR (rat lens) (4.7)
[3-Acetyl-3',4'-Dihydroxy-5,6,7-trimethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (16), AR (rat lens) (8.9)
[Acetyltrisulfate quercetin] (sulfated flavone)	Semi-synthetic derivative of Quercetin	AR (human lens) (0.1)
Acteoside (= Verbascoside; Kusaginidin) (phenolic ketone, phenyl propanoid glycoside)	<i>Stachys sieboldii</i> (Lamiaceae), <i>Buddleja globosa</i> , <i>B. officinalis</i> (Loganiaceae), <i>Forsythia</i> sp. [fruit] (Oleraceae), <i>Monochasma savatieri</i> , <i>Verbascum sinuatum</i> (Scrophulariaceae), Gesneriaceae, Oronbranchaceae, Acanthaceae, Bignonaceae, Verbenaceae, Plantaginaceae	AR (rabbit lens) (0.39) (5-LOX) [AI]
Amentoflavone (= 3',8''-Biapigenin) (biflavone)	<i>Rhus succedanea</i> (Anacardiaceae), <i>Viburnum prunifolium</i> (Caprifoliaceae), <i>Cycas revoluta</i> (Cycadaceae), <i>Ginkgo biloba</i> (Ginkgoaceae), <i>Podocarpus montanus</i> (Podocarpaceae)	AR (rat lens) (> 10) (COX, cAMP PDE) [antifungal]
Apigenin (= 5,7,4'-Trihydroxyflavone) (flavone)	<i>Apium graveolens</i> (Apiaceae), Lamiaceae, ferns [leaf surface], <i>Buddleja officinalis</i> (Loganiaceae) [flower]; <i>Digitaria exilis</i> (fonio, semi-arid zone millet variety) (Poaceae) [seed]; as glycoside in <i>Apium</i> (celery), <i>Petroselinum</i> (parsley) (Apiaceae), <i>Cosmos</i> , <i>Erigeron</i> , <i>Dahlia</i> (Asteraceae), <i>Amorpha</i> (Fabaceae) spp.	AR (rat lens) (1–10) (AROM, cAMP PDE, CDK2, PKA, MLCK, RTK (insulin-RTK, IGF-1-RTK)) [antibacterial, AI, diuretic, hypotensive, nodulation signal for <i>Rhizobium</i>]
Apiin (= Apigenin 7-Api-Glc; Apioside; 4',5,7-Trihydroxy-flavone-7-Api-Glc) (flavone O-glycoside)	<i>Apium graveolens</i> (celery), <i>Petroselinum crispum</i> (parsley) (Apiaceae) [leaf, seed], <i>Capsicum annuum</i> (Solanaceae)	AR (rat lens) (1–10) (cAMP PDE)
Astilbin (= Taxifolin-3-O-Rha) (dihydroflavonol glycoside)	<i>Engelhardtia chrysolepis</i> (Juglandaceae), <i>Astilbe</i> spp. (Saxifragaceae)	AR (rat lens & recombinant human)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) / in vivo effects/
Astragalin (= 3,5,7,4'-Tetrahydroxyflavone 3-O-Glc) (flavanol O-glycoside)	<i>Diospyros virginiana</i> (Ebonaceae), <i>Morus alba</i> (mulberry) (Moraceae), <i>Solenostemma argel</i> , <i>Polygonum salicifolium</i> (Polygonaceae), <i>Adiantum capillus-veneris</i> (Pteridaceae)	AR (rat lens) (1–10)
Avicularin (= Quercetin 3-O-Ara) (flavanol O-glycoside)	<i>Curatella americana</i> (Dilleniaceae), <i>Chimaphila umbellata</i> (Ericaceae), <i>Taxillus kaemhyferi</i> (parasitic) (Loranthaceae) [leaf]	AR (rat lens) (1–10)
Axillarin (= 5,7,3',4'-Tetrahydroxy-3,6-dimethoxyflavone; Quercetagenin 3,6-dimethyl ether) (flavanol)	<i>Matricaria chamomilla</i> (chamomile) [flower], <i>M. recutita</i> , <i>Achillea</i> spp., <i>Artemisia</i> spp. (Asteraceae) [aerial], <i>Didierea</i> spp. (Didieraceae)	AHR (rat brain) (<10), AR (bovine lens) (0.2) [0.2], AR (rat lens) (0.03) [0.02]
Baicalein (= 5,6,7-Trihydroxyflavone) (flavone)	<i>Scutellaria</i> spp. (Lamiaceae) [root, leaf], <i>Plantago major</i> (Plantaginaceae)	AR (rabbit lens) (1), AR (rat lens) (1–10) (glyoxalase-I, LOX) [antiallergic, AI, diuretic]
Baicalin (= Baicalein 7-O-glucuronide; 5,6,7-Trihydroxyflavone 7-O-glucuronide) (flavone O-glycoside)	<i>Scutellaria</i> spp. (Lamiaceae) [root], <i>Plantago major</i> (Plantaginaceae)	AR (rat lens) (< 10) [AI, diuretic]
6,6''-Bigenkwanin (biflavone)	<i>Ouratea spectabilis</i> (Ochnaceae) [leaf]	AR
Brevifolin carboxylic acid (phenolic ketone)	<i>Phyllanthus niruri</i> (Euphorbiaceae) [plant]	AR (rat lens) (2)
Capillarisin (flavonoid)	<i>Artemisia capillaris</i> (Asteraceae)	AR (bovine lens) (0.7)
2-Carbethoxy-5,7-dihydroxy-4'-methoxy-isoflavone (isoflavone)	Semi-synthetic	AR (rat lens) (1–10)
(+)-Catechin (= Catechinic acid; Catechuic acid; (+)-Cyanidanol; (2R,3S)-5,7,3',4'-Tetrahydroxyflavan-3-ol) (flavan-3-ol)	<i>Agrimonia eupatoria</i> (Rosaceae), <i>Salix caprea</i> (willow) (Salicaceae) [flower]	AR (rat lens) (100) (COX-1, COX-2) [antioxidant]
Chlorogenic acid (= 3-Caffeoylquinic acid) (phenylpropanoid)	<i>Chrysanthemum indica</i> , <i>Helianthus annuus</i> (Asteraceae) [flower], <i>Coffea arabica</i> (coffee bean) (Rubiaceae), <i>Theobroma cacao</i> (cocoa bean) (Sterculiaceae), <i>Camellia sinensis</i> (tea) (Theaceae) [leaf]	AR (rat lens) (2; 0.1–1) [antibacterial, antitumour, antiviral, oviposition stimulant]
Chrysin (= 5,7-Dihydroxyflavone) (flavone)	<i>Daucus carota</i> (Apiaceae), <i>Pinus</i> spp. (Pinaceae) [wood], <i>Populus</i> spp. (poplar) (Salicaceae) [leaf bud], <i>Escallonia</i> spp. (Saxifragaceae) [leaf]	AR (rat lens) (1–10) (cAMP PDE, ECMOX, 17 β HSOR, ITD, Nase) [antibacterial, AI, anxiolytic, inhibits histamine release]

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited (other targets) / in vivo effects/
Chrysoeriol (= Luteolin 3'-methyl ether; 5,7,4'-Trihydroxy-3'-methoxy-flavone) (flavone)	<i>Coleus amboinicus</i> (Lamiaceae) [leaf surface], <i>Arachis hypogaea</i> (Fabaceae), <i>Notholaena californica</i> (fern) (Pteridophyta) [frond surface]	AR (rat lens) (>10)
Chrysosplenol B (= 5,4'-Dihydroxy-3,6,7,3'-tetramethoxyflavone) (flavonol)	<i>Matricaria chamomilla</i> (chamomile) (Asteraceae)	AR (rat lens) (>10) AI, antispasmodic, sedative
Chrysosplenoside D (= 5,4'-Dihydroxy-3,6,7,3'-tetramethoxyflavone-4'-Glc) (flavonol O-glucoside)	<i>Matricaria chamomilla</i> (chamomile) (Asteraceae)	AR (rat lens) (>10) AI, antispasmodic, sedative
Cirsilineol (= 5,4'-Dihydroxy-6,7,3'-trimethoxyflavone) (flavone)	<i>Artemisia capillaris</i> (Asteraceae), <i>Thymus vulgaris</i> (thyme), <i>Salvia tomentosa</i> , <i>Sideritis</i> spp. (Lamiaceae) [leaf surface]	AR (bovine lens) (9), AR (rat lens) (7)
Cirsilineol 4'-Glc (= 5,4'-Dihydroxy-6,7,3'-trimethoxyflavone 4'-Glc) (flavone O-glucoside)	<i>Cirsium</i> sp. (Asteraceae)	AR (bovine lens) (0.6), AR (rat lens) (0.4) AR (rat & bovine lens)
Cirsiliol (= 5,3',4'-Trihydroxy-6,7-dimethoxyflavone) (flavone)	<i>Cirsium lineare</i> (Asteraceae), <i>Salvia officinalis</i> (sage), <i>Sideritis</i> spp. (Lamiaceae) [aerial]	AR (bovine lens) (1), AR (rat lens) (0.1) (5-LOX)
Cirsiliol 4'-Glc (= 5,3',4'-Trihydroxy-6,7-dimethoxyflavone 4'-O-Glc) (flavone O-glycoside)	<i>Cirsium</i> sp. (Asteraceae), <i>Teucrium polium</i> (Lamiaceae)	AR (bovine lens) (5), AR (rat lens) (8)
Cirsimaritin (= 5,4'-Dihydroxy-6,7-dimethoxyflavone) (flavone)	<i>Artemisia capillari</i> (Asteraceae), <i>Salvia officinalis</i> (sage) (Lamiaceae) [plant]	AR (bovine lens) (2; 5), AR (rat lens) (1)
Cirsimaritin 4'-Glc (= 5,4'-Dihydroxy-6,7-dimethoxyflavone 4'-Glc) (flavone O-glucoside)	<i>Salvia officinalis</i> (sage) (Lamiaceae) [plant]	AR (bovine lens) (1-10), AR (rat lens) (>10)
Cosmosiin (= Apigenin 7-O-Glc; 5,7,4'-Trihydroxyflavone-7-O-Glc) (flavone O-glycoside)	<i>Cosmos bipinnatus</i> (Asteraceae), <i>Agastache foeniculum</i> (Lamiaceae)	AR (rat lens) (1-10) [modulation signal for <i>Rhizobium</i>]
Delphinidin (= 3,5,7,3',4',5'-Hexahydroxyflavilium chloride) (flavilium, anthocyanidin)	<i>Abrus precatorius</i> (Fabaceae); glycosides in <i>Plumbago rosea</i> (Plumbaginaceae), <i>Delphinium consolida</i> (Ranunculaceae), <i>Solanum tuberosum</i> (Solanaceae), <i>Verbena hybrida</i> (Verbenaceae)	AR (rat lens) (10-100) [mauve pigment]
Demethoxy sudachitin (= 5,7,4'-Trihydroxy-6,8-dimethoxyflavone) (flavone)	<i>Citrus sudachi</i> (Rutaceae)	AR (rat & bovine lens, IC _{50s} 410 nM & 580 nM)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited (other targets) / in vivo effects/
Desmanthin-1 (= 2''-O-Galloylmyricitrin; 2''-O-Galloylmyricetin-3-O-Rha) (flavonol glycoside gallic acid ester)	<i>Myrcia multiflora</i> (Myrtaceae) [leaf]	AR (rat lens) (0.08)
[5,4'-O-Diacetyl cirsimaritin (=5,4'-O-Diacetyl-6,7-dimethoxyflavone)] (flavone)	Semi-synthetic	AR (rat lens) (10)
[3,8-Dicarboxy-5-methoxycoumarin] (coumarin)	Semi-synthetic	AR (bovine lens) (>10)
2,3-Dihydroluteolin (= Eriodictyol; 5,7,3',4'-Tetrahydroxyflavanone) (flavanone)	Widespread; <i>Eriodictyon californicum</i> (Hydrophyllaceae), Asteraceae, Lamiaceae, Fabaceae	AR (rat lens) (1-10) (PKA)
Dihydroquercetin (= Distylin; 3,5,7,3',4'-Pentahydroxyflavanone; Taxifolin) (dihydroflavonol)	Many Coniferae; <i>Engelhardtia chrysolepis</i> (Juglandaceae), <i>Acacia catechu</i> (Fabaceae), <i>Morus alba</i> (Moraceae), <i>Polygonum nodosum</i> (Polygonaceae), <i>Salix capraea</i> (Salicaceae),	AR (rat lens) (1-10) (5-LOX, NADH DH, succinate DH) [larval growth inhibitor]
[5,6-Dihydroxy-7,8-dimethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (26), AR (rat lens) (8)
[8,9-Dihydroxy-3-methoxycoumestan] (coumestan)	Semi-synthetic	AR (bovine lens) (>10), AR (rat lens) (>10)
5,7-Dihydroxy-6,8,3',4'-tetramethoxyflavone (= Hymenoxin) (flavone)	<i>Mentha piperita</i> (mint) (Lamiaceae)	AR (bovine lens) (>10), AR (rat lens) (>10)
[6,4'-Dihydroxy-5,7,8,3'-tetramethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (5), AR (rat lens) (6)
[6,4'-Dihydroxy-5,7,8-trimethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (0.4), AR (rat lens) (0.3)
5,4'-Dihydroxy-6,7,8-trimethoxyflavone (flavone)	<i>Thymus vulgaris</i> (thyme) (Lamiaceae) [leaf]	AR (bovine lens) (0.8), AR (rat lens) (0.5)
7,7''-Dimethoxy-agathisflavone (biflavone)	<i>Ouratea spectabilis</i> (Ochnaceae) [leaf]	AR
Ellagic acid (= Benzoic acid, Lagistase) (phenolic lactone)	Widespread; component of widespread Ellagitannins; <i>Phyllanthus niruri</i> (Euphorbiaceae) [plant], <i>Fragaria</i> spp. (Rosaceae)	AR (rat lens) (0.2) [anti-mutagen]
[Ellagic acid derivatives, variously acetylated & alkylated] (phenolic lactone)	Semi-synthetic derivatives of Ellagic acid	AR (rat lens) (0.1 to >10)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited (other targets) / in vivo effects/
[Ellagic acid derivatives, variously sulfated and polysulfated] (phenolic lactone)	Semi-synthetic derivatives of Ellagic acid	AR (rat lens) (0.02–0.09)
(–)-Epicatechin (= (2 <i>R</i> ,3 <i>R</i>)-5,7,3',4'-Tetrahydroxyflavan-3-ol) (flavan-3-ol)	Widespread; <i>Aesculus californica</i> (Hippocastanaceae), <i>Pterocarpus</i> spp. (Fabaceae) [bark], <i>Podocarpus nagi</i> (Podocarpaceae), <i>Crataegus monogyna</i> (Rosaceae), <i>Camellia sinensis</i> (Theaceae)	AR (rat lens) (10–100) (MAO, PKA) [antibacterial, AI, antioxidant]
Esculetin (= Aesculetin; Cichorigenin; 6,7-Dihydroxycoumarin; Esculetol) (coumarin)	<i>Anethum graveolens</i> (Apiaceae), <i>Artemisia capillari</i> (Asteraceae), <i>Euphorbia lathyris</i> (Euphorbiaceae) [seed], <i>Aesculus turbinata</i> (Hippocastanaceae) [wood], <i>Fraxinus</i> spp. (Oleaceae) [bark]	AR (rat lens) (0.1–1), AR (bovine lens) (4) [antibacterial, antifungal]
Esculin (= Aesculin; Crataegin; 6,7-Dihydroxycoumarin 6- <i>O</i> -Glc; Esculetin-Glc; Esculoside) (coumarin glycoside)	<i>Cichorium intybus</i> (Asteraceae), <i>Aesculus hippocastanum</i> (Hippocastanaceae), <i>Fraxinus</i> spp. (Oleaceae), <i>Bursaria spinosa</i> (Pittosporaceae), <i>Crataegus oxyacantha</i> (Rosaceae) [bark]	AR (rat lens) (10–100) [antibacterial]
Ethyl brevifolin carboxylate (phenolic ketone)	<i>Phyllanthus niruri</i> (Euphorbiaceae) [plant]	AR (rat lens) (5)
Eugenyl <i>O</i> -Glc (phenolic glycoside)	<i>Perilla frutescens</i> (Lamiaceae) [leaf]	AR (rat lens) (>100)
Eupatilin (= 5,7-Dihydroxy-6, 3', 4'-Trimethoxyflavone) (flavone)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower], <i>Sideritis</i> sp. (Lamiaceae), <i>Citrus reticulata</i> (Rutaceae)	AR (rat lens) (25)
Fisetin (= 5-Deoxyquercetin; 3,7,3',4'-Tetrahydroxyflavone) (flavonol)	<i>Acacia catechu</i> (Fabaceae); glycosides in <i>Rhus succedanea</i> (Anacardiaceae) [wood], Fabaceae	AR (rat lens) (1) (CDPK, ITD, 5-LOX, NADH DH, PKA, PKC) [antibacterial, allergenic, inhibits smooth muscle contraction]
Genistein (= Genisteol; Prunetol; Sophoricol) (isoflavone)	<i>Prunus</i> spp. (plum) (Rosaceae) [wood], <i>Genista</i> spp. (broom), <i>Trifolium brachycalycinum</i> , <i>T.</i> spp. (clover) (Fabaceae)	AR (rat lens) (~10) (PKA, RTK, TK, anti-oestrogenic) [blocks COX-2 & iNOS induction; antifungal, oestrogenic]
Gossypin (= Gossypetin 8- <i>O</i> -Glc; 8-Hydroxyquercetin 8- <i>O</i> -Glc; 3,5,7,8,3',4'-Hexahydroxyflavone 8- <i>O</i> -Glc) (flavonol <i>O</i> -glycoside)	<i>Gossypium indicum</i> (cotton), <i>Hibiscus vitifolius</i> (Malvaceae) [flower]	AR (rat lens) (10–100)
Guaijaverin (= Quercetin 3- <i>O</i> -Ara) (flavonol <i>O</i> -glycoside)	<i>Hypericum brasiliense</i> (Guttiferae) [leaf, flower], <i>Myrcia multiflora</i> (Myrtaceae) [leaf]	AR (human lens) (3), AR (rat lens) (0.2)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) / in vivo effects/
Hesperetin (= Eriodictyol 4'-methyl ether; 5,7,3'-Trihydroxy-4'-methoxy-flavanone) (flavanone)	<i>Mentha aquatica</i> (Lamiaceae), <i>Citrus</i> spp. (Rutaceae)	AR (rat lens) (1–10) (cAMP PDE) [antibacterial, antiviral, insect feeding deterrent]
Hesperidin chalcone (= Chalcone 2',4',6',3-tetrahydroxy-4-methoxy 4'- <i>O</i> -Rut) (chalcone <i>O</i> -glycoside)	<i>Citrus</i> sp. (Rutaceae)	AR (rat lens) (10–100)
Hesperidin (= Ciratin; Hesperetin 7- <i>O</i> -Rut; 5,7,3',4'- Tetrahydroxy-flavanone 4'-methyl ether 7- <i>O</i> -Rha-Glc) (flavanone glycoside)	<i>Mentha</i> spp., <i>Hyssopus</i> spp. (Lamiaceae), <i>Citrus sinensis</i> (orange), <i>C. limon</i> (lemon), <i>Citrus</i> spp., <i>Poncirus trifoliata</i> (Rutaceae) [leaf]	AR (rat lens) (10–100) (PKA) [oviposition stimulant]
4-Hydroxycoumarin (coumarin)	<i>Artemisia capillari</i> (Asteraceae)	AR (bovine lens) (3)
[7- <i>O</i> - β -Hydroxyethyl-querctin] (flavonol)	Semi-synthetic derivative of Quercetin	AR (human lens) (>10), AR (rat lens) (1–10)
[7- <i>O</i> - β -Hydroxyethylrutin] (flavone glycoside)	Semi-synthetic derivative of Quercetin	AR (rat lens) (10–100)
6-Hydroxyluteolin (= 5,6,7,3',4'- Penta-hydroxyflavone) (flavone)	As glycosides from <i>Vriesea sanguinolenta</i> (Bromeliaceae), <i>Thymus vulgaris</i> (thyme) (Lamiaceae), <i>Hebe stenophylla</i> , <i>H. stricta</i> (Scrophulariaceae)	AR (rat lens) (~1)
[6-Hydroxy-7-methoxy-coumarin] (coumarin)	Semi-synthetic	AR (human lens) (>10)
[4-Hydroxy-6,7-methylene-dioxycoumarin] (coumarin)	Semi-synthetic	AR (bovine lens) (~10), AR (rat lens) (~10)
[4'-Hydroxy-5,6,7,8,3'-pentamethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (1–10), AR (rat lens) (>10)
[6-Hydroxy-5,7,8-trimethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (>10), AR (rat lens) (>10)
Hyperoside (= Hyperin; Quercetin 3- <i>O</i> -Gal) (flavonol <i>O</i> -glycoside)	<i>Tussilago farfara</i> (Asteraceae), <i>Hypericum brasiliense</i> , <i>H. perforatum</i> (St John's wort) (Hypericaceae) [leaf, flower]	AR (rat lens) (1) [antibacterial]
Isoliquiritigenin (= 2',4',4-Trihydroxychalcone) (chalcone)	<i>Astragalus membranaceus</i> , <i>Glycyrrhiza glabra</i> (liquorice) (Fabaceae) [root, rhizome]	AR (320 nM) (COX, 5-LOX, MLCK) [PAI]
Isoliquiritin (flavonoid)	<i>Glycyrrhiza glabra</i> (liquorice), <i>G. uralensis</i> (Fabaceae) [root]	AR (rat lens)
Isoquercetrin (= Quercetin 3- <i>O</i> -Glc) (flavonol <i>O</i> -glycoside)	<i>Gossypium herbaceum</i> (Malvaceae) [flower], <i>Morus alba</i> (mulberry) (Moraceae) [leaf], <i>Punica granatum</i> (Punicaceae)	AR (human lens) (>10), AR (rat lens) (1–10) [antibacterial, feeding attractant]
Isoquercetyl-2''-malonate (= Quercetin 3- <i>O</i> -Glc-2''-malonate) (flavonol <i>O</i> -glycoside)	Semi-synthetic	AR (rat lens) (1)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited (other targets) / in vivo effects/
Isorhamnetin 3,7-disulfate (sulfated flavonoid)	<i>Polygonum hydropiper</i> (Polygonaceae)	AR (lens)
Juglanin (= 3,5,7,4'-Tetrahydroxyflavone 3-O-Ara) (flavonol O-glycoside)	<i>Aesculus hippocastanum</i> (horse chestnut) (Hippocastanaceae) [flower; leaf]	AR (rat lens) (1–10)
Kaempferide (= Kaempferol 4'-O-methyl ether; 4'-O-Methyl-3,5,7,4'-tetrahydroxyflavone) (flavonol)	<i>Pityrogramma triangularis</i> (fern) (Adiantaceae) [fern exudate], Betulaceae, <i>Baccharis</i> spp. (Asteraceae), <i>Prunus cerasus</i> (Rosaceae), <i>Linaria dalmatica</i> (Scrophulariaceae) [aerial], <i>Alpinia galanga</i> (Zingiberaceae)	AR (rat lens) (10) [AI (TPA induced)]
Kaempferol (= 3,5,7,4'-Tetrahydroxyflavone) (flavonol)	Widespread; <i>Hypericum brasiliense</i> (Guttiferae) [leaf, flower], <i>Azadirachta indica</i> (Meliaceae); glycosides in Hippocastanaceae [aerial], Fabaceae [wood, leaf]	AR (rat lens) (1–10) (ECMOX, F ₁ -ATPase, ITDI, MLCK, PKA, RTK (p56lck)) [antibacterial, antioxidant, AI, mutagenic]
Kaempferol 3-O-Rha (= 3,5,7,4'-Tetrahydroxyflavone 3-O-Rha) (flavonol O-glycoside)	<i>Cissus sicyoides</i> (Vitaceae) [leaf]	AR (rat lens) (1–10)
Kaempferol 3-O-neohesperidoside (= 3,5,7,4'-Tetrahydroxyflavone 3-O-neohesperidoside) (flavonol O-glycoside)	<i>Daphniphyllum calycinum</i> (Daphniphyllaceae)	AR (rat lens) (>10) {AO}
Kaempferol 7-O-Rha (= 3-O-Rha-3,5,7,4'-tetrahydroxyflavone) (flavonol O-glycoside)	Kaempferol 7-O-Rha-4'-O-Glc in <i>Pteridium aquilinum</i> (<i>Pteris aquilina</i>) (bracken fern) (Dennstaedtiaceae)	AR (rat lens) (>10)
Kolaviron (mixture of C-3/C-8-linked biflavonoids)	<i>Garcinia cola</i> (Clusiaceae)	AR (rat lens)
[LARI 1 (6,3',4'-Trihydroxy-5,7,8-trimethoxyflavone)] (flavone)	Semi-synthetic	AHR (rat brain) (<10), AR (bovine lens) (0.2) [0.2], AR (rat lens) (0.04) [0.03]
[LARI 2 (4'-Hydroxy-5,6,7,8-tetramethoxyflavone)] (flavone)	Semi-synthetic	AHR (rat brain) (<10), AR (bovine lens) (0.3) [0.4], AR (rat lens) (0.2) [0.1]
Licuraside (chalcone)	<i>Glycyrrhiza glabra</i> (Fabaceae) [root]	AR (rat lens)
Lithospermic acid (phenylpropanoid, benzofuran)	<i>Cnicus benedictus</i> (Asteraceae), <i>Anchusa officinale</i> , <i>Echium vulgare</i> , <i>Lycopus europaeus</i> , <i>L. virginicus</i> , <i>Lithospermum ruderale</i> , <i>L. officinale</i> (Boraginaceae), <i>Salvia deserta</i> (Lamiaceae) [root, rhizome]	AR (3) (AO/FRS, ProH)
Lonicerin (= Luteolin 7-O-Rha-Glc; 5,7,3',4'-Tetrahydroxyflavone 7-O-Rha-Glc) (flavone O-glycoside)	<i>Lonicera japonica</i> (Japanese honeysuckle) (Caprifoliaceae)	AR (rat lens) (~1)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) / in vivo effects/
Luteolin (= 5,7,3',4'-Tetrahydroxyflavone) (flavone)	Widespread; <i>Achillea millefolium</i> , <i>Chrysanthemum indicum</i> (Asteraceae) [flower], <i>Hypericum brasiliense</i> (Hypericaceae) [leaf, flower], <i>Buddleja officinalis</i> (Loganiaceae) [flower]; glycosides in Brassicaceae, Lamiaceae, Fabaceae, Scrophulariaceae [aerial, leaf exudate]	AR (rat lens) (1–10; 0.5) (ITD, NADH DH, succinate DH, MLCK, PKA, PKC) [antibacterial, AI, nodulation signal for <i>Rhizobium</i>]
Luteolin 7- <i>O</i> -Glc (flavone <i>O</i> -glycoside)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower], <i>Buddleja officinalis</i> (Loganiaceae) [flower], <i>Humulus japonicus</i> (Cannabaceae), <i>Salix</i> spp. (Salicaceae)	AR (rat lens) (1; 1–10) [insect feeding attractant; malonate ester an oviposition stimulant]
Luteolin-7- <i>O</i> -glucuronide (flavone <i>O</i> -glycoside)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	AR (rat lens) (3)
Macrocarpal A (phloroglucinol)	<i>Eucalyptus globulus</i> (Tasmanian blue gum) [leaf, calyx], <i>E. macrocarpa</i> [leaf] (Myrtaceae)	AR (2–3) antibacterial (Gram-positive)]
Macrocarpal B (phloroglucinol)	<i>Eucalyptus globulus</i> (Tasmanian blue gum) [leaf, calyx], <i>E. macrocarpa</i> [leaf] (Myrtaceae)	AR (2–3) [antibacterial (Gram-positive)]
Macrocarpal D (phloroglucinol)	<i>Eucalyptus globulus</i> (Tasmanian blue gum) [leaf, calyx], <i>E. macrocarpa</i> [leaf] (Myrtaceae)	AR (2–3) [antibacterial (Gram-positive)]
Macrocarpal G (phloroglucinol)	<i>Eucalyptus globulus</i> (Tasmanian blue gum) [leaf, calyx] (Myrtaceae)	AR (2–3) [antibacterial (Gram-positive)]
Matteuorientate A (= Matteucinol 7- <i>O</i> -[6''- <i>O</i> -hydroxymethylglutaryl]-Glc; 5,7-Dihydroxy-6,8-dimethyl-4'-methoxy flavanone 7- <i>O</i> -[6''- <i>O</i> -hydroxymethyl-glutaryl]-Glc) (C-methyl flavanol glycoside)	<i>Matteuccia orientalis</i> (Dryopteridaceae)	AR (rat lens) (1)
Matteuorientate B (= Demethoxymatteucinol 7- <i>O</i> -[6''- <i>O</i> -hydroxymethyl-glutaryl]-Glc) (C-methyl flavanol glycoside)	<i>Matteuccia orientalis</i> (Dryopteridaceae)	AR (rat lens) (1)
Matteuorientate C (= 2,3-Dehydrodemethoxymatteucinol 7- <i>O</i> -[6'- <i>O</i> -hydroxymethylglutaryl]-Glc) (C-methyl flavanol glycoside)	<i>Matteuccia orientalis</i> (Dryopteridaceae)	AR (rat lens) (2)
Matteuorientate A methyl ester (C-methyl flavanone glycoside)	<i>Matteuccia orientalis</i> (Dryopteridaceae)	AR (rat lens) (~100)
Mearnsitrin (= 5'- <i>O</i> -Methylmyricitrin; 5'- <i>O</i> -Methylmyricetin-3- <i>O</i> -Rha) (flavanol <i>O</i> -glycoside)	<i>Acacia decurrens</i> (Fabaceae), <i>Myrcia multiflora</i> (Myrtaceae) [leaf]	AR (rat lens) (1)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited (other targets) / in vivo effects/
4'- <i>O</i> -Methylapigenin (= 5,7-Dihydroxy-4'-methoxyflavone) (flavone)	As 7- <i>O</i> -Glc-8C-Glc-4'- <i>O</i> -Methylapigenin from <i>Trema aspera</i> (Ulmaceae)	AR (rat lens)
[7-Methylaxillarin (= Quercetagenin 3,6,7-trimethyl ether; 5,3',4'-Trihydroxy-3,6,7-trimethoxyflavone)] (flavone)	Semi-synthetic	AR (bovine lens) (0.9), AR (rat lens) (0.4)
[7-Methylsudachitin (= 5,4'-Dihydroxy-6,7,8,3'-tetramethoxyflavone)] (flavone)	Semi-synthetic	AR (bovine lens) (1–10), AR (rat lens) (> 10)
Morin (= 3,5,7,2',4'-Pentahydroxyflavone) (flavonol)	<i>Morus alba</i> , <i>M.</i> spp. (mulberry), <i>Artocarpus heterophyllus</i> , <i>A. integrifolia</i> , <i>Chlorophora tinctoria</i> (Moraceae)	AR (rat lens) (1–10) (ECMOX, F ₁ -ATPase, ITDI, 5-LOX, MLCK, PKA) [allergenic, antibacterial, antiviral, feeding attractant]
Myriciacetin (= 5,7,2',5'-Tetrahydroxy-6,8-dimethylflavanone) (dimethyl flavanone)	<i>Myrcia multiflora</i> (Myrtaceae) [leaf]	AR (rat lens) (13)
Myriciacitrin I (flavanone glucoside)	<i>Myrcia multiflora</i> (Myrtaceae) [leaf]	AR (rat lens) (3)
Myriciacitrin II (flavanone glucoside)	<i>Myrcia multiflora</i> (Myrtaceae) [leaf]	AR (rat lens) (15)
Myriciaphenone B (acetophenone glycoside)	<i>Myrcia multiflora</i> (Myrtaceae) [leaf]	AR (rat lens) (29)
Myricetin (= 3,5,7,3',4',5'-Hexahydroxyflavone) (flavonol)	<i>Azadirachta indica</i> , <i>Soymida febrifuga</i> (Meliaceae) [wood], <i>Haplophappus canescens</i> (Asteraceae) [aerial]	AR (human lens) (~10), AR (rat) (1–10), AR (porcine lens) (ECMOX, IKK, LOX, NADH DH, PK, succinate DH) [antibacterial, antigonadotropic]
Myricetin 3- <i>O</i> -(4''-acetyl)- α -Fuc (flavonol glycoside)	<i>Anthocephalus chinensis</i> (Rubiaceae)	AR (rat & porcine lens)
Myricitrin (= Myricetin 3- <i>O</i> -Rha; 3,5,7,3',4',5'-Hexaahydroxy flavone 3- <i>O</i> -Rha) (flavonol <i>O</i> -glycoside)	<i>Araucaria bidwillii</i> (Araucariaceae), <i>Myrica rubra</i> (Myricaceae) [bark], <i>Myrcia multiflora</i> (Myrtaceae) [leaf]	AR (human lens) (1), AR (rat lens) (0.1–1; 4) (HIV-1 INT) [antibacterial, AI (TPA induced)]
Naringenin (= 5,7,4'-Trihydroxyflavanone) (flavanone)	Widespread; <i>Artemisia</i> , <i>Baccharis</i> , <i>Centaurea</i> , <i>Dahlia</i> spp. (Asteraceae), <i>Citrus aurantium</i> , <i>C. paradisi</i> [grapefruit juice], <i>C.</i> spp. (Rutaceae)	AR (rat lens) (1–10) (cAMP PDE, CYP, EST-R, Nase) [antibacterial, antifungal]

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) / in vivo effects/
Naringin (= Naringenin 7- <i>O</i> -Rha-Glc; Naringenin 7- <i>O</i> -neohesperidoside; 5,7,4'-Trihydroxyflavanone 7- <i>O</i> -Rha-Glc) (flavanone <i>O</i> -glycoside)	<i>Ceterach officinarum</i> , <i>Adiantum</i> spp. (fern), <i>Origanum vulgare</i> (Lamiaceae), <i>Citrus aurantium</i> , <i>C. paradisi</i> [grapefruit juice], <i>C. spp.</i> (Rutaceae)	AR (rat lens) (1–10) [antioxidant, bitter taste, oviposition stimulant]
Nelumboside (= Quercetin 3- <i>O</i> -glucuronyl-Glc) (flavanol <i>O</i> -glycoside)	<i>Nelumbo nucifera</i> (kanwal, sacred lotus) (Nymphaeaceae); tonic, aphrodisiac	AR (rat lens) (1–10)
Neostilbin (dihydroflavonol glycoside)	<i>Engelhardtia chrysolepis</i> (Juglandaceae), <i>Astilbe</i> spp. (Saxifragaceae)	AR
Nevadensin (= 5,7-Dihydroxy-6,8,4'-trimethoxyflavone (flavone))	<i>Iva nevadensis</i> , <i>Helianthus</i> spp. (Asteraceae), <i>Lysionotus pauciflora</i> (Gesneriaceae), <i>Mentha piperita</i> , <i>Ocimum canum</i> (Lamiaceae) [leaf, flower]	AR (bovine lens) (9), AR (rat lens) (7) [antibacterial]
Orientin (= Luteolin 8-C-Glc; 5,7,8,3',4'-Pentahydroxyflavone 8-C-Glc) (flavone C-glycoside)	Widespread; <i>Vitex agnus-castus</i> L. (Lamiaceae), <i>Polygonum orientale</i> (Polygonaceae)	AR (rat lens) (1–10)
Oxyyanin A (= 5,2',5'-Trihydroxy-3,7,4'-trimethoxyflavone) (flavonol)	<i>Distemonanthus benthamianus</i> (ayan) (Fabaceae), <i>Zea mays</i> (Poaceae)	AR (rat lens) (>10)
Pectolinarigenin (= 5,7-Dihydroxy-6,4'-dimethoxyflavone) (flavone)	<i>Artemisia dracunculus</i> , <i>Dugaldia pinetorum</i> (Asteraceae); bee propolis (waxy excretion containing plant-derived compounds)	AR (rat lens) (>10)
Pectolinarin (= 7- <i>O</i> -Rha-Glc-5,7-Dihydroxy-6,4'-dimethoxyflavone) (flavone <i>O</i> -glycoside)	<i>Trifolium pratense</i> (red clover) (Fabaceae)	AR (rat lens) (>10)
Pelargonin chloride (= 3,5,4',7-Tetrahydroxyflavilium 3,5-bis- <i>O</i> -Glc chloride) (glycosylated flavilium anthocyanin)	<i>Centaurea cyanus</i> (Asteraceae), <i>Pelargonium zonale</i> (geranium) (Geraniaceae), <i>Gladiolus</i> spp. (Iridaceae) [flower]	AR (rat lens) (10–100) [red pigment]
5,6,7,3',4'-Pentaacetoxy-8-methoxyflavone (flavone)	Semi-synthetic	AR (bovine lens) (0.5; 1.1), AR (rat lens) (0.3; 0.1)
Pinocembrin 7- <i>O</i> -Rha-Glc (= 5,7-Dihydroxyflavone 7- <i>O</i> -Rha-Glc; Saratonoside) (flavone <i>O</i> -glycoside)	Aglycone Pinocembrin in <i>Helichrysum</i> spp. (Asteraceae), <i>Glycyrrhiza</i> spp. (Fabaceae), <i>Pinus cembra</i> (Pinaceae), <i>Prunus</i> spp. (Rosaceae)	AR (rat lens) (>100) [aglycone antibacterial, antifungal]
Puerarin (isoflavone)	<i>Pueraria montana</i> , <i>P. pseudo-hirsuta</i> , <i>P. lobata</i> (Fabaceae) [root]	AR
Quercetagenin (= 6-Hydroxy- quercetin; 3,5,6,7,3',4'-Hexahydroxyflavone) (flavonol)	<i>Acacia catechu</i> (Fabaceae), <i>Eupatorium gracile</i> (Asteraceae), other Asteraceae [flower]	AR (rat lens) (1–10) [antibacterial]

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited (other targets) / in vivo effects/
Quercetin (= 3,5,7,3',4'-Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passifloraceae, Rhamnaceae, Solanaceae; <i>Artemisia capillari</i> (Asteraceae), <i>Hypericum brasiliense</i> (Hypericaceae) [leaf, flower], <i>Oenothera biennis</i> (Onagraceae)	AR (bovine lens) (2,8), AR (human lens) (5), AR (rat lens) (0.1–1; 7) (ECMOX, F ₁ -ATPase, PK, RTK) [antibacterial, antiviral, AI]
[Quercetin 3- <i>O</i> -acetyl-7,3,4'-trisulfate] (sulfated flavonol)	Semi-synthetic flavonol derivative	AR (human lens) (0.1)
Quercetin 3- <i>O</i> -Gal (= Hyperin; Hyperoside) (flavonol <i>O</i> -glycoside)	<i>Hypericum perforatum</i> (St John's wort) (Hypericaceae) [leaf]	AR (human lens) (10) [antibacterial]
Quercetin 3- <i>O</i> -Glc (= Isoquercetrin) (flavonol <i>O</i> -glycoside)	Widespread; <i>Gossypium herbaceum</i> (Malvaceae) [flower], <i>Morus alba</i> (mulberry) (Moraceae) [leaf]	AR (human lens) (>10) [antibacterial, feeding attractant]
Quercetrin (= 3,5,7,3',4'-Pentahydroxyflavone 3- <i>O</i> -Rha; Quercetin 3- <i>O</i> -Rha) (flavonol <i>O</i> -glycoside)	Widespread; <i>Chamaemelum nobile</i> (Asteraceae), <i>Quercus tinctoria</i> (Fagaceae) [bark], <i>Hypericum brasiliense</i> (Hypericaceae) [leaf, flower], <i>Eucalyptus globulus</i> (Tasmanian blue gum), <i>Myrcia multiflora</i> (Myrtaceae) [leaf], <i>Polygonum</i> spp. (Polygonaceae)	AHR (rat brain) (<10), AR (human lens) (1), AR (bovine lens) (1; 3) [2], AR (rat lens) (~0.1; 0.2; 0.5; 1) [0.8] (PKA) [antibacterial, anti-mutagenic, antiviral, feeding attractant]
[Quercetryl-2''-acetate (= Quercetin 3- <i>O</i> -Rha-2''-acetate)] (flavonol <i>O</i> -glycoside)	Semi-synthetic	AR (rat lens) (<0.1)
Quercimeritrin (= Quercetin 7- <i>O</i> -Glc) (flavonol <i>O</i> -glucoside)	<i>Gossypium hirsutum</i> (cotton) (Malvaceae) [flower], <i>Camellia sinensis</i> (Theaceae)	AR (rat lens) (>10) [insect feeding stimulant]
Reynoutrin (= Quercetin 3- <i>O</i> -Xyl) (flavanol glycoside)	<i>Echinacea</i> spp. (Asteraceae) [leaf], <i>Vaccinium macrocarpon</i> (Ericaceae), <i>Malus domestica</i> (Rosaceae), <i>Houttuynia cordata</i> (Saururaceae)	AR (rat lens) (1–10)
Rhamnetin (= Quercetin 7-methyl ether) (flavanol)	<i>Coriandrum sativum</i> (Apiaceae), <i>Cistus</i> spp. (Cistaceae) [leaf resin]; Asteraceae, Lamiaceae [leaf]	AR (rat lens) (1–10)
Rhoifolin (= 5,7,4'-Trihydroxyflavone 7- <i>O</i> -Rha-Glc) (flavone glycoside)	<i>Citrus aurantium</i> , <i>C. paradisi</i> (grapefruit) (Rutaceae), <i>Boehmeria nivea</i> (Urticaceae)	AR (rat lens) (>10)
Robinin (= 3,5,7,4'-Tetrahydroxyflavone 7- <i>O</i> -Rha-3- <i>O</i> -Gal-Rha) (flavanol <i>O</i> -glycoside)	<i>Vinca minor</i> (Apocynaceae), <i>Robinia pseudacacia</i> [flower], <i>Pueraria</i> spp., <i>Vigna</i> spp. (bean) (Fabaceae)	AR (rat lens) (1–10) [antibacterial]

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) / in vivo effects/
Rosmarinic acid (phenylpropanoid)	<i>Symphytum officinale</i> (Boraginaceae), <i>Melissa officinalis</i> , <i>Mentha piperita</i> , <i>Ocimum sanctum</i> , <i>Origanum</i> , <i>Prunella</i> , <i>Rosmarinus officinalis</i> , <i>Teucrium</i> <i>scorodonia</i> , <i>Salvia officinale</i> , <i>S. deserta</i> , <i>S. miltiorhiza</i> (Lamiaceae), <i>Anethum</i> spp., <i>Levisticum</i> spp., <i>Sanicula</i> spp., <i>Astrantia major</i> (Apiaceae)	AR (4) (adenylate cyclase, AO/FRS. COX-1, COX-2, Gonadotropin release, HIV-1 INT) [AI; antiviral]
Rutin (= Quercetin 3-O-Rut; Quercetin 3-O-Rha-Glc; 3,5,7,3',4'-Pentahydroxy- flavone 3-O-Rut; Rutoside) (flavonol O-glycoside)	Widespread; <i>Sophora japonica</i> (Fabaceae), <i>Polygonum</i> spp. (Polygonaceae), <i>Ruta graveolens</i> (Rutaceae), <i>Viola tricolor</i> (Violaceae)	AR (5-LOX, MLCK, PKA) [antioxidant, feeding attractant, feeding deterrent, oviposition stimulant]
Salvianolic acid K (phenylpropanoid)	<i>Salvia deserta</i> , <i>S. miltiorhiza</i> (sage) (Lamiaceae) [root, rhizome]	AR (3)
Salviaflaside (glycosylated phenylpropanoid)	<i>Salvia deserta</i> , <i>S. miltiorhiza</i> (Lamiaceae) [root, rhizome]	AR (3)
Scopoletin (= Chrysatropic acid; Gelseminic acid; 7-Hydroxy-6- methoxycoumarin; 6-Methoxy-umbelliferone; β -Methylesculetin) (coumarin)	<i>Nerium</i> (Apocynaceae) [flower], <i>Artemisia</i> (Asteraceae) [flower], <i>Ipomoea</i> , <i>Convolvulus</i> (Convolvulaceae), <i>Diospyros</i> (Ebenaceae), <i>Gelsemium</i> (Loganaceae), <i>Avena sativa</i> L. (Poaceae), <i>Prunus serotina</i> (Rosaceae) [bark], <i>Atropa belladonna</i> (Solanaceae)	AR (bovine lens) (32)
Scutellarein (= 5,6,7,4'- Tetrahydroxyflavone; 6- Hydroxyapigenin) (flavone)	<i>Pulicaria rivularis</i> (Asteraceae) [leaf], <i>Scutellaria</i> spp. (Lamiaceae) [root], <i>Asphodeline</i> spp. (Liliaceae), <i>Citrus</i> <i>sinensis</i> (Rutaceae), <i>Digitalis orientalis</i> (Scrophulariaceae)	AR (rat lens) (1-10)
Sideroxydonal A (dimeric phloroglucinol)	<i>Eucalyptus sideroxylon</i> (Myrtaceae)	AR (1) [antibacterial]
Sideroxydonal B (dimeric phloroglucinol)	<i>Eucalyptus sideroxylon</i> (Myrtaceae)	AR (3) [antibacterial]
Silybin (flavanolignan)	<i>Silybum marianum</i> (Asteraceae) [fruit]	AR
Sorbarin (= 5,6,7,4'- Tetrahydroxyflavone 7-O-Rha) (flavone O-glycoside)	Corresponding 5,6,7,4'- Tetrahydroxyflavone 3-O-Rut from <i>Daphniphyllum calycinum</i> (Daphniphyllaceae)	AR (rat lens) (1-10)
Spiraeoside (= Quercetin 4'-O-Glc) (flavanol O-glycoside)	<i>Sarothamnus scoparius</i> (Scotch/Irish broom) (Fabaceae)	AR (rat lens) (~10)
Sudachitin A (= 5,7,4'- Trihydroxy-6,8,3'- trimethoxyflavone 4'-Glc) (flavone O-glycoside)	<i>Citrus sudachi</i> (Rutaceae)	AR (bovine lens) (>10), AR (rat lens) (>10)
Sudachitin (= 5,7,4'- Trihydroxy-6,8,3'- trimethoxyflavone) (flavone)	<i>Citrus sudachi</i> (Rutaceae)	AR (bovine lens) (7), AR (rat lens) (5)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited (other targets) / in vivo effects/
Sudachitin 7- <i>O</i> -glycoside (= 5,7,4'-Trihydroxy-6,8,3'-trimethoxyflavone 7- <i>O</i> -glycoside) (flavone <i>O</i> -glycoside)	<i>Citrus sudachi</i> (Rutaceae)	AR (bovine lens) (>10), AR (rat lens) (>10)
Taxifolin (= Dihydroquercetin; Distylin; 3,5,7,3',4'-Pentahydroxyflavanone) (dihydroflavonol)	Many Coniferae; <i>Engelhardtia chrysolepis</i> (Juglandaceae), <i>Acacia catechu</i> , <i>Robinia pseudoacacia</i> (Fabaceae), <i>Polygonum nodosum</i> (Polygonaceae), <i>Salix capraea</i> (Salicaceae)	AR (human lens) (8), AR (rat lens & recombinant human) (NADH DH, succinate DH, 5-LOX)
1,2,3,6-Tetra- <i>O</i> -galloyl- β -D-Glc (glucose gallic acid ester)	<i>Glycyrrhiza glabra</i> (Fabaceae) [root]	AR (rat lens)
[5,6,7,4'-Tetrahydroxy-8,3'-dimethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (3), AR (rat lens) (1)
[5,6,7,4'-Tetrahydroxy-8-methoxyflavone (= 8-Methoxyscutellarein)] (flavone)	Semi-synthetic	AR (bovine lens) (2), AR (rat lens) (1)
Tetramethylscutellarein (= 5,6,7,4'-Tetramethoxyflavone; 5,6,7,4'-Tetra- <i>O</i> -methylscutellarein) (flavone)	<i>Pulicaria rivularis</i> (Asteraceae) [leaf], <i>Scutellaria</i> spp. (Lamiaceae) [root], <i>Asphodeline</i> spp. (Liliaceae), <i>Citrus sinsensis</i> (orange) (Rutaceae) [orange juice], <i>Digitalis orientalis</i> (Scrophulariaceae)	AR (rat lens) (>10)
Trifolin (= 3,5,7,4'-Tetrahydroxyflavone 3- <i>O</i> -Gal) (flavonol glycoside)	<i>Campthoeca acuminata</i> (Cornaceae), <i>Trifolium pratense</i> (red clover) (Fabaceae)	AR (rat lens) (1–10)
5,7,4'-Trihydroxy-6,8-dimethoxyflavone (= 3'-Demethoxy sudachitin) (flavone)	<i>Citrus sudachi</i> (Rutaceae)	AR (bovine lens) (0.58), AR (rat lens) (0.4)
[5,6,7-Trihydroxy-8-methoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (5), AR (rat lens) (8)
[5,6,4'-Trihydroxy-7,8-dimethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (2), AR (rat lens) (0.9)
[5,7,4'-Trihydroxy-3,6-dimethoxyflavone] (flavone)	Semi-synthetic	AR (rat & bovine lens)
[5,6,4'-Trihydroxy-7,8,3'-trimethoxyflavone] (flavone)	Semi-synthetic	AR (bovine lens) (>10), AR (rat lens) (>10)
3,3',4-Tri- <i>O</i> -methyllellagic acid (dimeric phenolic lactone)	<i>Potentilla candicans</i> (Rosaceae) [root]	AR (rat lens) (>10)
3,3',4-Tri- <i>O</i> -methyllellagic acid 4'-sulfate potassium salt (sulfated dimeric phenolic lactone)	<i>Potentilla candicans</i> (Rosaceae) [root]	AR (rat lens) (0.08)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) part	Enzyme inhibited (other targets) / in vivo effects/
Verbascoside (= Acteoside; Kusagin) (phenyl propanoid glycoside)	<i>Echinacea</i> spp. (Asteraceae), <i>Buddleja globosa</i> , <i>B. officinalis</i> [leaf] (Loganiaceae), <i>Forsythia suspensa</i> [fruit] (Oleraceae), <i>Plantago media</i> (Plantaginaceae), <i>Verbascum sinuatum</i> (Scrophulariaceae); Acanthaceae, Bignoniaceae, Gesneriaceae, Orobanchaceae, Verbenaceae	AR (EGF-RTK, 5-LOX) [AI]
Umbelliferone (= Dichrin A; Hydrangin; 7-Hydroxycoumarin; Skimmetin) (coumarin)	<i>Artemisia capillari</i> (Asteraceae), <i>Ammi majus</i> , <i>Apium</i> , <i>Ferula</i> , <i>Heracleum</i> , <i>Pimpinella</i> spp. (Apiaceae), <i>Aegle marmelos</i> , <i>Citrus grandis</i> (Rutaceae), <i>Hydrangea paniculata</i> (Saxifragaceae), <i>Atropa belladonna</i> (Solanaceae) [root]	AR (bovine lens) (30)
Terpene		14.5t
7-O-Acetyl-8- <i>epi</i> -loganic acid (iridoid monoterpene glycoside)	<i>Monochasma savatieri</i> (Scrophulariaceae) [aerial]	AR (rabbit lens) (56)
Caryolane-1,9 β -diol (sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	AR (rat lens) (45)
Clovanediol (sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	AR (rat lens) (96)
Cryptotanshinone (abietane diterpenoid)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AR (rat lens) (10)
Danshenol A (abietane diterpenoid)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AR (rat lens) (0.1)
Danshenol B (abietane diterpenoid)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AR (rat lens) (2)
(-)-Danshexinkun A (abietane diterpenoid)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AR (rat lens) (0.9)
Demethylmussaenoside (iridoid monoterpene glycoside)	<i>Monochasma savatieri</i> (Scrophulariaceae) [aerial]	AR (rabbit lens) (61)
Dihydrotanshinone I (abietane diterpenoid)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AR (rat lens) (1)
3 β ,22 α -Dihydroxyolean-12-en-29-oic acid (oleane triterpene)	<i>Salacia oblonga</i> (Celastraceae) [root]	AR (rat lens) (~30)
19-Hydroxyferruginol (abietane diterpene)	<i>Salacia oblonga</i> (Celastraceae) [root]	AR (rat lens) (>100)
Kotalagenin 16-acetate (friedelane triterpene)	<i>Salacia oblonga</i> (Celastraceae) [root]	AR (rat lens) (~100)
Lambertic acid (abietane diterpene)	<i>Salacia oblonga</i> (Celastraceae) [root]	AR (rat lens) (>100)
Maytenfolic acid (triterpene)	<i>Salacia oblonga</i> (Celastraceae) [root]	AR (rat lens) (~100)
Oplopanone (sesquiterpene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	AR (rat lens) (>100)
Perilloside A (monoterpene glycoside)	<i>Perilla frutescens</i> (Lamiaceae) [leaf]	AR (recombinant human) (>100), AR (rat lens) (~100) [140]

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) [part]	Enzyme inhibited (other targets) / in vivo effects/
[Perilloside A tetraacetate] (monoterpene glycoside tetraacetate)	Semi-synthetic	AR (rat lens) (25)
Perilloside C (monoterpene glycoside)	<i>Perilla frutescens</i> (Lamiaceae) [leaf]	AR (recombinant human) (>100), AR (rat lens) (>100) [230]
[Perilloside C tetraacetate] (monoterpene glycoside tetraacetate)	Semi-synthetic	AR (rat lens) (71)
Perilloside D (monoterpene glycoside)	<i>Perilla frutescens</i> (Lamiaceae) [leaf]	AR (rat lens) (>100)
(-)-Phellandryl- β -D-Glc (monoterpene glycoside)	<i>Perilla frutescens</i> (Lamiaceae) [leaf]	AR (recombinant human) (~100), AR (rat lens) (~100)
[(-)-Phellandryl-2,3,4,6-tetra- <i>O</i> -acetyl- β -D-Glc tetraacetate] (monoterpene glycoside tetraacetate)	Semi-synthetic	AR (recombinant human) (~100 μ M), AR (rat lens) (~100)
Sitosterol 3- <i>O</i> -Glc (= Sitosterin 3- <i>O</i> -Glc; β -Sitosterol 3- <i>O</i> -Glc) (phytosterol triterpene glycoside)	Aglycone widespread; <i>Perilla frutescens</i> (Lamiaceae) [leaf]	AR (rat lens) (>100)
Sugiol (abietane diterpenoid)	<i>Juniperus communis</i> (Cupressaceae), <i>Salvia miltiorhiza</i> (Lamiaceae) [root], <i>Azadirachta indica</i> (Meliaceae)	AR (rat lens) (>10)
Tanshinone I (abietane diterpenoid)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AR (rat lens) (5)
Tanshinone IIA (abietane diterpenoid)	<i>Salvia miltiorhiza</i> (Lamiaceae) [root]	AR (rat lens) (1)
Other		14.5o
Prunasin (cyanogenic glycoside)	Some Asteraceae, Fabaceae, Myrtaceae, Myoporaceae, Scrophulariaceae; <i>Peridium aquilinum</i> , <i>Cystopteris</i> spp. (fern), <i>Perilla frutescens</i> (Lamiaceae), <i>Prunus laurocerasus</i> , <i>P.</i> spp. (Rosaceae) [leaf]	AR (rat lens) (>100)
(<i>S</i>)-Sambunigrin (= Prunasin epimer) (cyanogenic glycoside)	<i>Sambucus nigra</i> (Caprifoliaceae), <i>Perilla frutescens</i> (Lamiaceae), <i>Acacia glaucescens</i> (Fabaceae), <i>Ximenia americana</i> (Olacaceae)	AR (rat lens) (>100)
<i>cis</i> -Spiroketalnenoether polyene (polyacetylene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	AR (rat lens) (>100)
<i>trans</i> -Spiroketalnenoether polyene (polyacetylene)	<i>Chrysanthemum indicum</i> (Asteraceae) [flower]	AR (rat lens) (>100)
Non-plant reference		14.5n
[Hexahydroxybenzophenone] (benzophenone)	Synthetic	AR (human lens) (1–10)
[Sorbiniol (= (<i>S</i>)-6-Fluoro-spiro-chroman-4, 4-imidazolidine)-2,5-dione] (chromane)]	Synthetic chromane	AR (human lens) (0.2)

(continued)

Table 14.5 (Continued)

Compound (class)	Plant (family) part/	Enzyme inhibited (other targets) / in vivo effects/
[2',4',2,4-Tetrahydroxy-chalcone] (chalcone)	Synthetic	AR (7 nM)
[2',4',2-Trihydroxy-chalcone] (chalcone)	Synthetic	AR (0.2)

Table 14.6 Plant compounds with hypoglycaemic, antidiabetic and/or insulinotropic effects

Compound (class)	Plant source plant part/	Effect (other targets) / in vivo effects/
Alkaloids		14.6a
Arecoline (piperidine alkaloid)	<i>Areca catechu</i> (Palmae) [betel nut], <i>Piper betel</i> (Piperaceae)	HypoGlc
Castanospermine (piperidine alkaloid)	<i>Castanospermum australe</i> (Fabaceae) [seed]	HypoGlc (STZ-DB mouse) (IP) [α-glycosidase inhibitor]
Cryptolepine (indole alkaloid)	<i>Cryptolepis triangularis</i> , <i>C. sanguinolenta</i> (Asclepiadaceae)	HypoGlc (DB mouse), ↑ Glc uptake (3T3-L1 cells)
Dioscoretine (piperidine alkaloid)	<i>Dioscorea dumetorum</i> (Dioscoreaceae) [tuber]	HypoGlc (normal & ALL-DB rabbit) (IP)
N-Methylcytisine (= Caulophylline) (quinolizidine alkaloid)	<i>Baptisia tinctorial</i> , <i>Cytisus laburnum</i> , <i>Laburnum anagyroides</i> , <i>Lygos raelum</i> , <i>Sophora subprostrata</i> , <i>Spartium junceum</i> , <i>Ulex europaeus</i> (Fabaceae)	HypoGlc (DB mouse)
Serotonin (= 5-Hydroxytryptamine; 5HT) (indole)	<i>Ananas comosus</i> (pineapple) (Bromeliaceae), <i>Hippophae rhamnoides</i> (Elaeagnaceae), <i>Juglans regia</i> (walnut) (Juglandaceae), <i>Mucuna pruriens</i> (cowhage) (Fabaceae), <i>Musa sapientum</i> (banana) (Musaceae) [fruit], <i>Phalaris</i> spp. (Poaceae), <i>Lycopersicon esculentum</i> (tomato) (Solanaceae), <i>Theobroma cacao</i> (cocoa) (Sterculiaceae), <i>Urtica dioica</i> (stinging nettle hairs) (Urticaceae)	Inhibits insulin secretion (5HT-R agonist) [CNS stimulatory NT]
Phenolics		14.6p
Bellidifolin (xanthone)	<i>Gentiana lactea</i> , <i>Swertia japonica</i> & <i>S. chirata</i> (Gentianaceae) [aerial]	HypoGlc (STZ-DB rat) (MAO) ↓ AGEs
Cirsilineol (flavonoid)	<i>Artemisia capillaries</i> , <i>A. dracunculoides</i> (Asteraceae), <i>Salvia officinalis</i> , <i>Salvia tomentosa</i> , <i>Sideritis</i> sp., <i>Thymus vulgaris</i> (Lamiaceae)	
(-)-Epicatechin (flavan-3-ol)	Widespread; <i>Pterocarpus</i> spp. (Fabaceae), <i>Aesculus californica</i> (Hippocastanaceae), <i>Podocarpus nagi</i> (Podocarpaceae) [bark], <i>Crataegus monogyna</i> (Rosaceae), <i>Mitragyna speciosa</i> (Rubiaceae), <i>Camellia sinensis</i> (Theaceae)	↑ Insulin secretion; antioxidant

(continued)

Table 14.6 (Continued)

Compound (class)	Plant source plant part	Effect (other targets) / in vivo effects/
Eriodictyol (flavonoid)	<i>Eriodictyon californicum</i> (Hydrophyllaceae), <i>Ocimum basilicum</i> , <i>Origanum vulgare</i> , <i>Thymus vulgaris</i> (Lamiaceae), <i>Citrus paradisi</i> (Rutaceae)	↓ AGEs
Fraxidin (coumarin) 4-Hydroxybenzoic acid (phenolic acid)	<i>Teramnus labialis</i> (Fabaceae) [aerial] <i>Fagara macrophylla</i> , <i>Zanthoxylum</i> <i>rubescens</i> (Rutaceae), <i>Paratecoma</i> <i>peroba</i> , <i>Tabebuia impetiginosa</i> (Bignoniaceae), <i>Pterocarpus</i> <i>santalinus</i> (Fabaceae); <i>Vitis vinifera</i> (Vitaceae), <i>Pandanus odoratus</i> (Pandanaeae) [root]	HypoGlc (DB db/db mice) HypoGlc (STZ-DB rat), ↑ Glc consumption (normal & STZ-DB rat diaphragm)
2-Hydroxymatteucinol (flavanone)	<i>Matteuccia orientalis</i> (Dryopteridaceae)	HypoGlc (STZ-DB rat)
Isoferulic acid (phenolic acid)	<i>Helianthus annuus</i> (Asteraceae), <i>Catalpa ovata</i> (Bignoniaceae) [root], <i>Arachis hypogaea</i> (Fabaceae), <i>Triticum</i> <i>aestivum</i> (Poaceae), <i>Tamarix aphylla</i> (Tamaricaceae) [leaf] <i>Cimicifuga</i> <i>dahurica</i> & <i>C. racemosa</i> (Ranunculaceae) [rhizome]	HypoGlc (DB rat)
Kaempferol (flavonol)	Widespread; <i>Brassica oleracea</i> (Brassicaceae), <i>Aesculus</i> <i>hippocastanum</i> (Hippocastanaceae), <i>Azalia</i> spp., <i>Pisum sativum</i> , <i>Trifolium</i> <i>pratense</i> (Fabaceae) [wood], <i>Thespesia</i> <i>populnea</i> (Malvaceae), <i>Azadirachta</i> <i>indica</i> (Meliaceae)	LOX inhibition, AO, ↓ haemoglobin glycosylation
Kolaviron mixture (mixture of C-3/C-8 linked biflavonoids)	<i>Garcinia kola</i> (Guttiferae)	HypoGlc (normal & ALL-DB rabbit) (AR)
Leucodelphinidin bioactive (flavonoid anthocyanidin)	<i>Vicia faba</i> (Fabaceae), <i>Aesculus</i> <i>hippocastanum</i> (Hippocastanaceae), <i>Ficus bengalensis</i> (Moraceae) [bark], <i>Musa paradisiaca</i> (Musaceae)	HypoGlc (normal & ALL-DB rat)
Leucopelargonidin glycoside (flavonoid anthocyanidin glycoside)	<i>Hydnocarpus wightiana</i> (Flacourtiaceae), <i>Ficus bengalensis</i> (Moraceae) [bark], <i>Zea mays</i> (Poaceae), <i>Rumex hymenosepalus</i> (Polygonaceae)	HypoGlc, hypolipidaemic, insulinotropic (DB rat)
Mangiferin (xanthone)	<i>Mangifera</i> (Anacardiaceae), <i>Hiptage</i> (Malpighiaceae), <i>Cuscuta reflexa</i> (Cuscutaceae), <i>Gentiana lutea</i> , <i>Swertia</i> <i>chirata</i> (Gentianaceae), <i>Hypericum</i> (Hypericaceae), <i>Anemarrhena</i> <i>asphodeloides</i> (Liliaceae), <i>Athyrium</i> (Polypodiaceae) spp.; Iridaceae, Gentianaceae, Fabaceae, Flacourtiaceae, Convolvulaceae, Celastraceae, Sapotaceae	HypoGlc (KK–Ay DB but not normal mouse) [↑ insulin sensitivity]

(continued)

Table 14.6 (Continued)

Compound (class)	Plant source / plant part/	Effect (other targets) / in vivo effects/
Mangiferin-7-O- β -Glc (xanthone glycoside)	<i>Anemarrhena asphodeloides</i> (Liliaceae) [rhizome]	HypoGlc (KK-Ay D but not normal mouse) [\uparrow insulin sensitivity]
Marsupin (stilbenoid)	<i>Pterocarpus marsupium</i> (Fabaceae) [wood]	HypoGlc (STZ-DB rat) (IP)
Methylhydroxychalcone polymer (= MHCP) (chalcone)	<i>Cinnamomum zeylanicum</i> (cinnamon) (Lauraceae)	Mimics insulin in activating insulin-RTK autophos'n, glycogen synthase and Glc uptake (action inhibited by PI3K inhibitor Wortmannin)
Moracin M-3-O- β -D-Glc (benzofuran glycoside)	<i>Morus insignis</i> (Moraceae) [leaf]	HypoGlc (STZ-DB rat)
Mulberrofuran U (benzofuran glycoside)	<i>Morus insignis</i> (Moraceae) [leaf]	HypoGlc (STZ-DB rat)
Myricetin (flavonol)	Widespread; <i>Haplopappus canescens</i> (Asteraceae) [aerial], <i>Azadirachta</i> <i>indica</i> , <i>Soyimida febrifuga</i> (Meliaceae) [wood]	\uparrow Glc uptake (LOX, NADH oxidase)
Nordihydroguaiaretic acid (= Masoprocol) (phenylpropanoid lignan)	<i>Guaiacum sanctum</i> , <i>G. officinale</i> , <i>Larrea tridentata</i> , <i>L. spp.</i> (Zygophyllaceae) [resin]	HypoGlc (db/db & ob/ob DB mouse) (LOX) [antioxidant]
Pterostilbene (stilbenoid)	<i>Pterocarpus marsupium</i> , <i>P. santalinus</i> , <i>P. spp.</i> (Fabaceae) [wood], <i>Vitis</i> <i>vimifera</i> (Vitaceae) [wood]	HypoGlc (STZ-DB rat)
Quercetin (= 3,5,7,3',4'- Pentahydroxyflavone) (flavonol)	Widespread; Asteraceae, Passiflorae, Rhamnaceae, Solanaceae; <i>Podophyllum peltatum</i> (Berberidaceae), <i>Thymus vulgaris</i> (Lamiaceae), <i>Allium cepa</i> (Liliaceae), <i>Oenothera biennis</i> (Onagraceae), <i>Citrus paradisi</i> (Rutaceae) [grapefruit juice], <i>Camellia sinensis</i> (Theaceae)	\downarrow AGEs (LOX, PK) [AI, feeding] stimulant]
Silibinin (flavanolignan)	<i>Silybum marianum</i> (Asteraceae) [fruit]	\downarrow Insulin release
Swerchirin (xanthone)	<i>Gentiana lactea</i> , <i>Swertia chirayita</i> , <i>S. chirata</i> (Gentianaceae)	HypoGlc (normal & Glc-loaded rat) (MAO)
Terpenes		14.6t
Bakuchiol (monoterpene)	<i>Otholobium pubescens</i> , <i>Psoralea</i> <i>corylifolia</i> (Fabaceae)	HypoGlc (db/db mouse, STZ-DB rat), \downarrow triglyceride (STZD rat)
Bassic acid (triterpene acid)	<i>Bumelia sartorum</i> (Sapotaceae) [rootbark]	HypoGlc, \uparrow insulin (ALL- DB rat) [\uparrow insulin secretion]
Cacalol (furanoreophilane sesquiterpene)	<i>Psacalium decompositum</i> (Asteraceae) [root]	HypoGlc (DB ob/ob mouse)
Christinin-A (triterpene saponin glycoside)	<i>Zizyphusspina christi</i> (Rhamnaceae) [leaf]	HypoGlc (STZ-DB but not normal rat) [\uparrow insulin secretion]
<i>trans</i> -Dehydrocrotonin (nor-clerodane diterpene)	<i>Croton cajucara</i> (Euphorbiaceae) [bark]	HypoGlc (N & AD rat)

(continued)

Table 14.6 (Continued)

Compound (class)	Plant source plant part	Effect (other targets) / in vivo effects/
Escin Ia (triterpene saponin)	<i>Polygala senega</i> (Polygalaceae) [root]	HypoGlc (Glc-loaded rat) [↓ intestinal Glc transport]
Escin IIa (triterpene saponin)	<i>Polygala senega</i> (Polygalaceae) [root]	HypoGlc (Glc-loaded rat) [↓ intestinal Glc transport]
Furanosesesquiterpenes (sesquiterpenes)	<i>Commiphora myrrha</i> (Bursaceae)	HypoGlc
Glycyrrhizin (triterpene saponin)	<i>Glycyrrhiza glabra</i> (Fabaceae) [root & rhizome]	HypoGlc (KK-CA(y) obese DB & ALL-DB mouse)
Gymnemic acid (triterpene glycoside mixture)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	↓ Glc absorption (↓ Glc- stimulated GIP secretion via a Glc receptor that is not the Glc transporter)
Gymnemic acids III, V, VII (triterpene saponins)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	↓ Glc absorption
Gymnemoside b (triterpene glycoside)	<i>Gymnema sylvestre</i> (Asclepiadaceae) [leaf]	↓ Glc absorption
Hederagenin (triterpene)	<i>Hedera helix</i> , <i>Kalopanax pictus</i> (Araliaceae) [bark], <i>Humulus lupulus</i> (Cannabaceae), <i>Medicago sativa</i> (Fabaceae)	HypoGlc, hypocholesterolaemic, hypolipidaemic (STZ-DB rat)
3-Hydroxycacalolide + epi-3-Hydroxycacalolide (eremophilanolide sesquiterpene)	<i>Psacalium decompositum</i> (Asteraceae) [root]	HypoGlc (DB ob/ob mouse)
Kalopanax saponin A (triterpene saponin)	<i>Kalopanax pictus</i> (Araliaceae) [bark]	HypoGlc, hypocholesterolaemic, hypolipidaemic (STZ-DB rat)
Momordin Ic (triterpene saponin)	<i>Kochia scoparia</i> (Chenopodiaceae) [fruit]	↓ Gastric emptying, ↓ interstitial Glc uptake (rat)
Oleanolic acid 3-O-GlcA (triterpene acid glycoside)	<i>Lonicera nigra</i> (Caprifoliaceae), <i>Beta vulgaris</i> (Chenopodiaceae) [sugar beet]	↓ Gastric emptying, ↓ interstitial Glc uptake (rat)
Prototimosaponin AIII (triterpene saponin)	<i>Anemarrhena asphodeloides</i> (Liliaceae) [rhizome]	HypoGlc (but no Glc uptake or insulin release effect) (STZ-DB mouse) [gluconeogenesis, glycogenolysis]
Pseudoprototimosaponin AIII (triterpene saponin)	<i>Anemarrhena asphodeloides</i> (Liliaceae) [rhizome]	HypoGlc (but no Glc uptake or insulin release effect) (STZ-DB mouse) [↓ gluconeogenesis, glycogenolysis I]
SP-18904, SP-18905 (terpene quinones)	<i>Pycnanthus angolensis</i> (Myristicaceae) [aerial]	HypoGlc (ob/ob & db/db mice – both hyperglycaemic & hyperinsulinaemic) [↑ insulin- mediated Glc uptake]
Senegin II (triterpene glycoside)	<i>Polygala senega</i> (Polygalaceae)	HypoGlc (N & KK-Ay mouse) (IP administration), no HypoGlc (ALL-DB mouse), ↓ gastric emptying, ↓ intestinal Glc uptake (rat)

(continued)

Table 14.6 (Continued)

Compound (class)	Plant source / plant part/	Effect (other targets) / in vivo effects/
Senegin III (triterpene glycoside)	<i>Polygala senega</i> (Polygalaceae)	HypoGlc (N & KK–Ay mouse) (IP administration), no HypoGlc (ALL-DB mouse), ↓ gastric emptying, ↓ intestinal Glc uptake (rat)
Spirostanol glycoside (triterpene glycoside)	<i>Polygonatum biflorum</i> (Solomon's seal) (Liliaceae) [root]	HypoGlc (normal & STZ-DB mouse) (IP administration)
Steviol (kaurane diterpene)	<i>Stevia rebaudiana</i> (Asteraceae) [leaf]	HypoGlc (human), ↑ Glc-induced Insulin secretion (β cells) [activity like Gibberellin, insulinotropic]
Stevioside (kaurane diterpene glycoside)	<i>Stevia rebaudiana</i> (Asteraceae) [leaf]	HypoGlc (human), ↑ Glc-induced Insulin secretion (β cells) [sweet (300× >sucrose), insulinotropic]
[α-, β-, γ- & δ-Tocopherols (= Vitamin E)] (chromanol isoprenoid)	Green vegetables, palm, safflower, sunflower oil, wheat germ; <i>Helianthus annuus</i> (Asteraceae), <i>Ipomoea aquatica</i> (Convolvulaceae), <i>Triticum aestivum</i> (Poaceae), <i>Portulaca oleracea</i> (Portulacaceae); discovered by Herbert M. Evans (Berkeley, USA, 1922)	Anti-retinopathy (AO/FRS, PKC) [anti-ageing nutraceutical, antioxidant]
5,6,4'-Trihydroxy-7,8,3'-trimethoxyflavone (flavonoid)	<i>Thymus vulgaris</i> (Lamiaceae)	↓ AGEs
Other compounds		14.6o
Acemannan (carbohydrate)	<i>Aloe vera</i> (aloe vera) (Liliaceae) [leaf, gel]; most popular cosmetic & toiletry ingredient in USA ; for burns, bruises, wounds	HypoGlc [↑ NO, IL-6 & TNF-α in macrophage]
S-Allyl cysteine sulfoxide (amino acid)	<i>Allium sativum</i> (Liliaceae) [bulb]	HypoGlc (ALL-DB rat), ↑ insulin secretion (N rat β cells)
8-Debenzoylpaconiflorin (sugar derivative)	<i>Paeonia lactiflora</i> (Paeoniaceae) [root]	HypoGlc (STZ-DB rat) [↑ Glc use]
Fagomine (N-containing sugar)	<i>Xanthocercis zambesiaca</i> (Fabaceae) [root, leaf]	HypoGlc ↑ plasma insulin (STZ-DB mouse)
β-Glucan (glucan)	<i>Rhoeo spathacea</i> (Commelinaceae), <i>Hordeum vulgare</i> , <i>Triticum</i> sp. (Poaceae)	HypoGlc (IDDM & NIDDM human)
2-β-D-Glc-oxy-1-hydroxy-5(E)-tridecene-7,9,11-tri-ene (polyacetylenic glycoside)	<i>Bidens pilosa</i> (Asteraceae) [aerial]	HypoGlc
3-β-D-Glc-oxy-1-hydroxy-6(E)-tetradecene-8,10,12-tri-ene (polyacetylenic glycoside)	<i>Bidens pilosa</i> (Asteraceae) [aerial]	HypoGlc

(continued)

Table 14.6 (Continued)

Compound (class)	Plant source plant part	Effect (other targets) / in vivo effects/
Guar gum (polysaccharide)	<i>Cyamopsis tetragonolobus</i> (Fabaceae) [seed flour, guar]; dietary hypoglycaemic	HypoGlc (IDDM human), ↓ cholesterol (normal dog), postprandial GIP & insulin
Hemicellulose (glycan)	<i>Zea mays</i> (Poaceae) [seed bran]	HypoGlc (NIDDM human)
4-Hydroxyisoleucine (amino acid)	<i>Trigonella foenum graecum</i> (Fabaceae) [seed]	HypoGlc (DB rat, dog), insulinotropic (rat β cells); lactone form inactive
3-Hydroxy-3-methylglutaric acid (organic acid)	<i>Tillandsia usneoides</i> (Bromeliaceae)	HypoGlc (normal mouse)
γ-Linolenic acid (unsaturated fatty acid)	Widespread in plants; <i>Borago officinalis</i> (Boraginaceae), <i>Cucumis sativus</i> (Cucurbitaceae), <i>Ribes nigrum</i> (Grossulariaceae), <i>Salvia sclarea</i> , <i>Satureja hortensis</i> (Lamiaceae), <i>Linum usitatissimum</i> (Linaceae), <i>Oenothera</i> spp. (Onagraceae)	Prevents deficit in sciatic nerve conduction velocity (STZ-DB rat)
Lithium ion (Li ⁺)	Environmental	GSK3β [normal GSK Ser phosphorylation & inhibition by insulin-activated PKB; bipolar mood disorder & manic depression treatment]
S-Methylcysteine sulfoxide (amino acid)	<i>Allium cepa</i> (Liliaceae) [bulb]	HypoGlc, ↓ cholesterol synthesis (AD rat)
<i>Momordica</i> polypeptide-P (11 kDa protein)	<i>Momordica charantia</i> (bitter melon) (Cucurbitaceae) [fruit, seed]	HypoGlc (humans, other primates, subcutaneous)
<i>Morus</i> Moran (22 kDa glycoprotein)	<i>Morus alba</i> (Moraceae) [root bark]	HypoGlc (STZ-DB mouse), ↑ Glc transport (fat cells)
Paeoniflorin (glycosylated benzoic acid derivative)	<i>Paeonia lactiflora</i> , <i>P. moutan</i> , <i>P. suffruticosa</i> (Paeoniaceae) [root]	HypoGlc (STZ-DB rat) [↑ Glc use]
Panaxans A, B, C, D, E, Q, R, S, T & U (glycans)	<i>Panax ginseng</i> (Araliaceae) [root]	HypoGlc (normal & ALL-DB mouse)
Pectin (acidic polysaccharide)	General; plant cell wall polysaccharide	HypoGlc, ↓ postprandial GIP & insulin
Phytic acid (phosphorylated cyclohexitol)	Widespread; <i>Cucurbita pepo</i> (Cucurbitaceae), <i>Phaseolus vulgaris</i> , <i>Vigna unguiculata</i> (Fabaceae), <i>Triticum aestivum</i> (Poaceae)	↓ Starch digestion, sequesters Ca ²⁺ (human)
Potato POT II (protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae)	HypoGlc (delays gastric emptying, ↓ postprandial Glc, GIP & insulin)
Psyllium preparation (polysaccharide)	<i>Plantago psyllium</i> (Plantaginaceae)	HypoGlc (NIDDM human) [anti-constipation, anti-haemorrhoid, water-absorbant]
Quinquefolans A, B, C (glycans)	<i>Panax quinquefolium</i> (Araliaceae) [root]	HypoGlc (normal & ALL-DB mouse)

(continued)

Table 14.6 (Continued)

Compound (class)	Plant source / plant part/	Effect (other targets) / in vivo effects/
<i>Solanum</i> cathepsin D inhibitor (protein)	<i>Solanum tuberosum</i> (potato) (Solanaceae) [tuber]	Overcomes protease increase in STZ-DB rat skin to restore normal collagen synthesis in wounded skin
Trichosans A, B, C, D & E (glycans)	<i>Trichosanthes kirilowii</i> (Cucurbitaceae) [root]	A-E – HypoGlc (normal mouse); A – HypoGlc (ALL-DB mouse)
Trihydroxy-octadecadienoic acids (unsaturated fatty acids)	<i>Bryonia alba</i> (Cucurbitaceae) [root]	↓ Lipid abnormalities elevated in DM (e.g. non-esterified FA) (AD rat)
<i>Triticum</i> α-Amylase inhibitor (protein)	<i>Triticum</i> sp. (wheat) (Poaceae) [seed]	HypoGlc, delays CHO absorption (normal dog, normal & NIDDM human)
Water soluble polysaccharide fractions (polysaccharide)	<i>Psacalium decompositum</i> (Asteraceae)	HypoGlc (normal & ALL-DB mouse)
Non-plant reference		14.6n
[Acarbose] (cyclohexenylamino-trisaccharide)	<i>Actinoplanes</i> (fungus)	α-Glucosidase [antidiabetic, inhibits intestinal glucose absorption]
[Aminoguanidine] (guanidine)	Synthetic	Scavenges aldehydes [↓ AGE formation]
[Bis(maltolato)oxovanadium(IV)] (vanadium pyrone complex)	Synthetic; complex of oxoV(IV) with Maltol (= 3-Hydroxy-2-methyl-4-pyrone)	Potent insulin mimetic
[Demethylasterriquinone B-1(= DMAQ-B1)] (quinone)	<i>Pseudomassaria</i> sp. (tropical fungus)	INS-RTK agonist [First orally active Insulin-mimetic small molecule; induces INS-RTK activation & phos'n, IRS-1 phos'n, PI3K, PKB & Glc uptake activation]
[Glibenclamide (= Glyburide)] (aryl sulfonylurea)	Synthetic	ATP-K ⁺ CH [1 nM] (CFTR) [antidiabetic, ↑ insulin secretion]
[Gliclazide (= Diamicron)] (aryl sulfonylurea)	Synthetic	ATP-K ⁺ CH [antidiabetic, ↑ insulin secretion]
[Glimepiride] (aryl sulfonylurea)	Synthetic	ATP-K ⁺ CH [antidiabetic, ↑ insulin secretion]
Glucagon-like peptide-1 (= GLP-1) (protein)	Animals <i>ex</i> brain, intestine	Anorexigenic, insulinotropic [possible therapeutic agent for type 2 diabetes]













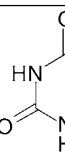
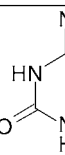
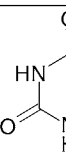
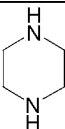

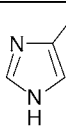

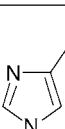
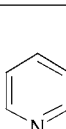
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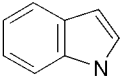
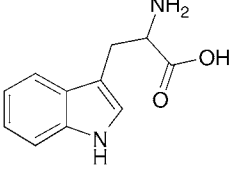
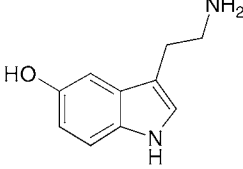
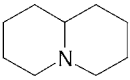
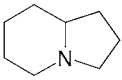
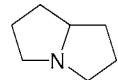
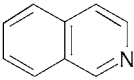
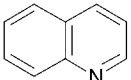
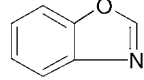
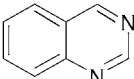
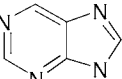
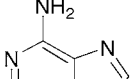
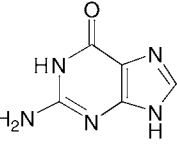
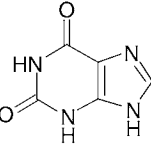
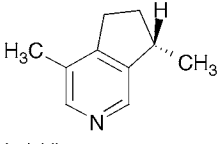
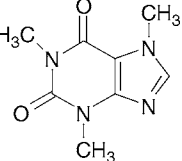
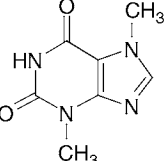
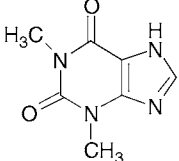
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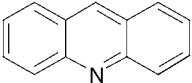
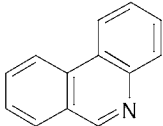
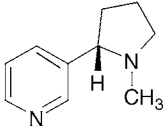
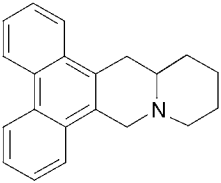
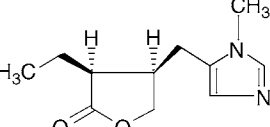
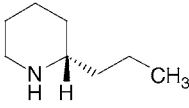
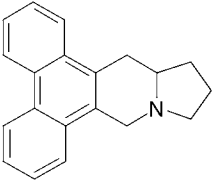
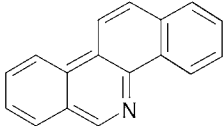
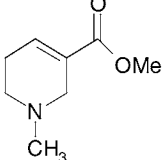
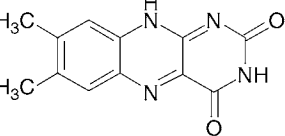
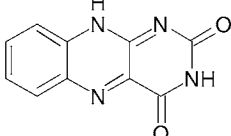
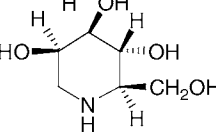
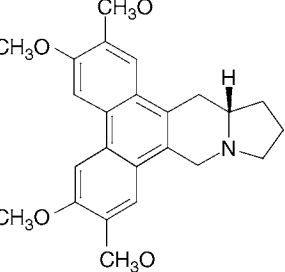
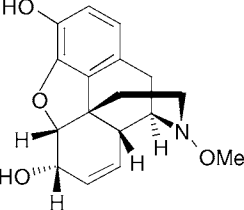
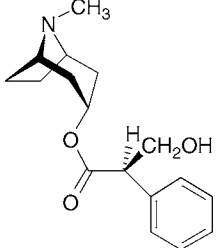
Compound (class)	Plant source plant part	Effect (other targets) / in vivo effects/
[Insulin] (5 kDa S–S-linked heterodimer; 3 S–S; A 21 aa, B 30 aa); insulin coma therapy for schizophrenia – applied to John Nash (USA, mathematician, Nobel Prize, Economics, 1994, game theory)	Animals <i>ex</i> pancreatic β cells; discovery (1922) by Frederick Banting, J.B. Collip, Charles Best, J. Macleod (Canada; Nobel Prize, Medicine, to Banting & MacLeod, 1923); sequence by Fred Sanger (1953) (UK, Nobel Prizes, Chemistry, 1958 [insulin sequence] & 1980 [RNA sequencing]); for treatment of Type 1 and advanced Type 2 diabetes mellitus	INS-RTK agonist [hypoG]; overdose yields hypoglycaemia, diabetic coma & death; Claus von Bulow convicted & thence acquitted through Alan Dershowitz of attempted murder by insulin of his wealthy wife Sunny left in a comatose state (1980s)
[LY333531]	Synthetic	PKC β [\downarrow angiogenesis, \downarrow diabetic retinopathy]
[Metformin] (biguanidine)	Synthetic	Promotes insulin action at RTK [\downarrow gluconeogenesis, \uparrow muscle Glc uptake, \downarrow AGE formation]
[Miglitol] (pseudomonosaccharide)	Synthetic	HypoGlc [smooths postprandial blood Glc]
[Repaglinide] (carbamoylmethyl benzoic acid)	Synthetic	ATP-K ⁺ CH [antidiabetic, \uparrow insulin secretion]
[Troglitazone] (thiazolidinedione)	Synthetic	Promotes insulin action at RTK [\downarrow insulin resistance]

Appendix: Structures of key parent and representative compounds

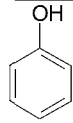
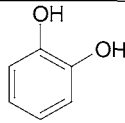
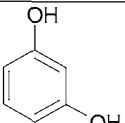
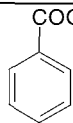
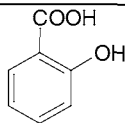
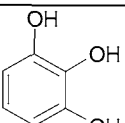
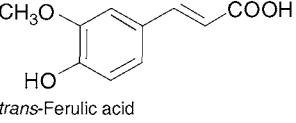
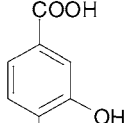
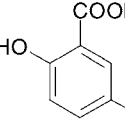
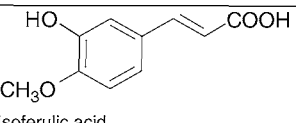
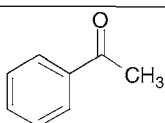
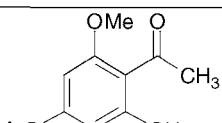
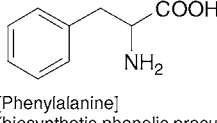
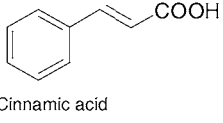
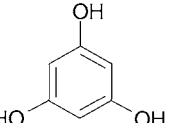
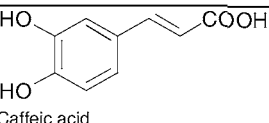
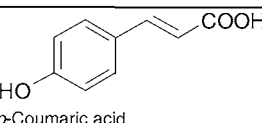
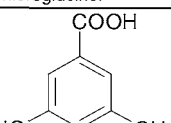
1. N-containing heterocyclics, alkaloids and pseudoalkaloids

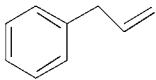
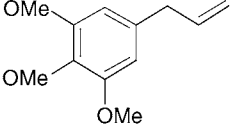
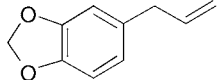
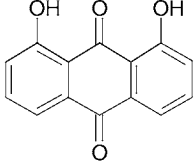
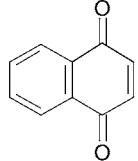
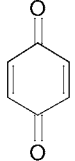
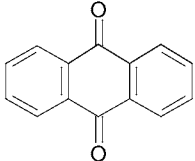
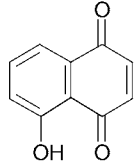
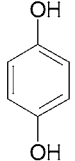
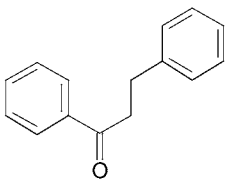
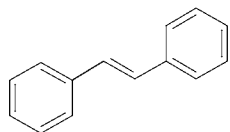
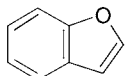
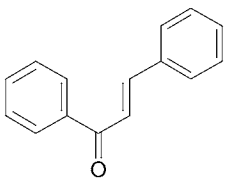
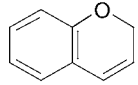
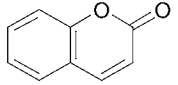
 Azetidine	 Pyrrolidine	 Piperidine (Hexahydropyridine)
 Pyrrole	 Oxazole	 Isoxazole
 Pyridine	 Pyridone	 Imidazole
 Pyrazine	 Pyrimidine	 Thiazole
 Uracil	 Cytosine	 Thymine
 Piperazine (Hexahydropyrazine)	 Triazine	 Histamine
 Nicotinic acid	 Histidine	 Nicotinamide

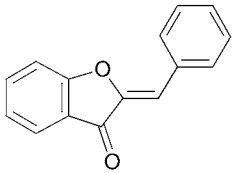
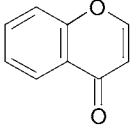
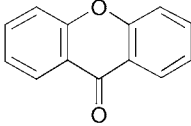
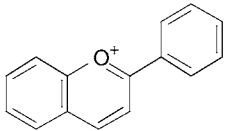
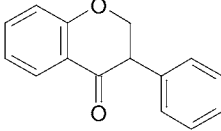
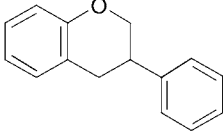
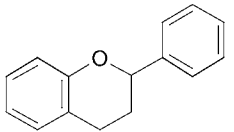
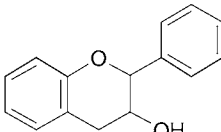
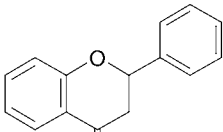
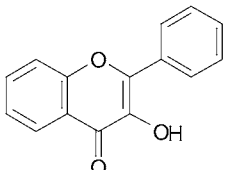
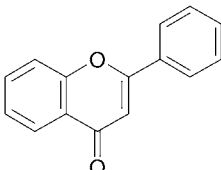
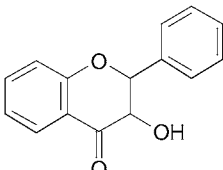
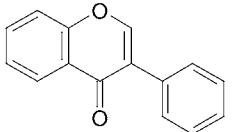
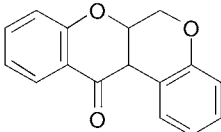
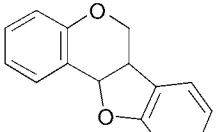
 <p>Indole</p>	 <p>Tryptophan</p>	 <p>Serotonin (5-Hydroxytryptamine)</p>
 <p>Quinolizidine</p>	 <p>Indolizidine</p>	 <p>Pyrrolizidine</p>
 <p>Isoquinoline</p>	 <p>Quinoline</p>	 <p>Benzoxazole</p>
 <p>Quinazoline</p>	 <p>Purine</p>	 <p>Adenine</p>
 <p>Guanine</p>	 <p>Xanthine (2,6-Dioxopurine)</p>	 <p>Actinidine (monoterpene alkaloid)</p>
 <p>Caffeine (1,3,7-Trimethylxanthine)</p>	 <p>Theobromine (3,7-Dimethylxanthine)</p>	 <p>Theophylline (1,3-Dimethylxanthine)</p>

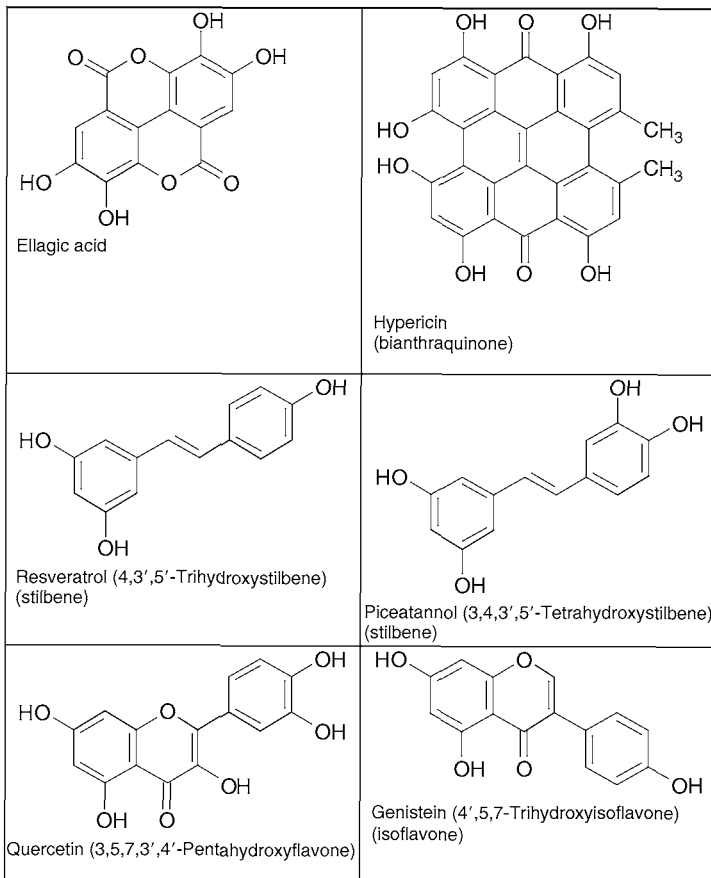
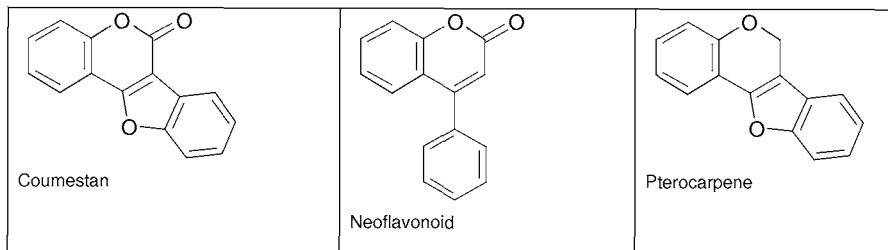
 <p>Acridine</p>	 <p>Phenanthridine</p>	 <p>Nicotine</p>
 <p>Phenanthroquinolizidine</p>	 <p>Pilocarpine</p>	 <p>(+)-Coniine ((S)-2-Propylpiperidine)</p>
 <p>Phenanthroindolizidine</p>	 <p>Benzophenanthridine</p>	 <p>Arecoline</p>
 <p>7,8-Dimethylisoxalazine</p>	 <p>Isoalloxazine</p>	 <p>Deoxymannojirimycin</p>
 <p>Tylophorine (phenanthroindolizidine)</p>	 <p>Morphine (morphinan isoquinoline)</p>	 <p>Atropine (Tropine tropate) (tropane alkaloid)</p>

2. Phenolics and related aromatic compounds

 <p>Phenol</p>	 <p>Catechol</p>	 <p>Resorcinol</p>
 <p>[Benzoic acid]</p>	 <p>Salicylic acid</p>	 <p>Pyrogallol</p>
 <p><i>trans</i>-Ferulic acid</p>	 <p>Protocatechuic acid</p>	 <p>Gentisic acid</p>
 <p>Isoferulic acid</p>	 <p>[Acetophenone]</p>	 <p>Xanthoxylin</p>
 <p>[Phenylalanine] (biosynthetic phenolic precursor)</p>	 <p>Cinnamic acid</p>	 <p>Phloroglucinol</p>
 <p>Caffeic acid</p>	 <p><i>p</i>-Coumaric acid</p>	 <p>Gallic acid</p>

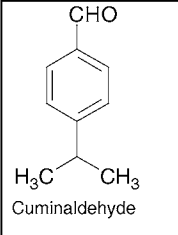
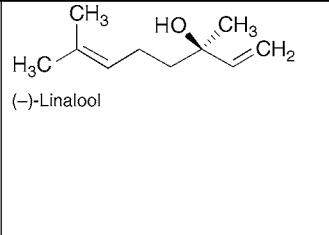
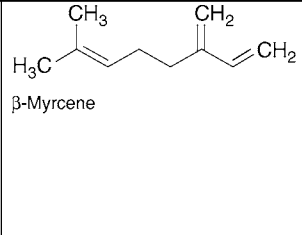
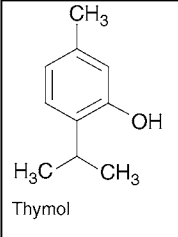
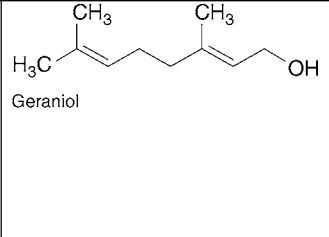
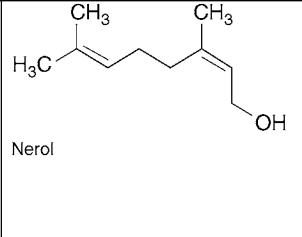
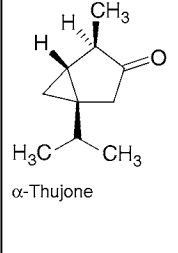
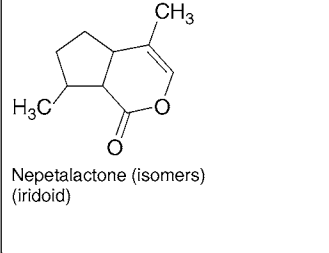
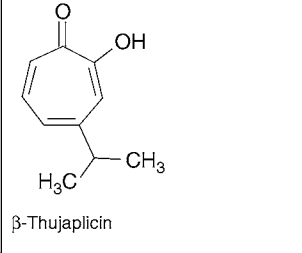
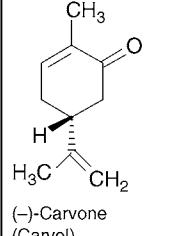
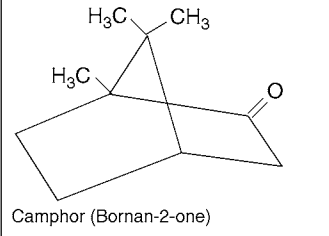
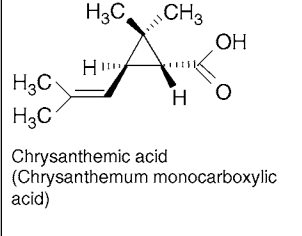
 <p>[Allylbenzene]</p>	 <p>Elemicine</p>	 <p>Safrole</p>
 <p>Chrysazin (1,8-Dihydroxyanthraquinone)</p>	 <p>1,4-Naphthoquinone</p>	 <p>1,4-Benzoquinone (Quinone)</p>
 <p>9,10-Anthraquinone</p>	 <p>Juglone (5-Hydroxynaphthoquinone)</p>	 <p>Hydroquinone</p>
 <p>Dihydrochalcone</p>	 <p><i>trans</i>-Stilbene</p>	 <p>Benzofuran</p>
 <p>Chalcone</p>	 <p>Chromene</p>	 <p>Coumarin</p>

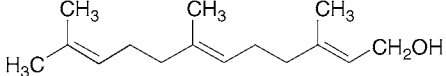
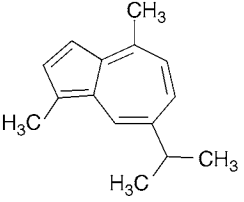
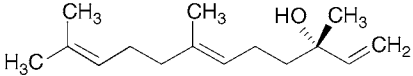
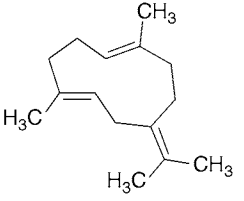
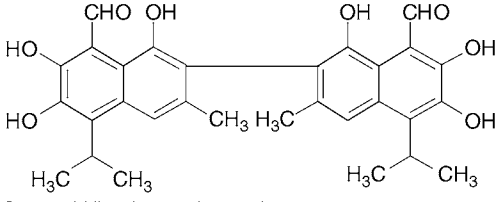
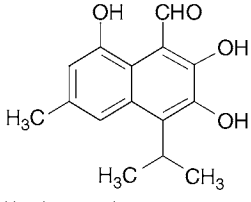
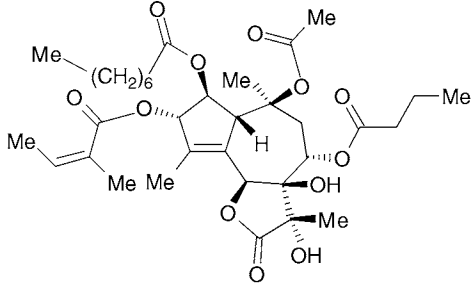
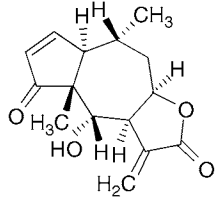
 <p>Aurone</p>	 <p>Chromone</p>	 <p>Xanthone</p>
 <p>Anthocyanidin</p>	 <p>Isoflavanone</p>	 <p>Isoflavan</p>
 <p>Flavan</p>	 <p>Flavan-3-ol</p>	 <p>Flavanone</p>
 <p>Flavonol</p>	 <p>Flavone</p>	 <p>2,3-Dihydroflavonol</p>
 <p>Isoflavone</p>	 <p>Rotenoid</p>	 <p>Pterocarpan</p>



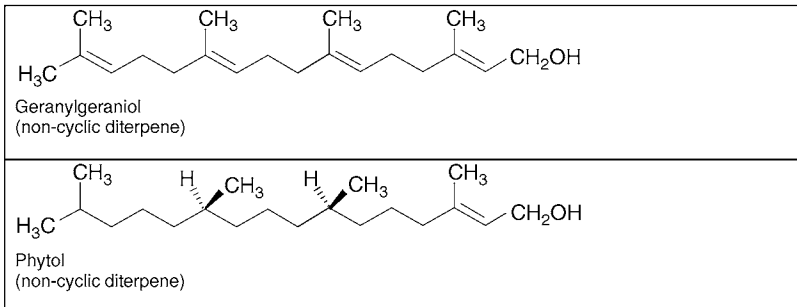
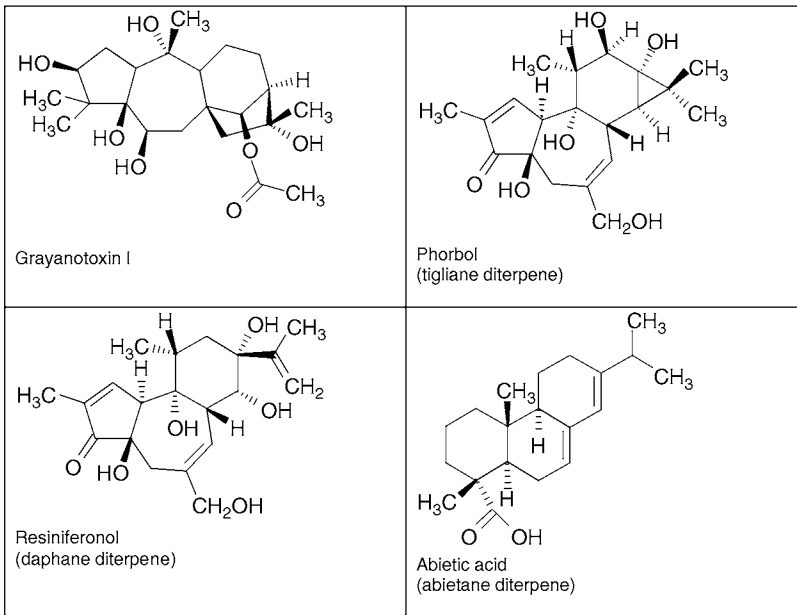
3. Terpenes

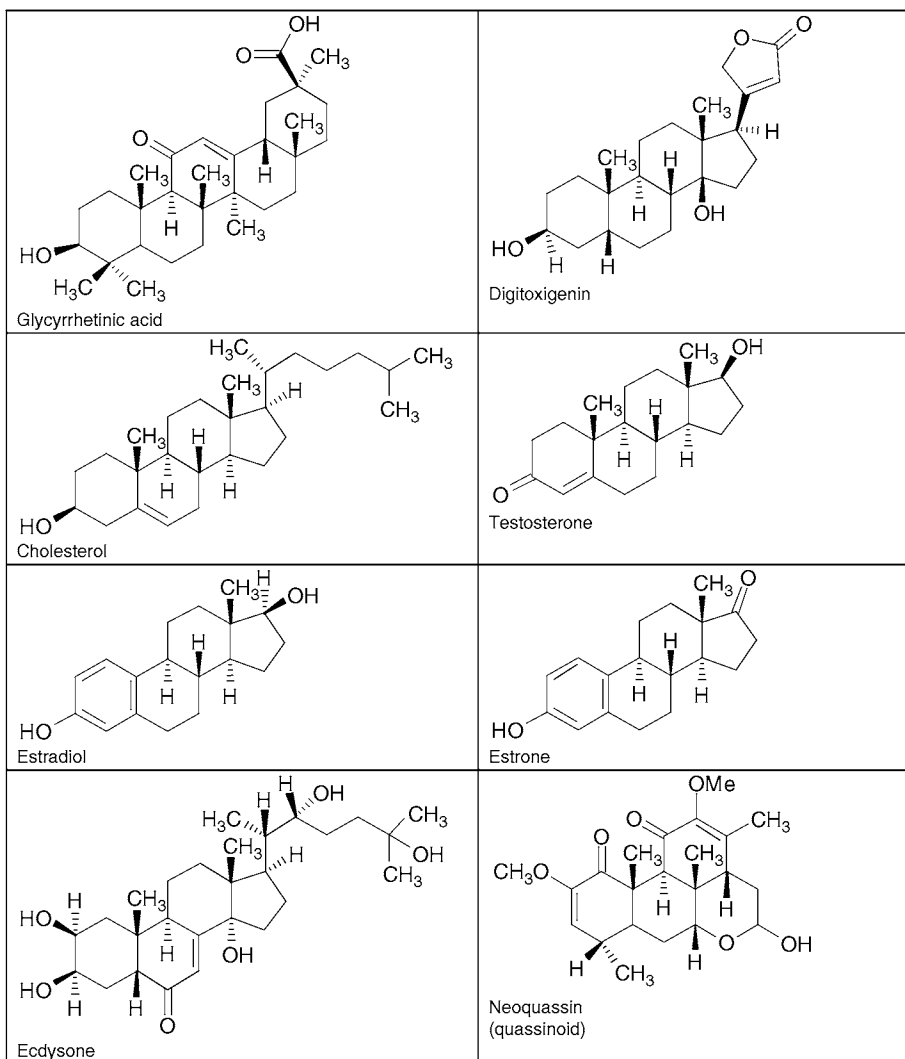
Monoterpenes

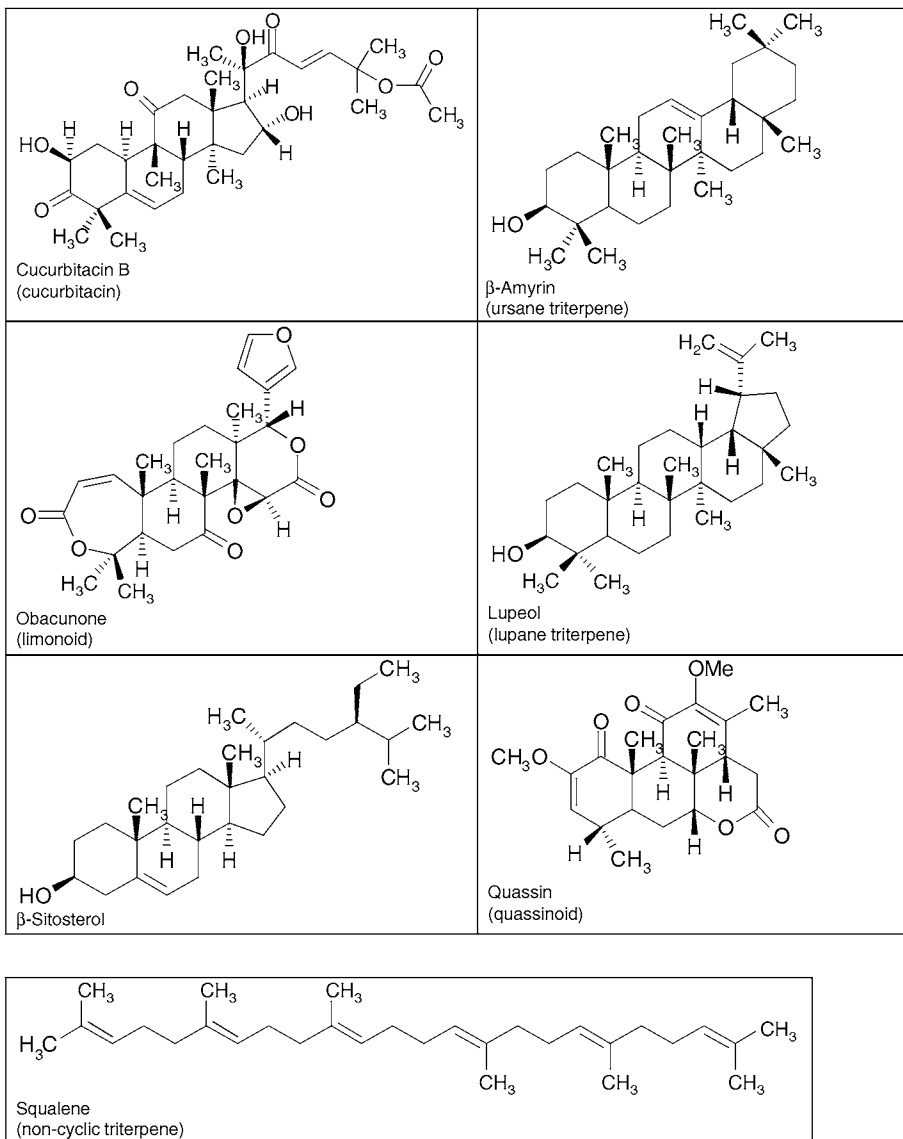
 <p>Cuminaldehyde</p>	 <p>(-)-Linalool</p>	 <p>β-Myrcene</p>
 <p>Thymol</p>	 <p>Geraniol</p>	 <p>Nerol</p>
 <p>α-Thujone</p>	 <p>Nepetalactone (isomers) (iridoid)</p>	 <p>β-Thujaplicin</p>
 <p>(-)-Carvone (Carvol)</p>	 <p>Camphor (Bornan-2-one)</p>	 <p>Chrysanthemic acid (Chrysanthemum monocarboxylic acid)</p>

 <p><i>trans, trans</i>-Farnesol</p>	 <p>Guaiazulene</p>
 <p>(+)-Nerolidol</p>	 <p>Germacrene B</p>
 <p>Gossypol (dimeric sesquiterpene)</p>	 <p>Hemigossypol</p>
 <p>Thapsigargin (guaianolide)</p>	 <p>Helenalin (pseudoguaianolide)</p>

Diterpenes

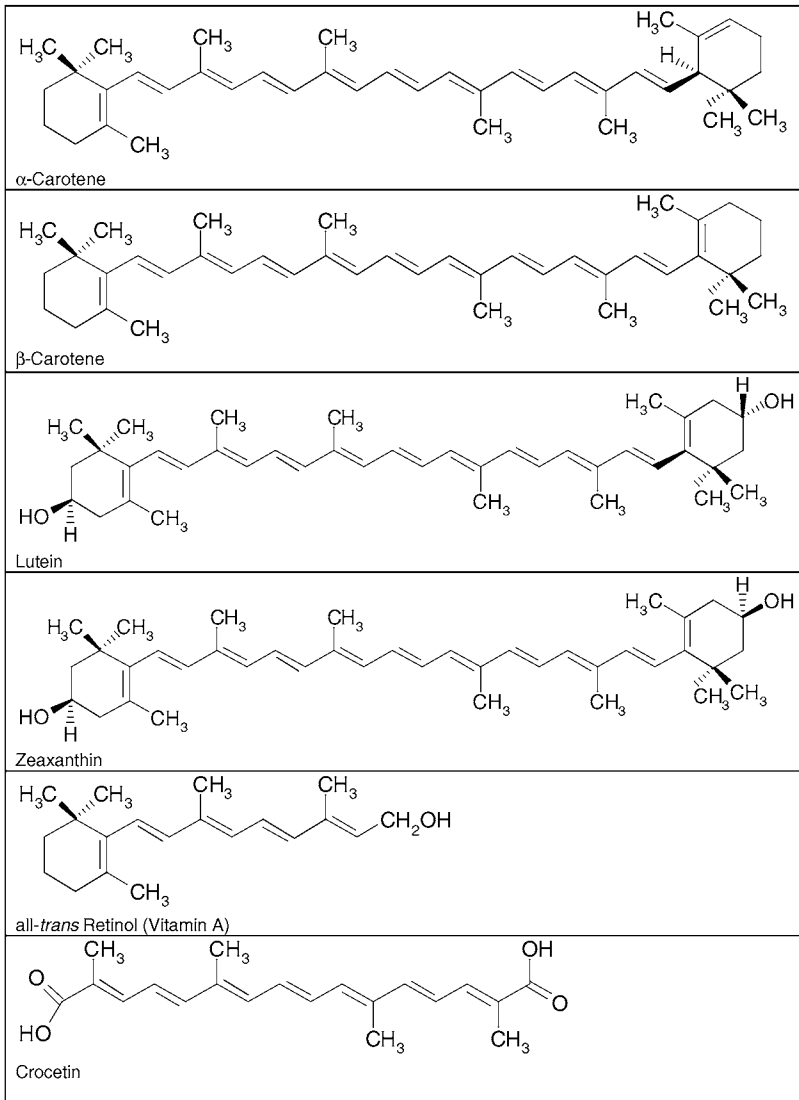


Triterpenes















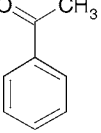
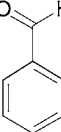
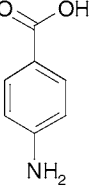
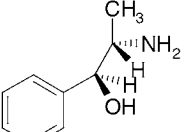
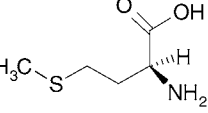
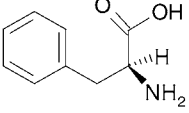
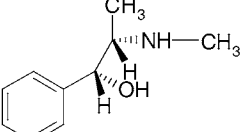


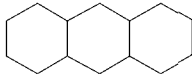
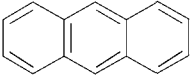
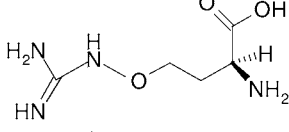
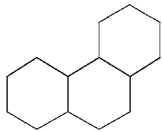
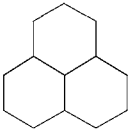
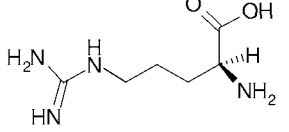
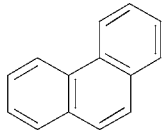
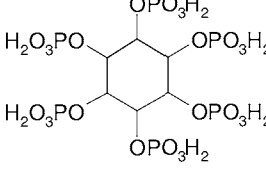
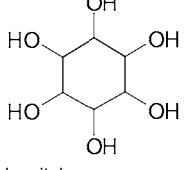
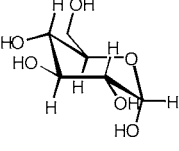
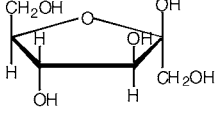
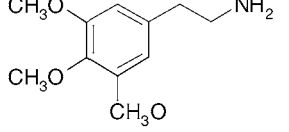
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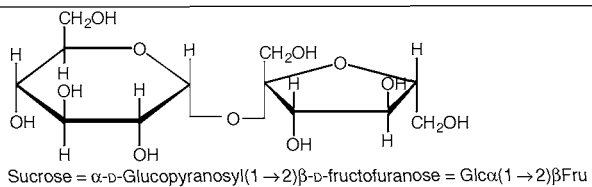
Carotenes



4. Other compounds

 Cyclopropane	 Cyclobutane	 Cyclopentane
 Cyclohexane	 Cycloheptane	 Cyclooctane
 Tetrahydrothiophene	 Thiophene	 Benzene
 Tetrahydrofuran	 Tetrahydropyran	 Dioxan
 Furan	 Pyran-2-one	 Acetophenone
 Benzaldehyde	 <i>p</i> -Aminobenzoic acid	 D-Cathine (Norpseudoephedrine)
 L-Methionine (α -amino acid)	 L-Phenylalanine (α -amino acid)	 L-Ephedrine

 <p>Perhydroanthracene (C6 C6 C6) (linear)</p>	 <p>Anthracene (Phe Phe Phe) (linear)</p>	 <p>L-Canavanine</p>
 <p>Fully saturated phenanthrene (C6 C6 C6) (angular)</p>	 <p>Fully saturated phenalene (C6* C6* C6*)</p>	 <p>L-Arginine (α-amino acid)</p>
 <p>Phenanthrene (Phe Phe Phe) (angular)</p>	 <p>Phytic acid (Inositolhexaphosphate)</p>	 <p>Inositol (Hexahydroxycyclohexane)</p>
 <p>α-Glucose</p>	 <p>β-D-Fructofuranoside (Haworth projection)</p>	 <p>Mescaline (from methylation of precursor phenolic)</p>



Bibliography

This book was compiled from a huge literature involving scores of thousands of publications. There is simply not the space to even minimally reference each compound, plant, target and physiological effect entry. However, the information given in the tables permits ready and rapid access to such specific documentation via Web search engines such as PubMed and Google and key abstracting compendia such as Chemical Abstracts and Biological Abstracts (which are also accessible on-line). The references given below are to major textbooks, compendia, review journals and primary scientific literature journals that are sources of much of the information summarized in this book.

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Absynthine 10.2t
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Acetylepiloganic acid 14.5t
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Aminocampthoecine 9.3Fa
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 Boldine 8.1a, 14.2a
 Boldine dimethyl ether 4.4Aa, 7.4a
 Bombesin 5.8A
 Bongkreki acid 13.7A
 Borenolide 9.7t
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Brassica KPI-like BnD22 13.5K
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Brassica napins 7.1o, 12.4C
Brassica napin PIs 13.5M
Brassica PI-IIs 13.5O
Brassica thrombin inhibitor 13.5I
Brassinolide 11.1Gt
Brazilin 6.1E
Brazzein 10.1o
Bredinin 9.3Dn
Brefeldin A 9.7n
Brein 13.4Ht
Brein-myristate 13.4Ht
Brein-palmitate 13.4Ht
Brevetoxins 4.2n
Brevifolin 14.1Ap
Brevifolin carboxylic acid 14.5p
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Brisbagenin-Rha-Ara 7.4t
Brisbagenin-Rha-[Rha]-acetylAra 7.4t
Brisbagenin-Rha-[Rha]-Ara 7.4t
Bromobenzoyl-methyl-dimethoxybenzofuran 6.3n
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Bromoergocryptine 5.4a, 8.3O
Bromoeudistomin 4.4En
Brousoaurone A 14.1Ap
Brousochalcone 14.1Ap
Brousoflavonol F 14.1Ap
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Brownioside 7.4t
Bruceantin 9.2t
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Brucein C 10.2t
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Bryodulcosigenin glycoside 10.1t
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Bryonia RIP-I 9.1A
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Buchapine 9.5Ba
Buddledin A 14.1At
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Bullatacin 13.6Bo
Bullatacinone 13.6Bo
Bullatalicin 13.6Bo
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Butyl butyrate 10.4o
Butyl-deoxygalactonojirimycin 13.1a
Butyl-desmethylbogaine 3.3Aa
Butylheptylpyrrolidine 3.4An
Butylidene-tetrahydro-dihydroxy-isobenzofuranone 4.1Ap
Butylphenyl-deoxyguanosine-triphosphate 9.3Dn
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 Carboxycyclopropylglycine 5.5Bn
 Carboxy-hydroxyphenylglycine 5.5Bn
 Carboxy-phenylcyclopropyl-glycine 5.5Bn
 Carboxyphenylglycine 5.5Bn
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13.8ZA, 14.1Ap, 14.2p, 14.5p
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Catechin-dihydroxyphenyl-dihydro-pyranone-
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dihydroxyphenyl-pentanoate 8.1p
Catechin (4 α \rightarrow 8)epicatechin 5.3Ap, 5.3Bp,
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Catechin-hydroxy-dihydroxyphenyl-pentanoate
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- Dahlia* DEF 12.4A
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 13.6Ap, 14.1Ap
 Daidzein-Glc 9.3Gp
 Daidzein-methyl ether 11.1Ip
 Daidzin 9.3Gp, 11.1Ip
 Daleformis 13.4E
 Dalsaxin 5.3Bt
 Damascenine 10.4a
 Damascenone 10.4t
 Damascone 10.4t
 Dammaradienol 13.4Ht
 Dammarane glycosides 10.1t
 Damnacanthal 8.1p, 8.3Hp, 9.3Gp
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 Danshenol B 14.5t
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 Danthron 8.1p, 9.3Ap, 9.3Gp, 12.1p
 Dantron 8.1p, 9.3Ap, 9.3Gp, 12.1p
 Daphnetoxin 8.2t, 8.2p
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 Daucol 10.4t
Daucus LTP 12.4B
Daucus phytocystatin 13.5B
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 Daunomycinone daunosamine 9.3An, 9.3Bn,
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- Davidiin 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p
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 Deacetylappaconitine 4.2a
 Deacetylnudicauline 3.1Ba
 Deacetylovatifolin 14.2t
 Deacylphosphatidic acid 9.3Do
 Deacylphosphatidylinositol 9.3Do
 Debenzoylpaconiflorin 14.6o
 Decadienal 10.4o
 Deca-diene-hydroxy-ynolide 9.3Ft
 Decalactone 10.4o
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 Decenal 10.4o
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 Deguelin 13.6Bp
 Dehydroalangimagine 13.8L
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 Dehydroascorbate 14.2o
 Dehydrocholesterol 11.2It
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 Dehydrocortisone 11.1Dn
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 Dehydroepiandrosterone-sulfate 5.8Tn
 Dehydroevodiamine 5.3Aa, 6.4a
 Dehydrogingerdione 14.1Ap
 Dehydroleucodin 11.1Jt
 Dehydroosthol 7.3Bp
 Dehydroperilloxin 14.1Ap
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Demethyl arecaidine 5.2Aa
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Demethylcoclaurine 7.3Aa
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Demethylepidihydrocorymine 3.2Ba, 3.3Da
Demethyleupatilin 14.1Ap
Demethylharmaline 5.3Aa
Demethylhomopterocarpin 14.1Ap
Demethylisothalicberine 4.4Aa
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Demethylplumbagin 13.8Kp
Demethylsuberosin 7.3Bp
Denatonium benzoate 10.2n
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Deoxyadenophorine 13.1a
Deoxyadenosine 9.3En
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Deoxybidensyneoside B 7.3Bo
Deoxybullatacin 13.6Bo
Deoxy-chiro-inositol 10.1o
Deoxycumambrin B 11.1Jt
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Deoxydesmethyl-[methylsuccinimido-benzoyl]-aconitine 3.1Ba
Deoxy-dihydroxyecdysone 11.1Gt
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Deoxy-hydroxyphorbol-oxide-hexadecatrienoic acid ester 8.2t
Deoxy-hydroxy-sapintoxin A 8.2t
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Deoxylactucin 10.2t
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Deoxymiroestrol 11.1It
Deoxynivalenol 9.2n
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Diacetyl-dimethoxyflavone 14.5p
Diacetylgingerol 14.1Ap
Diacetyl-khellactone 7.4p
Diacetyl vaginiol 7.4p
Diacetylverrucarol 9.2n
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Diacylglycerol-3-phosphate 9.3Do
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 Dihydroakuammine 5.6a
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 Dihydroconstrictosine 5.2Ba
 Dihydrocorymine 3.2Ba, 3.3Dn
 Dihydrocorynantheine 5.3Aa, 5.3Ba, 5.5Da
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 Dihydroerythroidine 3.1Ba
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 Dihydro-pentahydroxyflavone 5.1Ap, 8.1p
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- Dihydrotoxiferine 3.1Ba
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Dihydroxy-dimethoxybibenzyl 7.3Bp
Dihydroxy-dimethoxy-dihydrochalcone 11.1Ip
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Dihydroxy-dimethoxy-phenanthrene 7.3Bp
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Dihydroxy-methoxyflavanone 5.1Ap
Dihydroxy-methoxyflavone 14.5p
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Dihydroxy-methyl-coumarin 14.1Ap, 14.2p
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Dihydroxy-nitrophenyl-isopropyl-dichloroacetamide 9.2n
Dihydroxynitrosulfamoyl-benzoquinoxaline 3.3Bn
Dihydroxyoctadeca-diene-diynyl acetate 14.1Ao
Dihydroxyoleanoic acid 14.5t
Dihydroxy-oxo-ursenoic acid 13.4At
Dihydroxy-pentamethoxyflavone 7.3Bp
Dihydroxyphenethyltrimethylammonium 3.1Ap
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Dihydroxyphenylglycine 5.5Bp
Bis-Dihydroxyphenyl-heptanol-Glc 8.1p
Bis-Dihydroxyphenyl-heptanol 8.1p
Dihydroxyphenyl-hydroxy-methoxy-benzofuran 11.1Ip
Dihydroxypyridine 11.2Fa
Dihydroxypyridine-glucuronide 11.2Fa
Dihydroxytetramethoxyflavone 3.2Ap, 7.3Bp, 14.5p
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Dihydroxy-trimethoxyflavone 8.1p, 9.3Fp, 14.5p
Dihydroxy-trimethoxyflavone-Glc 14.5p
Dihydroxy-trimethoxyisoflavone 14.1Ap
Dihydroxy-trimethoxyisoflavone-Glc 14.1Ap
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Diltiazem 4.4An
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Dimethoxy-hydroxybenzoic acid 13.8ZOp
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Dimethoxy-hydroxy-dibenzyl-butyrolactone-diGlc 7.4p
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Dimethoxymethylflavone 3.2Ap
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- Dimethoxyphenylpropene 12.1p
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 Dimethoxy-spirostan-Glc-Glc 10.2t
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 Dimethoxy-trihydroxyflavone 14.2p
 Dimethoxy-vinyl- β -carboline 7.3Ba
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 Dimethylaminomethylindole 5.5Da
 Dimethyl-*bis*[dimethoxyphenyl]-tetrahydrofuran 5.7Gn
 Dimethylcaffeoyl-cinnamoylmussatioside 7.4p
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 Dimethylgrisabine 5.4a
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 Dimethylphenylxanthine 5.1Aa
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 Dimethyltetrahydro-furoguaiacin B 5.7Gp
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Dioclea guianensis lectin 12.2A
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 Dioclein 7.3Bp
 Dioscin 7.4t, 9.7t
 Dioscoretine 14.6a
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 Diosgenin-Rha-Gal-Glc 7.4t
 Diosgenin-Rha-Glc 7.4t
 Diosgenin-Rha-Glc-Glc 7.4t
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 Diosmin 9.7p, 13.8Yp
 Diospyrin 9.3Fp
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 Dipentene 10.4t
 Diphenylacetoxy-methylpiperidine 5.2Bn
 Diphenyl-picrylhydrazyl 14.3Bn
 Diphenylpiperazinium 3.1An
 Diphenyl-propenone 8.3Cn
 Diphosphatidylglycerol 9.3Do
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Dronabinol 5.7Ep, 5.8C, 6.3p, 11.1Ap, 13.6Bp
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Glc-furostandiol-Rha-[Glc]-Glc 7.4t
Glc-furostendiol-Rha-[Glc]-Glc 7.4t
Glc-gallic acid 13.4Ip
Glc-Glc 10.1o, 10.2p
Glc-Glc-methylapigenin 14.5p
Glc- α -homonojirimycin 13.1a
Glc-methylfurosaetriol-Rha-[Rha]-Glc 7.4t
Glc-oxy-hydroxy-tetradecene-triayne 14.6o
Glc-oxy-hydroxy-tridecene-triayne 14.6o
Glc-protopanaxadiol 9.7n
Glc-sorbitol 10.1n
Gliadin 7.2Ao
Gliadin (43–49) 5.6o
Gliadin peptides 7.2Ao
Glial cell line-derived neurotrophic factor 8.3E
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Gliclazide 4.3An, 14.6n
Glimepiride 4.3An, 14.6n
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Glipizide 4.3An
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Glucagon-like peptide-1 14.6n
Glucan 14.6o
Glucarate 13.1o
Glucaro-1,4-lactone 13.1o
Glucitol 10.1o
Gluconolactam 13.1o
Gluconolactone 13.1o
Glucopyranose 10.1o
Glucoraphanin 14.4A
Glucose 10.1o
Glucosinolates 10.6o, 11.2E, 14.2o
Glucosylorientin 11.2Fp
Glucosylvitexin 11.2Fp
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Glutamine 10.1o
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Glutamyl-L-hypoglycin A
Glutaric acid 10.3o
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- Gluten exorphin A4 5.6o
 Gluten exorphin A5 5.6o
 Gluten exorphin B4 5.6o
 Gluten exorphin B5 5.6o
 Gly-Ala-Leu 10.2o
 Glyburide 4.3An, 4.5An, 14.6n
 Glyceollin I 11.1Ip, 13.6Bp
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 Glycerol 10.1o
 Glyceryl trinitrate 7.2Cn, 7.3Do
 Glycine 3.2Bo, 3.3Ao, 3.3Do
Glycine β 1,3-Glucanase 12.2E
Glycine 2S napin 12.4C
Glycine BBIs 5.7J, 13.5G
Glycine CaM 7.3Do
Glycine CaM SCaM-1 7.3Do
Glycine CaM SCaM-4 7.3Do
Glycine chitinase 12.2D
Glycine concanavalin A 8.3Co, 8.3Ho, 13.5E
Glycine cystatins 13.5B
Glycine insulin-binding protein Bg 8.3Ho
Glycine insulin-binding proteins 8.3Ho
Glycine insulin-like protein 8.3Ho
Glycine KPIs 13.5K
Glycine Kunitz PI STI 5.7J
Glycine lectins 5.8D, 12.2A
Glycine lunasin 9.6B
 Glycitein 7.3Ap, 7.3Cp, 11.1Ip
 Glycolic acid 10.3o
 Glycycoumarin 7.4p
 Glycycoumarin-methyl ether 7.4p
 Glycyphyllin 10.2p
 Glycyrin 7.4p
 Glycyrol 7.4p
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 Glycyrrhetin 5.8K, 8.1t, 13.4Ht, 13.8ZC
 Glycyrrhetic acid 4.1Ct, 5.8K, 8.1t, 8.2t, 11.1C, 11.1D, 11.1E, 11.1F, 11.1It, 11.1Kt, 13.4Ht, 13.8N, 13.8ZC
 Glycyrrhetic acid-glucuronosyl-glucuronide 8.1t
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 Glycyrrhizinic acid 4.1Ct, 8.1t, 10.1t, 11.1C, 11.1D, 11.1E, 11.1F, 11.1It, 13.8N, 13.8ZC
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 Gomisin 9.5Bp
 Gonadotropin releasing hormone 5.8M
 Goniiodomin A 9.6A
 Goniotalamin 9.7o
 Gonosan 3.2Bp, 4.2p, 6.3p, 6.5p, 14.1Ap
 Gossypetin 14.1Ap
 Gossypetin-Glc 13.4Ap, 14.1Ap, 14.5p
 Gossypin 13.4Ap, 14.1Ap, 14.5p
Gossypium chitinase 12.2d
Gossypium PGIP 13.3
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 Granisetron 3.3En
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 Grapenol 7.3Bp
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 Grayanotoxin II 4.2t
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 Guajaverin 13.1p, 14.5p
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 Guanylin 7.2Cn
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 Gurmarin 10.1o
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 Gymnemoside b 14.6t
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- Gypenoside 4.1Ct, 9.7t
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Gypsophila Gypsophilin 9.1A
Gypsophila RIP-I 9.1A
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GYYPT 5.6o
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- H7 8.1n
H89 8.1n
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Heliantriol C myristate 13.4Ht
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Heptadecatrienediyne 14.1Ao
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Heptanedioic acid 10.3o
Heptanol 8.1p, 10.4o
- Heptenone 10.4o
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- Himbeline 5.2Ba
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 Hinokiresinol 7.4p, 11.1Ip
 Hinokitiol 13.4Gt, 14.1At
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 Histamine 5.7Ea
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 HODE 5.7Ho
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 Homoaromoline 5.4a
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 Homocysteic acid 3.3Ao
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Hordeum CBP 12.2C
Hordeum chitinase 12.2D
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 Hydroxy-coumarinyl-phenyl-propane 13.4An
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- Hydroxy-[dihydroxyphenyl]-phenyl-heptanone 14.1Ap
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Hydroxy-dimethoxydalbergiquinol 11.1Ap
Hydroxy-dimethoxyflavone 5.1Ap
Hydroxy-dimethoxyisoflavone 8.1p, 8.3Cp, 13.8C
Hydroxy-dimethoxy-neoflavene 11.1Ap
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Hydroxy-dimethyltryptamine 5.5Da
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Hydroxy-hydroxy-methoxyphenyl-phenyl-heptanone 14.1Ap
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Hydroxy-methoxybenzoic acid 5.8R
Hydroxy-methoxycinnamaldehyde 6.1F
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Hydroxy-methoxyphenyl-phenylheptenone 6.1F, 13.8B, 14.1Ap
Hydroxy-methylcoumarin 8.1p
Hydroxy-methylenedioxy coumarin 14.5p
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Hydroxy-[methylglutaroyl]-spirostenediol-Rha-[Glc]-Glc 7.4t
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Hydroxymethyl-methylallyl-tetrahydroxy-chalcone-coumarate 11.1Jp
Hydroxy-methyl-[methylpentenyl-chromene]-dihydroxyphenyl-propanone 14.1Ap
Hydroxy-methyl-naphthalenedione 8.1p
Hydroxy-methyl-naphthoquinone 9.3Ap, 12.1p
Hydroxy-methyl-pyrone 10.4o, 14.6n
Hydroxymethyl α -terthiophene 8.1n
Hydroxymethyl-trimethylpsoralen 9.3An, 12.1n
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Hydroxyobtustystyrene 14.1Ap
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Hydroxy-oxoheneicosadienyl acetate 7.3Bo
Hydroxy-oxo-pyridinealanine 11.2Fa
Hydroxy-pentadecanoic acid lactone 8.1o
Hydroxy-pentadecenyl-benzoic acid 14.1Ap
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Hydroxyphenethylactinidine 6.4a
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Hydroxyphenyl-butanone-[di-*O*-galloyl]-Glc 13.4Ip
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Hydroxyphenyl-ethanolamine 5.3Ap
Hydroxyphenylglycine 5.5Bp
Hydroxy-phenyl-[methoxy-hydroxyphenyl]-heptane 14.1Ap
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- Hydroxystearic acid 8.1o
 Hydroxysuccinic acid 10.3o
 Hydroxy- Δ^6 -tetrahydrocannabinol 6.3p
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 Ichangin 10.2t
 Idanosine 9.5Bn
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 Ile-Arg-Ala-Gln-Gln 13.5C
 Ile-Tyr 13.5C
 Ile-Tyr-Pro-Gly-Cys-Pro 10.2o
 Ile-Tyr-Pro-Gly-Cys-Pro-Ser-Thr 10.2o
 Ile-Val-Tyr 13.5C
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 Indocycin 5.5Da
 Indolylmethyl-azabicyclo[3.2.1]octane 3.3An
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Isocoryne 3.2Ba
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Isoescin Ia 13.4At
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Isoferulic acid 5.7C, 14.6p
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Isoliquiritigenin-Glc 14.1Ap
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Jesaconitine 4.2a
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Kadsurenin K 5.7Gp
Kadsurenin L 5.7Gp
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Leucosceptoside A 8.1p
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Lupeol linoleate 8.1t, 13.4Ht, 13.8Yt
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Mercaptomethylpentanol 10.4o
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Methoxy-dihydroluteolin 8.1p
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Methoxy-methyl-naphthaleneacetic acid 14.1Ap
Methoxy-[methylpentenyl] coumarin 14.1Ap
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Methoxyscutellarein 14.5p
Methoxyseselin 7.3Bp
Methoxytaxifolin 10.1p
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Methoxytetrahydronorharman 6.5a
Methoxytrihydroxyflavone 3.2Ap
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- Methoxyumbelliferone 7.3Ap, 14.5p
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 Methylbutanol 10.4o
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 Methylchavicol 10.4p
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 Methylcytosine 3.1Aa, 14.6a
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 Methyl delcosine 3.1Ba
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 Methyl-dihydroxytetrahydroisoquinoline 5.4a
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- Tetracycline 9.2n, 13.8Qn
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Trihydroxy-oleanen-epoxy-al-Xyl-Glc-[Glc]-
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Trihydroxy-oleanenoic acid methyl ester 7.4t
Trihydroxy-oleanenoic acid-Rha-Glc-[Glc]-
Ara-Glc ester 7.4t
Trihydroxy-oleanenoic acid-Rha-Glc-[Glc]-
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Anacardium 6.1F, 14.1Ap Cashew
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Anadenanthera 5.5Da Cohoba, Curupay
Anagyris 3.1Aa, 4.2a, 4.3Aa, 4.3Ca Bean trefoil
Anamirta 3.2Bt, 3.3Dt Indicus cocculus
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Aniba 12.1p Aniba
Anisochilus 7.3Ap Anisochilus
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Antirrhinum 11.2Gp, 13.8ZA Snapdragon
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- Balanophora* 8.1t, 13.4At, 13.4Gt, 13.4Ht, 13.8Yt Fungus root (parasitic plant)
- Balduina* 8.1t, 11.1Jt, 13.6Dt, 13.8Qt Honeycomb head
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- Bergenia* 5.1Ap, 13.4Ip Bergenia, Heart leaf
- Bersama* 4.1Ct Bersama
- Beta* 5.7C, 5.8R, 8.1t, 9.1A, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 10.1o, 10.3o, 10.4a, 10.4p, 10.5o, 10.5p, 10.6o, 12.2C, 12.2D, 12.4A, 12.4E, 13.1t, 13.4At, 13.8U, 14.1At, 14.2p, 14.6t Beet
- Betula* 5.1Ap, 7.3Bp, 8.1t, 9.3Gt, 10.4p, 10.4t, 10.5p, 14.1Ap, 14.3A Birch
- Bidens* 4.1Cp, 7.3Bo, 8.1p, 8.3Cp, 9.7p, 11.1Bp, 13.6Ap, 13.6Cp, 13.8Qp, 14.1Ao, 14.6o Beggarticks, Bur-marigold
- Billia* 13.8D Billia, Horse chestnut
- Biota* 5.1Ap, 5.7Gt Arborvitae, Oriental arborvitae, Chinese arborvitae
- Bixa* 8.1t Bixa Lipstick tree
- Blechnum* 7.4t Midsorus fern
- Bleekeria* 9.3Aa, 9.3Ba, 9.3Ga, 12.1a Alchornea, Iporuru
- Blighia* 13.8D Blighia, Akee
- Blumea* 10.4t Blumea, False oxtongue

- Bocconia* 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 5.8Xa,
6.1A, 6.1B, 7.4a, 8.1a, 9.3Ca, 14.1Aa
Bocconia, Parrot weed
- Boehmeria* 9.2a, 11.1Bo, 14.5p False nettle
- Boerhaavia* 4.4Ap, 5.8R Spiderling
- Bolbostemma* 8.2t Bolbostemma, Tubeimu
- Boldea* 8.1a Boldo, Peumus
- Borago* 14.6o Borage
- Boronia* 10.4t, 12.1p Boronia
- Boswellia* 9.3Ft, 9.3Gt, 10.4t, 13.4Ht, 14.1At
Boswellia, Frankincense
- Bougainvillea* 9.1A Bougainvillea, Paperflower
- Bouvardia* 9.2a Bouvardia, Firecracker bush
- Boweringia* 12.2A Boweringia, Hong Kong
arborescent fern
- Brassica* 3.3Aa, 3.3Bp, 3.3C, 5.5Bo, 5.6a, 6.1C,
7.1o, 7.4p, 10.2a, 10.4o, 10.4p, 10.5o, 10.6o,
10.6t, 10.7, 11.1Gp, 11.1Gt, 11.1Ip, 11.1Jp,
11.1Kp, 11.2Bo, 11.2E, 11.2Go, 12.2E, 12.4B,
12.4C, 13.5I, 13.5J, 13.5K, 13.5M, 13.5O,
13.7F, 13.8ZM, 14.1Ao, 14.2t, 14.4A, 14.6p
Broccoli, Brussel sprouts, Cabbage, Canola,
Cauliflower, Kohlrabi, Mustard, Rape
- Brickellia* 13.8P Brickellbush
- Brodiaea* 7.4t Brodiaea
- Brosimum* 11.1Ap Brosimum, Breadnut
- Broussonetia* 11.1Jp, 13.1a, 14.1Ap Broussonetia,
Paper mulberry
- Brucea* 9.2t, 10.2t Brucea
- Brunsvigia* 9.2a Amaryllis, Naked lady
- Bryonia* 9.1A, 10.1t, 10.2t, 13.5P, 14.6o Bryony
- Bryophyllum* 10.3o Devil's backbone
- Buddleja* 5.1Ap, 7.4p, 8.3Cp, 8.1p, 10.2p, 10.2t,
10.6t, 11.1Hp, 11.1Jp, 11.1Kp, 11.2Ap,
11.2Bo, 11.2Fp, 13.7Hp, 14.1Ap, 14.1At,
14.2p, 14.5p Butterflybush
- Bumelia* 14.6t Gum bully
- Bupleurum* 4.1Ct, 5.8Q Bupleurum, Thorow wax
- Bursaria* 14.1Ap, 14.5p Christmas box tree
- Bursera* 3.1Bt, 10.4t, 10.5t Bursera, Elephant tree
- Butea* 4.1Cp, 8.1p, 8.3Cp, 9.7p, 11.1Bp, 13.6Ap,
13.8Qp Butea, Bengal tree
- Cacalia* 10.6t Cacalia, Indian plantain
- Cactus* 8.1p Cactus, Prickly pear
- Caesalpinia* 6.1E Nicker
- Calamintha* 10.2p Calamint
- Calendula* 8.2t, 14.1Ao Calendula
- Callitris* 9.3Gp, 9.6Ep Cypress pine
- Calluna* 9.7t, 14.1At Heather
- Calophyllum* 9.5Bp Calophyllum, Alexandrian
laurel
- Calotropis* 4.1Ct Calotropis, Giant milkweed
- Calycanthus* 3.3Da Sweetshrub
- Cabystegia* 12.2B, 13.1a, 13.5E False bindweed
- Camassia* 9.7t, 10.2t Camass
- Camellia* 4.1Bp, 4.1Cp, 4.3Aa, 4.3Ap, 4.3Ba,
4.3Ca, 4.4Aa, 4.4D, 4.4E, 5.1Aa, 5.3Ap,
5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p, 6.1B, 6.1F,
6.1G, 6.2o, 6.5p, 7.3Ap, 7.3Bp, 7.3Cp, 7.4a,
7.4p, 8.1p, 8.2t, 8.3Cp, 8.3D, 8.3I, 8.3L,
8.3N, 8.3R, 9.3Cp, 9.3Dp, 9.3Fp, 9.3Gp,
9.5Ap, 9.5Bp, 9.7p, 9.7t, 10.2a, 10.2p, 10.4a,
10.4o, 10.4p, 10.4t, 10.5p, 10.5t, 10.6t,
11.1Ap, 11.1Bp, 11.1Hp, 11.1Gt, 11.1Ip,
11.1Jp, 11.2Fp, 12.3t, 13.1p, 13.4Ap, 13.4Fp,
13.4Gp, 13.4Hp, 13.4Ip, 13.6Ap, 13.6Bp,
13.7Ho, 13.7Hp, 13.7I, 13.8Qp, 13.8Yp,
13.8ZB, 13.8ZJ, 13.8ZOp, 14.1Ao, 14.1Ap,
14.2a, 14.2p, 14.5p, 14.6p Camellia, Tea
- Campanula* 3.1Aa, 3.1Ba Bell flower
- Camptotheca* 9.3Fa, 12.1a, 14.5p Camptotheca
- Cananga* 10.4o, 10.4p, 10.4t, 10.5o, 10.6o
Ilang-ilang
- Canarium* 10.1p, 10.4p, 12.1p Olive
- Canavalia* 7.3Co, 9.7o, 9.6D, 12.2A, 12.2C,
13.5G, 13.5K, 13.5N, 13.8E, 13.8Z, 13.8ZL,
14.1Ao, 14.2t Jackbean
- Cannabis* 5.7Ep, 5.8C, 6.3p, 11.1Ap, 13.6Bp
Cannabis, Hemp, Marijuana
- Capparis* 10.1o Caper
- Capsella* 10.3o Shepherd's purse
- Capsicum* 3.4Bp, 4.2p, 4.3Cp, 4.4Aa, 5.3Ap,
5.7C, 5.8V, 6.4a, 6.1F, 7.4p, 10.4o, 11.2Ct,
12.2D, 12.2E, 12.4B, 12.4D, 12.4E, 12.4F,
13.5O, 14.1At, 14.2o, 14.2t, 14.5p Cayenne
pepper, Pepper
- Caragana* 11.1Gp, 12.2A, 14.1Ap Pea shrub
- Carex* 11.1Gp, 14.1Ap Sedge
- Carica* 3.1Aa, 12.2D, 13.5B, 13.5K Carica,
Papaya
- Carnegiae* 5.3Ap, 5.4p, 11.2Jp Cactus, Giant cactus
- Carpesium* 7.3At Carpesium
- Carthamus* 4.4Ap, 14.1Ao Distaff thistle
- Carum* 6.1F, 7.3Ao, 10.4t Carum Caraway
- Carya* 8.1p, 11.1Hp, 13.8Kp Hickory
- Caryophyllus* 13.4It Clove
- Caryopteris* 10.2t, 10.6t Caryopteris
- Casimiroa* 4.4Aa, 5.3Ao, 5.3Co, 5.5Da, 5.7Ea,
10.2t Sapote
- Cassia* 4.1Ca, 5.8H, 6.1F, 6.2a, 6.5p, 7.3Ap,
8.1p, 9.3Dp, 9.7p, 9.2p, 9.3Ap, 9.3Gp, 9.7p,
10.1o, 10.4p, 10.4t, 11.1Ip, 12.1p, 12.4A,
12.4B, 13.5J, 13.6Ap, 13.6Cp, 13.8ZN,
13.8ZOp, 14.1Ap, 14.2p Cassia, Sensitive pea
- Cassytha* 5.3Aa Cassytha, Devil's gut
- Castanea* 12.2D, 12.4E, 13.4Hp Chestnut
- Castanopsis* 9.3Ap, 12.1p Chinquapin
- Castanospermum* 13.1a, 14.6a Australian chestnut,
Moreton Bay chestnut
- Castela* 10.2t, 13.8W Castela, Goatbush
- Castilloa* 4.1Ct Panama rubber tree
- Casuarina* 4.3Ap, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p,
5.6p, 7.3Bp, 13.1a, 13.6Bp Sheoak
- Catalpa* 5.7C, 10.2t, 10.6t, 13.8ZOp, 14.6p
Catalpa

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- Catha* 5.3Co, 6.2p, 6.3o, 7.3At, 11.2E, 13.1p, 14.1At Catha, Khat
- Catharanthus* 4.2a, 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 5.6a, 5.8D, 6.3a, 9.3Ga, 10.2t, 12.1a, 13.7Ha
Madagascar Periwinkle, Periwinkle
- Caulophyllum* 3.1Aa Cohosh
- Ceanothus* 13.8Zop New Jersey tea, Redroot
- Ceiba* 14.1Ap Ceiba, Kapok tree, Pochote
- Celastrus* 4.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p, 14.1Ap, 14.2p Bittersweet
- Cenchrus* 7.1o Sanbur
- Centaurea* 7.4p, 10.2p, 11.1E, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.8Kp, 13.8Yp, 14.1Ao, 14.5p Cornflower, Knapweed, Star thistle
- Centaurium* 5.2Ba, 5.2At, 10.2t, 13.4At, 13.4Ht, 13.8Jt Centaury
- Centella* 8.1t, 13.8Jt Centella, Spadeleaf
- Centrosema* 14.1Ap, 14.2t Butterfly pea
- Cephaelis* 9.2a, 9.3Aa, 9.5Ba, 12.1a Cephaelis, Ipecac
- Cephalotaxus* 7.3Ao, 9.2a, 9.7a Cephalotaxus
- Ceratonia* 3.3Aa, 3.3Bp, 3.3C, 5.5Bo, 7.3Do, 10.1o Ceratonia, St John's bread
- Ceratopetalum* 8.1t New South Wales Christmas bush
- Cerbera* 4.1Ct, 14.2p Grey milkwood
- Cercidiphyllum* 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 13.4Ap Katsura tree
- Ceterach* 8.1p, 10.2p, 11.2Fp, 14.5p Miltwaste
- Cetraria* 9.3Co, 9.5Bo, 9.5Bt Iceland moss, Lichen
- Chamaecyparis* 7.4p, 11.1Ip Cedar
- Chamaemelum* 7.4p, 14.5p Dogfennel
- Chamaerops* 10.1o Fan palm
- Chelidonium* 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 5.8Xa, 6.1A, 6.1B, 6.4a, 6.6B, 7.4a, 8.1a, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 13.5B, 14.1Aa Celandrine
- Chenopodium* 5.8N, 5.8O, 7.1o, 7.3Bp, 7.3Bt, 9.1A, 10.2t, 10.3o, 10.4o, 10.4t, 10.5o, 11.1Gt
Goosefoot, Lambsquarters
- Chionodoxa* 7.4t Chionodoxa, Glory of the snow
- Chirita* 11.2Gp Cay rita moc, Chirita
- Chlorophora* 7.4p, 8.1p, 9.3Cp, 11.1Hp, 13.4Ap, 13.6Ap, 13.8Qp, 13.8Yp, 14.1Ap, 14.2p, 14.5p African teak
- Chimaphila* 8.1p, 8.3Cp, 13.4Ip, 14.5p
Chimaphila, Prince's pine
- Chondria* 3.3Ba Chondria (red alga)
- Chondrodendron* 3.1Aa, 3.1Ba, 3.2Ba, 3.3Ea
Chondrodendron, Curare, Pareira
- Chorizanthe* 14.2p Spineflower
- Christia* 14.2t Iceland pea
- Chrysanthemum* 4.2t, 5.5Dt, 5.7C, 5.8N, 5.8O, 6.2t, 7.3At, 7.3Bo, 7.3Bp, 7.3Bt, 7.3Cp, 7.4p, 8.1t, 9.7t 10.4t, 10.6t, 11.1Jt, 13.4Ht, 13.7D, 14.1At, 14.5o, 14.5p, 14.5t Chrysanthemum, Daisy, Feverfew, Tansy
- Chrysophyllum* 6.1B Chrysophyllum, Star apple
- Cicer* 7.4p, 8.1p, 8.3Cp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2A, 12.4E, 13.6Ap, 13.8ZI, 14.2t
Cicer, Chick pea
- Cichorium* 3.2Aa, 5.3Ba, 5.5Da, 6.5a, 9.5Ap, 10.1o, 10.2t, 10.4o, 14.5p Chickory
- Cicuta* 3.2Bo Water hemlock
- Cimicifuga* 5.7C, 14.6p Bugbane
- Cinchona* 4.2a, 4.3Ca, 5.5Da, 6.5a, 8.1p, 9.2p, 9.3Ap, 9.3Gp, 6.5a, 10.2a, 11.1Ha, 12.1p, 13.7Ha, 13.8Qa, 13.8ZOp, 14.1Ap, 14.2p
Chinchona, Quinine
- Cinnamomum* 4.4Ap, 5.7K, 6.1F, 6.5p, 7.3Ap, 8.3Hp, 9.1A, 9.1B, 10.1p, 10.4p, 10.4t, 10.6t, 12.1p, 12.2B, 13.4Ip, 13.8Mp, 13.8Qp, 14.1Ap, 14.6p Camphor tree, Cinnamon
- Cinnamosma* 3.4Bt Voamasoandro, Cinnamosma
- Cirsium* 8.1p, 8.3Cp 14.1Ap, 14.5p Thistle
- Cissampelos* 4.4Aa, 5.7Ga, 7.1a, 9.7a, 13.4Da
Cissampelos, Pareira brava
- Cissus* 9.2a, 14.5p Treebine
- Cistanche* 14.2p Cistanchis
- Cistus* 4.3Co, 5.1Ap, 7.4p, 10.4o, 14.5p Rockrose
- Citrullus* 9.1A, 10.2t, 11.1D, 13.5P, 14.2o
Watermelon
- Citrus* 3.1Bt, 3.2Ap, 4.5A, 5.1Ap, 5.3Ap, 5.3Bp, 5.5Da, 5.8R, 5.8W, 6.3p, 6.4t, 6.5p, 7.3Bp, 7.3Bt, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.3Ap, 9.5Ap, 9.5Bp, 9.6Bt, 9.6Et, 9.7p, 9.7t, 10.1n, 10.2p, 10.2t, 10.3o, 10.4a, 10.4o, 10.4p, 10.4t, 10.5o, 10.5p, 10.5t, 10.6o, 10.6t, 11.1E, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ct, 11.2Fp, 12.1p, 12.2B, 12.2C, 13.4Gp, 13.5K, 13.6Ap, 13.7Hp, 13.8C, 13.8Jp, 13.8Kp, 13.8Qp, 13.8Yp, 13.8ZOp, 14.1Ap, 14.2o, 14.2p, 14.2t, 14.5p, 14.6p Grapefruit, Lemon, Lime, Orange, Tangelo, Tangerine
- Cladonia* 13.8T, 13.8ZH Reindeer lichen
- Clarisa* 8.1p Clarisa
- Clausenia* 5.8W, 7.3Bp, 10.1p, 10.4p, 14.1Ap
Clausenia
- Cleistanthus* 9.7p Cleistanthus, Weeping cleistanthus
- Clematis* 10.2o, 14.3Bo Clematis, Virgin's bower
- Cleome* 7.3Bp Spider flower
- Clerodendron* 4.3Ao, 4.3At, 5.1Ap, 5.2Ao, 9.5Ap, 11.1Jp, 11.1Kp, 13.7Hp, 13.8C Chau wu tong
- Clitoria* 12.4A Clitoris flower, Pigeon wings
- Cneoridium* 5.8W, 7.3Bp, 14.1Ap Berry rue
- Cneorum* 9.6Et, 10.2t Spurge olive
- Cnicus* 4.4Ap, 7.2B, 14.2p, 14.5p Thistle
- Cnidium* 7.3Bp, 7.3Bt Snow parsley
- Cocculus* 3.1Ba Coralbead
- Cocos* 5.2Bo, 10.1o, 10.5o, 10.6o, 11.1Bo, 11.2Bo
Coconut palm
- Codium* 12.2A Dead man's fingers (green alga)
- Coelocline* 3.1Ba, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 9.3Aa, 9.5Ba, 12.1a Xylopia, Ethiopian pepper

- Coffea* 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 9.2p, 10.2a, 10.2t, 10.4a, 10.4o, 10.4p, 10.4t, 13.8ZOp, 14.1Ap, 14.2p, 14.5p Coffee
- Coix* 13.2, 13.5F Job's tears
- Cola* 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 10.2a Cola
- Colchicum* 3.2Ba, 3.3Da, 9.6Ea, 13.5E Colchicum
- Coleus* 3.1Ba, 4.4At, 7.2At, 11.1Ht, 13.7Et, 13.7Ht, 14.5p Coleus
- Commiphora* 6.1F, 6.5p, 7.3Bt, 10.4p, 10.4t, 14.6t Myrrh
- Conium* 3.1Aa, 7.3Ao, 9.2p, 10.1o, 13.8ZOp, 14.1Ap, 14.2p Hemlock
- Conopharyngia* 3.2Aa, 3.3Aa, 3.4Aa, 4.2a, 5.6a Tabernaemontana, Toad tree
- Consolida* 3.1Ba Knight's spur
- Convallaria* 4.1Ct Lily of the valley
- Convolvulus* 7.3Ap, 12.2B, 13.5E, 14.5p Bindweed
- Coryza* 9.3Ft, 13.4Ht, 13.8ZOp Horseweed
- Copaifera* 10.4t Copaifera
- Coptis* 3.1Ba, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 7.3Bp, 9.3Aa, 9.3Fa, 9.3Ga, 9.5Ba, 12.1a, 14.1Aa Goldthread
- Corchorus* 4.1Ct Corchorus, Jute
- Cordia* 10.6t, 11.1Jp Cordia, Manjack
- Coreopsis* 4.1Cp, 8.1p, 8.3Cp, 9.7p, 11.1Bp, 13.6Ap, 13.6Cp, 13.8Qp Tickseed
- Coriandrum* 3.1Bt, 5.8R, 10.4o, 10.4t, 10.5t, 14.5p Coriander
- Coriaria* 3.2Bt, 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 8.1p, 13.4Ap, 13.8ZJ Coriaria
- Cornus* 7.3At Dogwood
- Coronilla* 6.5p, 8.1p, 9.3Ap, 12.1p Crownvetch
- Corydalis* 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.3Ca, 5.5Da, 5.7Ga, 6.1B, 6.4a, 7.4a, 8.1a, 9.3Aa, 9.5Ba, 12.1a, 14.1Aa, 14.5a Fumewort
- Corynanthe* 5.3Aa, 5.3Ba, 5.5Da, 11.1Ha Pseudocinchona
- Coryphantha* 5.3Ap Beehive cactus
- Cosmos* 6.5p, 7.3Ap, 8.1p, 8.3D, 8.3F, 8.3Hp, 11.1Hp, 11.1Ip, 13.4Ap, 13.6A, 13.7Hp, 13.8C, 13.8Yp, 14.1Ap, 14.5p Cosmos
- Costus* 7.3Bp, 7.4t, 12.3t Costus
- Cotinus* 4.1Bp, 13.1p, 13.6Bp, 13.8ZOp Smoketree
- Cotoneaster* 8.1p, 8.3Cp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.6Ap Cotoneaster
- Cotula* 8.1p Waterbuttons
- Couroupita* 7.3Aa, 11.2Aa, 14.1Aa Cannonball tree
- Crambe* 10.4p, 12.4F Crambe
- Crataegus* 4.3Cp, 5.3Cp, 5.4p, 5.5Dp, 6.5p, 7.4p, 8.1p, 8.1t, 8.3Hp, 10.2p, 13.4At, 13.4Ip, 13.8Jt, 14.1Ap, 14.5p, 14.6p Hawthorn
- Cratoxylum* 8.1p Geronggang
- Cratylia* 12.2A Cratylia
- Crepis* 14.1Ao Hawksbeard
- Crinodendron* 10.2t, 11.1Gt Chilean lantern plant, Lantern tree, White lily tree
- Crinum* 3.1Aa, 6.4a, 9.2a Swamplily
- Crocus* 7.3Ao, 8.1p, 8.1t, 10.2p, 10.4t, 12.2B, 14.1At, 14.2t Crocus
- Crossopetalum* 9.2t, 9.3At, 12.1t, 13.7Ht Christmas berry, Crossopetalum
- Crotalaria* 10.5a, 12.2A Rattlebox, Rattleweed
- Croton* 3.1Ba, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.8I, 5.8S, 8.2t, 10.1o, 10.3o, 10.4p 12.1p, 13.4Gt, 13.7C, 14.6t Croton
- Cryptocarya* 4.4Aa, 5.3Aa, 5.3Ba, 5.3Ca, 5.5Da, 9.2a Red laurel
- Cryptolepis* 5.2Ba, 9.3Aa, 9.3Ga, 9.7a, 12.1a, 14.6a Cryptolepis, Curroria
- Cryptomeria* 10.6p Japanese cedar
- Cryptostegia* 4.1Ct Rubbervine
- Cucumis* 5.8La, 6.5a, 10.2t, 10.4o, 10.5o, 10.6o, 11.1Bo, 11.1Gt, 11.2Bo, 12.2D, 13.5P, 14.1Ao, 14.6o Cucumber, Melon
- Cucurbita* 9.1A, 10.1o, 12.2B, 12.4C, 13.5A, 13.5N, 13.5P, 13.5R, 14.6o Gourd, Pumpkin, Squash
- Cuminum* 6.1F, 7.3Bp, 7.3Cp, 7.3Do, 7.4p, 8.1p, 10.4p, 10.4t, 10.5t Cumin
- Cuphea* 11.1Bp, 11.1Jp, 13.8ZE Waxweed
- Cupressus* 5.7Gt, 7.4p, 9.5Bp, 10.4t, 14.1At Cedar, Cypress
- Curatella* 14.5p Curatella, Tachicon
- Curculigo* 10.1o Curculigo
- Curcuma* 4.4At, 5.7C, 6.1F, 6.4t, 7.3Ap, 7.3Bt, 8.1p, 9.3Fp, 9.3Gp, 9.5Ap, 10.1o, 10.4t, 10.6t, 13.6Ap, 14.1Ap Turmeric
- Cuscuta* 4.5A, 6.5p, 8.1p, 8.3Cp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.8C, 13.8Jp, 14.6p Dodder
- Cyamopsis* 14.6o Cyamopsis
- Cyanotis* 11.1Gt Pussy ears, Tradescantia
- Cycas* 3.2Ap, 3.3Bo, 5.5Bo, 6.3o, 7.4p, 8.3A, 8.3M, 9.5Bp, 12.1o, 13.7I, 14.1Ap, 14.5p Cycad, Sago palm
- Cyclamen* 12.3t Cyclamen
- Cyclea* 4.4Aa, 5.7Ga, 7.1a, 9.7a, 13.4Da Patha
- Cydonia* 10.1o Cydonia, Quince
- Cymbidium* 12.2B Cymbidium
- Cymbopogon* 10.4t, 10.5t, 12.1p Lemongrass
- Cynanchum* 3.3Bp, 9.2a Swallowwort
- Cynodon* 10.4a, 10.5p, 10.6a, 10.6o, 10.6p Bermuda grass
- Cynara* 14.2p Artichoke, Cynara, Globe artichoke
- Cynomorium* 13.4At, 13.4Ht, 13.8Jt Maltese mushroom (parasitic plant)
- Cyperus* 3.2At, 5.3Ap Flatsedge
- Cyphomandra* 13.8U Cyphomandra, Tree tomato
- Cystopteris* 9.3Do, 14.5o Bladderfern
- Cytisus* 3.1Aa, 3.1Ba, 4.2a, 4.3Aa, 4.3Ca, 5.3Ap, 5.3Cp, 5.4p, 11.2Jp, 12.2A, 14.6a Broom

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- Dacrydium* 7.4p Huon pine
Dactylis 10.4o Orchard grass
Dahlia 5.8R, 7.3Ap, 7.4p, 8.1p, 8.3D, 8.3F, 8.3Hp, 10.2p, 10.4p, 10.5p, 11.1E, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.4A, 13.4Ap, 13.6Ap, 13.6Cp, 13.7Hp, 13.8C, 13.8Kp, 13.8Yp, 14.1Ap, 14.2p, 14.5p Dahlia
Dalbergia 4.1Cp, 5.3Bt, 8.1p, 8.3Cp, 9.5Ap, 9.7p, 11.1Ap, 11.1Bp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.1p, 13.4Ap, 13.6Ap, 13.8C, 13.8Qp, 14.1Ap Rosewood
Dalea 13.4E Prairie clover
Damnacanthus 12.1p Damnacanthus
Daphne 8.2p, 8.2t, 9.2t Daphne
Daphniphyllum 8.4t, 14.2p, 14.5p Daphniphyllum
Datisca 5.1Ap, 7.4p, 13.7Hp, 13.8C, 14.1Ap Datisca
Datura 3.1Ba, 5.2Ba, 12.2A, 13.5E Datura, Jimsonweed, Thornapple
Daucus 3.2Ap, 4.5A, 4.5C, 5.1Ap, 6.5p, 7.3Ao, 7.3Bo, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.3Cp, 10.1o, 10.2p, 10.3o, 10.4p, 10.4t, 11.1Hp, 11.1Jp, 11.1Kp, 11.2Cn, 11.2Ct, 12.1p, 12.4B, 12.4E, 13.5B, 14.1Ao, 14.5p Carrot
Davidsonia 5.3Cp, 5.4p, 5.6p, 6.1B, 6.1G, 7.3Ap, 7.3Bp, 8.1p, 8.3Cp, 8.3D, 8.3I, 8.3N, 8.3R, 9.3Fp, 9.3Gp, 9.5Bp, 9.7p, 11.1Ap, 11.1Bp, 11.1Ip, 13.4Gp, 13.4Hp, 13.4Ip, 13.6Ap, 13.6Bp, 13.7Hp, 13.7I, 13.8ZJ, 13.8ZOp, 14.1Ap, 14.2p Davidson's plum
Decodon 14.1Aa Decodon
Delphinium 3.1At, 3.1Ba, 4.2a, 4.5A, 6.5p, 8.1p, 8.3Cp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.7Ht, 13.8C, 13.8Jp, 14.5p Delphinium, Larkspur
Dendrodium 4.1Ca Dendrodium (orchid)
Dendrophthora 12.4F Tropical mistletoe
Derris 8.1p, 13.1a Derris
Desmodium 4.3Bt, 5.5Da, 14.2t Ticktrefoil
Desmos 8.1a, 8.1p, 8.3Cp Gic nambo
Dianthus 9.1A, 10.4o, 10.5o, 10.6o, 11.1Jp, 11.1Kp, 11.2Gp Carnation, Sweet William
Dioscoreophyllum 10.2t Serendipity berry
Dicentra 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 5.8Xa, 6.1A, 6.1B, 6.4a, 7.4a, 8.1a, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 14.1Aa Bleeding heart
Dichelostemma 7.4t Bluedicks, Snake lily
Dicranum 14.1Ao Dicranum moss
Dictamnus 4.4Aa, 4.4At, 5.5Da, 9.6Et, 10.2t, 10.4p, 12.1a Dictamnus, Gasplant
Didierea 13.8ZOp, 14.5p Octopus tree
Didymocarpus 10.4t Milkvetch
Digenea 3.3Ba Wireweed
Digitalis 3.2Ap, 4.1Ct, 5.1Ap, 8.1p, 9.2a, 9.2p, 9.2t, 9.5Bp, 4.1Ct, 10.2a, 10.3o, 10.5t, 12.3t, 13.8ZOp, 14.1Ap, 14.2p, 14.5p Foxglove
Digitaria 4.5A, 4.5C, 5.1Ap, 7.1o, 7.3Ap, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.3F, 8.3Hp, 9.5Ap, 9.7p, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.2Fp, 13.4Ap, 13.6Ap, 13.8Cp, 13.8Yp, 14.5p Crabgrass
Dillenia 13.7Hp Dillenia
Dioclea 7.3Bp, 9.7o, 12.2A, 13.5G Dioclea, Clusterpea
Dionaeae 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp Venus flytrap
Dionysia 5.1Ap, 7.4p, 8.1p, 8.3Cp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ap, 13.7Hp, 14.1Ap Dionysia
Dioscorea 9.7t, 11.1At, 12.3t, 14.6a Yam
Dioscoreophyllum 10.1o Dioscoreophyllum, Serendipity berry
Diosma 13.8Yp Buchu, Diosma
Diospyros 4.3At, 6.5p, 7.3Ap, 8.1p, 8.1t, 9.3Ap, 9.3Fp, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp, 14.5p Diospyros, Persimmon
Diphylleia 9.3Gp, 9.6Ep Umbrella leaf
Diplazium 11.1Gt False spleenwort, Twinsorus fern
Diploclisia 11.1Gt, 11.1Ht Diploclisia
Dipterocarpus 8.1t Curjun, Keruing, Yang
Dipteryx 8.1p, 10.2p, 10.4p Dipteryx, Tonka bean
Distemonanthus 14.5p Movingui
Dolichos 8.1p, 8.3Cp, 11.1Ip, 12.2A, 14.2t Bean
Doryphora 10.4p Doryphora
Draba 10.4p Draba
Dracaena 11.1Ip, 11.1Kp, 13.8Kp, 14.1Ap, 14.2p Dracaena, Dragon tree
Draconis 14.1Ap Dragon's blood
Dracunculus 10.4a Dracunculus
Drosera 5.7Ea, 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp Sundew
Dryobalanops 10.4t Borneo teak, Kapur
Drymis 10.6t Wintersbark
Duboisia 3.1Aa, 5.2Ba, 6.2a Pituri
Dugaldia 14.5p Sneezeweed
Duguetia 5.3Aa Pindaiba
Dunbaria 14.2t Dunbaria
Durio 10.4o Durio, Durian

Ecballium 9.6A, 10.6t, 13.5P Squirting cucumber
Echinacea 8.1p, 8.3Cp, 9.5Ap, 14.1Ao, 14.1Ap, 14.2p, 14.5p Echinacea, Coneflower
Echinocystis 13.5P Echinocystis, Wild cucumber
Echium 5.7C, 9.3Fp, 9.3Gp, 13.8ZF, 14.5p Paterson's curse, Salvation Jane, Vipersbugloss
Eclipta 14.1Ap Eclipta, False daisy
Ekebergia 5.2At Cape ash, Ekebergia
Eleagnus 3.2Aa, 5.8R Russian olive
Elettaria 5.7Et, 10.4t, 10.6t Elettaria, Cardamom
Eleusine 12.4B, 13.2, 13.5L, 13.5Q Finger millet, Goosegrass
Eleutherococcus 14.1Ap Eleutherococcus
Elytrigia 10.1o Quackgrass
Engelhardtia 7.4p, 14.1Ap, 14.5p Engelhardtia
Enterolobium 13.5K Enterolobium

- Ephedra* 5.3Co Jointfir
Epidendrum 5.6t Orchid
Epilobium 4.1Bp, 11.1Bp, 11.1Jp, 13.1p, 13.6Bp,
 13.8ZE, 13.8ZOp Willowherb
Epinetrum 3.1Ba Epinetrum
Epipactus 12.2B Helleborine orchid
Equisetum 3.1Aa, 3.1Ba, 6.1G, 6.2a, 10.2a
 Horsetail
Eremanthus 7.3At Eremanthus
Eremocitrus 10.2p Eremocitrus, Desert lime
Eremophila 12.1p Weeping emu bush
Erica 5.8R, 13.4Ip Heath
Erigeron 6.5p, 7.3Ap, 8.1p, 8.3D, 8.3F, 8.3Hp,
 11.1Hp, 11.1Ip, 13.4Ap, 13.6Ap, 13.7Hp,
 13.8C, 13.8Yp, 14.1Ap, 14.5p Erigeron,
 Fleabane
Eriodictyon 8.1p, 9.7p, 11.1Ip, 11.1Jp, 13.6Ap,
 14.5p, 14.6p Yerba santa
Eriosema 13.4Dp, 13.4Fp Sandpea
Eryngium 10.4p Erynga
Erythraea 10.2t Centaury
Erythrina 3.1Ba, 4.1Ep, 5.3Aa, 5.3Ba, 5.3Ca,
 5.5Da, 12.2A, 13.5G, 13.5K Coral tree,
 Erythrina
Erythrophleum 4.1Ca, 6.4a Sassafras
Erythroxylum 3.2Ba, 4.2a, 5.2Ba, 5.3Ap, 5.3Bp,
 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.8E, 5.9, 6.3a,
 6.4a, 8.1t, 13.4Ap, 13.4At, 13.4Gt, 13.4Ht,
 13.8Jp, 13.8Yt Coca
Escallonia 3.2Ap, 4.1Cp, 5.1Ap, 6.5p, 7.4p, 8.1p,
 8.4t, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ap,
 13.7Hp, 13.8C, 13.8Yp, 14.1Ap, 14.5p
 Redclaws
Eschscholtzia 3.1Aa, 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa,
 5.2Ba, 5.5Da, 5.6a, 5.8Xa, 6.1A, 6.1B, 7.4a,
 8.1a, 9.3Ca, 12.1a California poppy
Esenbeckia 4.4Aa, 5.5Da, 12.1a Jopoy
Eucalyptus 3.3Ep, 4.3Ap, 4.4At, 5.3Ap, 5.3Bp,
 5.4p, 5.6p, 5.8H, 6.4t, 6.1F, 6.4t, 6.5p, 7.3Ap,
 7.3Bp, 7.4p, 8.1p, 9.3Dp, 9.5Bp, 9.7p, 10.4t,
 10.5t, 10.6t, 11.1Bp, 11.1Ip, 11.1Jp, 13.4Ip,
 13.6Ap, 13.6Bp, 13.6Cp, 13.8Jp, 13.8ZE,
 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p, 14.5p Blue
 gum, Eucalyptus, Gumtree, Red gum
Euchresta 5.6a Euchresta
Euclea 9.3Fp Dudiho
Eucommia 7.4p Eucommia
Eugenia 5.3Cp, 6.1F, 9.3Dp, 9.7p, 10.4p, 10.4t,
 13.1a, 13.8Qp, 14.1Ap Stopper
Euodia 5.1Aa, 9.5Ba Euodia
Euonymus 10.1o, 12.2B Spindle tree
Eupatorium 4.1Cp, 4.4B, 7.2B, 7.3Bp, 8.1p, 8.1t,
 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 11.1Jt, 13.8P,
 13.6Ap, 13.6Dt, 13.8P, 14.1Ap, 14.5p
 Snakeroot
Euphorbia 3.4Bt, 5.3Ap, 5.3Bp, 5.4p, 5.5Bp,
 5.5Dp, 5.6p, 5.7Ep, 5.9, 8.2t, 9.3Gt, 9.5Bt,
 13.8Jp, 13.8ZOp, 14.1Ap, 14.5p Sandmat
Euphrasia 7.3At Eyebright
Eurycoma 10.2t Tongkat ali
Eusteralis 10.5t Dysophila, Eusteralis
Evodia 3.1Ba, 3.4Ba, 4.4Aa, 5.2Ba, 5.3Aa,
 5.3Ba, 5.5Da, 6.1B, 6.4a, 7.3Aa, 9.3Aa,
 9.5Ba, 10.4t, 12.1a, 14.1Aa Evodia
Fabiana 10.1o Fabiana, Pichi pichi
Fagara 5.1Aa, 5.5Da, 5.7Gn, 9.3Ap, 9.3Ca,
 9.5Ba, 10.4p, 12.1a, 12.1p, 14.6p Satinwood
Fagopyrum 5.9, 7.1o, 8.1p, 8.3Cp, 13.1a, 13.5N
 Buckwheat
Fagus 7.4p Beech
Falcaria 7.3Ao, 14.1Ao Falcaria, Sickleweed
Feijoa 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.6p, 7.3Bp,
 13.6Bp, 13.7Ho Feijoa, Pineapple guava
Ferula 3.2Ap, 4.4Ap, 5.7C, 6.1F, 14.2p, 14.5p
 Ferula
Festuca 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 8.3O, 10.4o
 Fescue
Ficus 5.1Ap, 6.5p, 8.1p, 8.1t, 9.2a, 9.3Ap, 10.4p,
 12.1p, 12.2D, 13.4At, 13.4Gt, 13.4Ht, 13.8Yt,
 14.6p Fig
Filipendula 5.3Bp, 5.3Cp, 5.4p, 5.6p, 5.7Ep
 Queen, Queen of the Meadow
Fissistigma 4.2a, 5.2Aa, 5.2Ba, 5.3Aa, 5.3Ba,
 5.5Da, 7.4a, 9.3Ga Fissistigma
Flemingia 14.2t Flemingia, Wildhops
Flindersia 4.4Aa, 5.8W, 7.3Bp, 12.1a, 14.1Ap
 Queensland maple
Foeniculum 7.3Bp, 7.3Bt, 8.1p, 10.1p, 10.4p,
 10.4t, 12.1p, 14.1Ap Fennel
Forsythia 7.4p, 8.1p, 8.3Cp, 10.2p, 14.1Ap, 14.2p,
 14.5p Forsythia
Fragaria 7.3Bp, 7.3Bt, 7.4p, 8.1p, 9.3Ap, 9.3Fp,
 9.3Gp, 9.5Ap, 10.3o, 10.4o, 11.2Gp, 12.1p,
 12.4D, 13.8Jp, 13.8ZB, 13.8ZJ, 14.5p
 Strawberry
Frangula 5.7D, 8.3B, 9.2p Buckthorn
Fraxinus 5.8R, 7.3Ap, 10.1o, 13.8ZOp, 14.1Ap,
 14.1Ap, 14.2p, 14.5p Ash
Fritillaria 5.2Ba Fritillary
Frullania 8.2t, 14.1Ap Frullania (liverwort)
Fuchsia 4.1Bp, 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.5Dp,
 5.6p, 5.7Ep, 5.9, 8.1p, 13.1p, 13.4Ap, 13.6Bp,
 13.8ZJ, 13.8ZOp Fuchsia
Fucus 5.7Et, 10.1o Bladderwrack
Fumaria 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 5.3Aa,
 5.3Ba, 5.5Da, 5.8Xa, 6.1A, 6.1B, 6.4a, 7.4a,
 8.1a, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 14.1Aa
 Fumitory
Gaillardia 4.4B, 8.1t, 11.1Jt, 13.6Dt, 13.8Qt
 Blanket flower
Galactia 14.2t Milkpea
Galanthus 3.1Aa, 6.4a, 12.2B Snowdrop
Galbulimima 5.2Ba Magnolia
Galium 8.1p, 8.4t, 9.5Ap, 10.2p, 13.6Dp Bedstraw

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- Garcinia* 4.1Ap, 5.5Dp, 5.7Ep, 6.1A, 7.4p, 8.1p, 9.5Bp, 11.1Ip, 13.4Ap, 13.8ZC, 14.2p, 14.5p, 14.6p *Garcinia*
Gardenia 7.3At, 8.1t, 14.1Ap *Gardenia*
Gastrodia 3.3Bo, 6.1E, 6.6A *Potato orchid*
Gaultheria 10.4p, 14.1Ap, 14.3A *Snowberry*
Geigeria 13.6Dt *Geigeria*
Geijera 4.4Aa, 12.1a *Australian willow, Wilga*
Gelonium 9.1A, 9.3Ao, 9.5Ao, 12.1o *Suregarda*
Gelsemium 7.3Ap, 14.5p *Trumpet flower*
Genipa 7.3At *Genipa*
Genista 3.1Aa, 3.1Ba, 3.2Bp, 4.2a, 4.2p, 4.5A, 4.5C, 5.1Ap, 5.7C, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Gp, 9.7p, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 14.1Ap, 14.2p, 14.5p *Broom*
Gentiana 5.2Ba, 5.2At, 9.3Ft, 10.2t, 14.6p *Gentian*
Geranium 4.1Bp, 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 13.1p, 13.4Ap, 13.6Bp, 13.8Zop, 14.1Ap *Geranium*
Gerbera 10.2o, 12.4B *Gerbera, Daisy*
Geum 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.6p, 13.4At, 13.8Jt *Avens*
Ginkgo 3.2Ap, 3.2At, 3.3At, 5.2At, 5.7Gt, 7.3Ap, 7.3At, 7.4p, 8.1p, 8.3Cp, 8.3E, 8.3R, 9.7t, 10.2t, 10.5t, 10.6t, 11.1M, 13.8ZC, 14.1Ap, 14.2t, 14.5P *Ginkgo, Maidenhair tree*
Gladiolus 6.5p, 14.5p *Gladiolus, Cornflag*
Glaucium 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ca, 5.8Xa, 6.1A, 6.1B, 7.4a, 8.1a, 10.3o, 14.1Ao *Hornpoppy*
Glechoma 5.7Ho, 8.1t *Glechoma, Ground ivy*
Gleditsia 7.4p *Locust*
Gliciridia 7.4p *Gliciridia*
Gloriosa 3.2Ba, 3.3Da, 9.6Ea *Flame lily*
Glycine 3.2Bp, 3.3Aa, 3.3Ao, 3.3Bp, 3.3C, 4.1Cp, 4.2a, 4.4Aa, 4.5A, 4.5C, 5.1Ap, 5.3Ba, 5.5Bo, 5.7J, 5.8D, 5.8Lo, 7.3Ap, 7.3Co, 7.3Cp, 7.3Do, 7.4p, 8.1p, 8.3Co, 8.3Cp, 8.3Ho, 9.3Dt, 9.3Gp, 9.6B, 9.7p, 10.2o, 10.7o, 11.1Bo, 11.1Gp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Bo, 11.2Fp, 12.2A, 12.2D, 12.2E, 12.4C, 13.4Ap, 13.4Da, 13.4Fp, 13.4Ht, 13.5B, 13.5C, 13.5E, 13.5G, 13.5K, 13.6Ap, 13.6Bp, 13.6Bp, 13.7Ep, 13.7Hp, 13.8C, 13.8ZI, 13.8ZOp, 14.1Ao, 14.1Ap, 14.2t *Soya bean*
Glycosmis 4.4Aa, 5.1Aa, 5.5Da, 12.1a *Glycosmis, Axis tree*
Glycyrrhiza 4.1Ct, 4.4Aa, 5.8K, 7.4p, 8.1p, 8.1t, 8.2t, 10.1t, 10.4o, 11.1C, 11.1D, 11.1E, 11.1F, 11.1Ip, 11.1It, 11.1Jp, 11.1Kt, 13.4Ht, 13.4Ip, 13.6Cp, 13.8N, 13.8Qp, 13.8ZC, 14.1Ap, 14.3A, 14.5p, 14.6t *Licorice*
Goebelia 5.6a *Goebelia*
Goniotalamus 9.7o, 12.1a, 13.6Bo
Goniotalamus, Lim panas
Gonystylus 5.8R *Ramin*
Gordonia 9.7p *Gordonia*
Gossypium 4.1At, 4.4Aa, 4.4At, 5.3Cp, 5.5Dp, 5.8R, 7.1t, 7.4p, 8.1p, 8.1t, 9.3Dp, 9.3Dt, 10.2o, 10.5t, 10.6o, 10.6t, 11.1Bo, 11.1E, 11.2Bo, 12.2D, 13.3, 13.4Ap, 13.8N, 14.1Ao, 14.1Ap, 14.1At, 14.2p, 14.5p *Cotton*
Gratiola 11.1D *Hedgehyssop*
Grevillea 14.1Ap *Grevillea*
Griffonia 12.2A *Griffonia*
Grindelia 13.8P *Gumweed*
Guaiacum 4.3Bp, 4.3Cp, 4.4Ap, 10.4p, 10.4t, 10.5p, 14.1Ap, 14.6p, 14.1Ap *Guaiacum, Lignum vitae*
Guatteria 3.1Ba, 4.2a, 4.4Aa, 5.2Aa, 5.2Ba, 5.3Aa, 5.5Da, 7.4a, 9.3Fa *Guatteria*
Guiera 9.3Dp *Guiera*
Gymnadenia 5.8R, 10.4p, 10.5p, 14.2p *Gymnadenia, Fragrant orchid*
Gymnema 5.8J, 10.1o, 10.1t, 10.2t, 13.7Et, 14.6t *Gymnema, Miracle fruit*
Gymnosporia 10.1o *Redspike thorn*
Gymnostemma 4.1Ct, 9.7t *Gymnostemma*
Gypsophila 9.1A *Baby's breath*
Haemanthus 5.1Aa, 9.2a *Blood lily*
Haematoxylum 5.1Ap *Logwood*
Haematoxylum 4.3Ap, 4.3Bp *Bloodwood tree, Haematoxylum*
Hamamelis 5.1Ap, 5.3Cp, 5.4p, 5.6p, 6.1B, 6.1G, 7.3Ap, 7.3Bp, 8.1p, 8.3Cp, 8.3D, 8.3I, 8.3N, 8.3R, 9.3Fp, 9.3Gp, 9.5Bp, 9.7p, 10.2p, 11.1Ap, 11.1Bp, 11.1Ip, 13.4Gp, 13.4Hp, 13.4Ip, 13.6Ap, 13.6Bp, 13.7Hp, 13.7I, 13.8ZJ, 13.8ZOp, 14.1Ap, 14.2p *Witch hazel*
Handelia 10.6t *Handelia*
Hannoa 10.2t *Abo*
Haplopappus 4.1Cp, 7.3Cp, 7.4p, 8.1p, 9.3Cp, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.7p, 11.1Bp, 11.1Hp, 11.1Jp, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap, 13.8P, 13.8Yp, 13.8ZB, 14.1Ap, 14.5p, 14.6p *Golden weed*
Haplophragma 7.3Cp, 9.3Fp, 9.5Bp, 9.7p *Bignonia, Heterophragma*
Haplophyllum 4.4Aa, 5.5Da, 5.8W, 7.3Bp, 9.5Bp, 12.1a, 14.1Ap *Haplophyllum*
Hardenbergia 12.4A *Hardenbergia, Native lilac*
Hardwickia 9.3Dt *Hardwickia*
Harpagophytum 10.2t *Devil's claw, Grapple plant*
Harrisonia 9.6Et, 10.2t *Harrisonia, Mkidori*
Hebe 14.5p *Hebe, Veronica*
Hedeoma 10.4t *Pennyroyal*
Hedera 7.3Ao, 8.1t, 9.2a, 9.3Aa, 12.1a, 12.3t, 13.1t, 13.4Ht, 13.8Jt, 13.8Mt, 14.1Ao, 14.6t *Ivy*
Heimia 14.1Aa *Heimia*
Heisteria 14.1Ao *Heisteria*
Helenium 4.4B, 7.2B, 8.1t, 10.2o, 10.2t, 11.1Jt, 12.1t, 13.6Dt, 13.8Qt, 13.8ZP *Sneezeweed*

- Helianthus* 3.1Ao, 5.2Ao, 5.5Da, 5.7C, 5.8O, 6.1B, 6.1D, 7.3Do, 8.2t, 10.2o, 10.3o, 11.1Bo, 11.1Gt, 11.1M, 11.2Bo, 12.2B, 12.3t, 13.4Ht, 13.4Ht, 13.4Ip, 13.5B, 13.5H, 13.5I, 14.1Ao, 14.2o, 14.2p, 14.5p, 14.6p, 14.6t
Sunflower
- Helichrysum* 11.2Gp, 14.2p, 14.5p Immortelle, Strawflower
- Heliotropium* 10.4p Heliotrope
- Hemsleya* 10.1t, 10.2t Luo guo di
- Heracleum* 3.1Ba, 7.3Bp, 7.3Bt, 9.3Ap, 12.1p, 14.5p Cowparsnip
- Hermidium* 5.3Ap, 5.3Cp, 5.4p, 11.2Jp Four o'clock, Hermidium
- Heuchera* 12.4A Alumroot
- Hevea* 8.1t, 12.2C, 12.2D, 12.2E, 13.4At, 13.4Gt, 13.4Ht, 13.8Yt, 14.2o Rubber tree
- Hibiscus* 7.4p, 9.7p, 10.3o, 13.4Ap, 13.4Ip, 13.8N, 14.1Ap, 14.5p Hibiscus, Ribwort, Rosemallow
- Himantandra* 5.2Ba Galbulimima, Magnolia
- Himatanthus* 6.5p Himatanthus
- Hippeastrum* 3.1Aa, 6.4a, 9.2a, 12.2B
Barbados lily
- Hippophae* 3.1Aa, 3.2Aa, 3.3Ea, 10.5a, 12.1a, 14.6a Seabuckthorn
- Hippomane* 3.1Aa, 6.4a, 8.2t, 14.1Ap
Hippomane, Manchinceel
- Hiptage* 14.6p Hiptage
- Homogyne* 10.6t Alpine coltsfoot
- Houttuynia* 14.5p Chameleon
- Hordeum* 3.3Ao, 5.3Aa, 5.3Ba, 5.3Bp, 5.5Da, 5.8La, 5.8Lo, 6.3p, 6.5a, 6.5p, 8.1o, 9.1A, 9.2o, 9.3Aa, 9.3Ga, 10.1o, 10.2p, 10.3o, 10.4o, 10.4p, 10.6a, 10.6p, 12.1a, 12.2B, 12.2C, 12.2D, 12.2E, 12.4A, 12.4B, 12.4E, 12.4F, 13.2, 13.5B, 13.5E, 13.5K, 13.5N, 13.5Q, 13.6Ba, 14.2p, 14.6o Barley
- Hortia* 3.4Ba, 14.1Aa Hortia
- Hovenia* 10.1t Hovenia, Japanese raisin tree
- Humulus* 6.3p, 10.2p, 10.4o, 10.4t, 10.6o, 11.1Ip, 11.1It, 11.2Gp, 14.5p, 14.6t Hops
- Hunteria* 3.2Ba, 3.3Da Hunteria
- Huperzia* 6.4a Clubmoss
- Hura* 8.2t Sandbox tree
- Hyacinthoides* 13.1a Hyacinthoides
- Hyacinthus* 10.4p, 13.1a Hyacinth
- Hydnocarpus* 14.6p Chaulmoogra
- Hydrangea* 10.1p, 10.2t, 14.5p Hydrangea
- Hydrastis* 3.1Ba, 3.2Ba, 3.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 9.3Aa, 9.5Ba, 12.1a Hydrastis, Goldenseal
- Hymenocallis* 3.1Aa, 6.4a, 9.2a, 9.5Ba
Spiderlily
- Hymenoclea* 9.7t, 10.6t Cheesebush,
- Hymenophyllum* 10.2p Filmy fern
- Hymenoxys* 7.2B, 10.1p, 12.1t, 13.6Dt Rubber weed
- Hyoscyamus* 3.1Ba, 5.2Ba Henbane
- Hypericum* 3.2Ap, 3.4Ap, 4.4Ap, 5.4p, 5.6p, 5.8G, 5.8O, 5.8T, 5Bp, 6.1C, 6.3p, 7.3Ap, 8.1p, 8.4p, 9.5Ap, 9.5Bp, 9.7p, 11.1Hp, 11.1Kp, 11.2Fp, 11.2Jp, 13.1p, 13.4Dp, 13.4Fp, 13.6Ap, 14.5p, 14.6p St John's wort
- Hypoestes* 7.3At, 8.1t Hypoestes
- Hypolaena* 14.1Ap Hypolaena
- Hyptis* 14.1Ap Bushmint
- Hyssopus* 8.1p, 10.4t, 14.2p, 14.5p Hyssop
- Iberis* 11.1D, 11.1Gt Candytuff
- Ilex* 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 10.2a, 14.2p Holly, Maté
- Illicium* 3.2Bt, 5.7Gp, 6.1A, 8.3M, 10.1p, 10.3o, 10.4p, 10.4p, 12.1p, 13.8Qp Anise tree, Star anise
- Impatiens* 11.1Bp, 13.8ZOp Touch-me-not
- Indigofera* 7.3Co, 13.8G, 14.2t Indigo
- Intsia* 5.8H, 6.5p, 7.3Ap, 8.1p, 9.3Dp, 9.7p, 11.1Ip, 13.6Ap, 13.6Cp, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p Ifil
- Inula* 3.1Ba, 4.4B, 5.7C, 7.2B, 7.3At, 8.1t, 10.1p, 10.6t, 11.1Jt, 13.6Dt Yellowhead
- Iostephane* 4.4At Helianthella, Kachana
- Ipehion* 7.4t, 11.1Gt, 11.1Ht Spring starflower
- Ipomoea* 4.4Ap, 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 7.3Ap, 8.2o, 8.3O, 9.2p, 9.5Bp, 10.4t, 11.2Ct, 13.1a, 13.5K, 13.8U, 13.8ZOp, 14.1Ap, 14.5p, 14.6t Morning glory, Sweet potato
- Iris* 3.2Bo, 3.3Do, 6.3o, 8.2t, 9.1A, 10.4t, 11.1Gp, 11.2Bo, 14.1Ap, 14.2p Iris
- Isatis* 7.3Aa, 11.2Aa, 14.1Aa Woad
- Isodon* 7.3At, 10.2t, 10.5t, 10.6t, 11.1Jt Akichouji
- Isopyrum* 5.3Ca, 13.4Da False rueanemone
- Iva* 9.7t, 10.6t, 12.1t, 14.5p Marsh elder
- Ixiolaena* 14.1Ao Stalked plover daisy
- Jacaranda* 14.1Ao Jacaranda
- Jasminum* 5.7Et, 10.4a, 10.4o, 10.5o, 10.6o, 13.4Dt Jasmine
- Jateorrhiza* 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 9.3Aa, 9.3Fa, 9.5Ba, 10.2t, 12.1a Calumba
- Jatropha* 4.4At, 5.5Bt, 12.1t Nettlespurger, Oil nut
- Juglans* 3.1Aa, 3.3Ea, 5.1Ap, 5.5Da, 7.3Ap, 7.3Bp, 8.1p, 9.3Ap, 9.5Bp, 10.4t, 10.5a, 11.1Hp, 12.1p, 13.6Bp, 13.8F, 13.8Kp, 14.1Ap, 14.6a Walnut
- Juniperus* 4.4At, 5.7Gt, 6.4t, 7.4p, 9.3Gp, 9.5Bp, 9.6Ep, 10.1p, 10.4t, 12.1p, 14.1At, 14.5t Juniper
- Jurinea* 10.6t, 14.1At Jurinia
- Justicia* 5.5Da, 6.4a, 7.3Bp Water willow
- Kadsura* 5.7Gp Kadsura
- Kaempferia* 5.8Q, 10.4t Kaempferia, Resurrection lily

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- Kalanchoe* 7.4a Neverdie, Widow's thrill
Kalmia 4.2t, 5.8J, 8.1p, 8.3Cp, 10.2p, 11.1Hp, 11.1Ip, 11.2Gp, 13.6Ap, 13.7Ep, 13.7I
Mountain Laurel
Kalopanax 14.6p, 14.6t Castoralaria
Kandelia 13.6Bp Kandelia (mangrove)
Karwinskia 9.3Gp, 9.7p Karwinskia
Kochia 14.6t Molly
Koelreuteria 4.1Cp, 4.5A, 5.1Ap, 6.5p, 7.1p, 7.3Ap, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.2p, 9.3Dp, 9.3Gp, 9.5Bp, 11.1E, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap, 13.7Hp, 13.8C, 13.8Jp, 13.8X, 13.8Yp Golden raintree
Kunzea 10.4t Kunzea
Lablab 8.1p, 8.3Cp, 11.1Ip, 13.2 Lablab, Hyacinth bean
Laburnum 3.1Aa, 3.1Ba, 4.1Ep, 7.3Ap, 8.1p, 12.2A, 13.6Ap, 14.2p, 14.6a Goldenchain tree, Laburnum
Lactuca 9.5Ap, 10.2t Lettuce
Lagenaria 13.5P Bottle gourd, Lagenaria
Lagerstroemia 14.1Aa Crape myrtle, Lagenaria, Pride of India
Laminaria 10.1o Kelp
Lamium 10.2t, 11.1Gt Deadnettle
Lapsana 14.2p Nipplewort
Larix 5.8R, 10.1o 10.4o Larch
Larrea 4.3Cp, 4.4Ap, 14.1Ap, 14.6p Creosote bush
Laser 10.6t Laser
Laserpitium 10.6t Bastard lovage
Lathyrus 3.3Ao, 3.3Bo, 5.3Ba, 5.8Lo, 6.3o, 8.3A, 8.3M, 12.2A, 13.8Z, 14.1Ap Grass pea, Pea, Sweet pea
Latua 3.1Ba Sorcerers' tree
Laurelia 8.1a Tepa
Laurus 5.7C, 7.3At, 7.3Bt, 13.7D, 13.8Mt
Laurel, Sweet bay
Lavandula 3.1Bt, 5.2At, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.1t, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Bt, 10.4o, 10.4p, 10.4t, 10.5t, 10.6t, 13.1t Lavender
Lawsonia 14.1Ap, 14.2p Lawsonia
Ledum 10.4t Labrador tea
Lemna 5.8U Duckweed
Lens 12.2A, 13.8Zl, 14.2t Lentil
Lepidium 10.4p Pepperweed, Pepperwort
Leptospermum 3.2Ap Teatree
Lespedeza 13.4Dp Lespedeza
Letharia 13.6Cp Wolf lichen
Lethedon 9.3Fp Lethedon
Leucaena 9.3Ao, 11.2Fa, 11.2Fp, 12.1o, 14.3Bo
Jumbie bean, Lead tree
Leucojum 3.1Aa, 6.4a, 9.2a Snowflake
Leucothoe 4.2t Doghobble
Levisticum 6.5p, 7.2B, 7.3Bp, 7.3Bt, 8.1p, 9.3Ap, 9.5Ap, 11.2Gp, 12.1p, 13.4Hp, 14.1Ap, 14.2p, 14.5p Levisticum, Lovage
Liatris 5.7C, 13.8P Blazing star
Libanotis 7.4p Seseli, Moon carrot
Ligularia 10.6t, 13.8P Ragwort
Ligusticum 4.4Aa, 7.4p Licorice root
Ligustrum 4.2a, 6.5p, 10.2t, 13.8Kp, 13.8ZP, 14.1Ap, 14.1At, 14.2p Privet
Lilium 7.4t, 14.2t Lily
Linaria 3.2Ap, 8.1p, 8.3Cp, 13.7Hp, 14.5p Toad flax
Lindera 5.3Aa, 10.4t, 10.6t Spicebush, Bollywood
Linum 5.7Et, 5.8R, 7.3Ap, 10.2o, 11.1Bo, 11.2Bo, 13.5N, 14.1Ao, 14.6o Flax
Lippia 10.1t, 10.2p, 10.4t, 14.1Ap Lippia, Spanish thyme
Liquidambar 7.3Bp, 10.4p, 13.6Bp Liquidambar, Storax, Sweetgum
Liriodendron 4.4Aa, 4.4Ap, 5.2Aa, 5.3Aa, 5.2Ba, 8.1a, 9.3Ga, 10.1o, 10.6t Tulip tree, Yellow poplar
Litchi 9.7t, 10.4o, 10.4p, 10.4t, 13.8D, 13.8ZA, 14.2p Lychee
Lithospermum 5.7C, 9.3Fp, 9.3Gp, 9.7p, 13.8ZF, 14.5p Puccoon, Stoneseed
Litsea 8.1a Brown beech
Lloydia 11.1Gt Alp lily
Lobelia 3.1Aa, 3.1Ba, 6.2t, 13.1a, 13.4Gt Lobelia
Lolium 4.3Ba, 4.4B, 5.2Ba, 5.3Ba, 6.3p, 6.5p, 7.4a, 9.7o, 10.4o, 13.8ZG Fescue, Rye grass
Lomatia 8.1p, 11.1Hp, 13.8Kp Lomatia
Lonchocarpus 12.2A, 13.1a, 13.5G, 13.6Bp
Lancepod
Lonicera 5.8R, 8.1t, 9.3Ct, 9.3Ft, 9.3Gt, 13.1t, 13.4At, 14.1At, 14.5p, 14.6t Honeysuckle
Lophocereus 11.1Gt Totem pole cactus, Senita cactus
Lophopetalum 13.8Mt Bajan, Katbo, Perupok
Lophophora 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 6.3p, 6.5p, 11.2Jp Lophophora, Peyote, Mescal
Lophophytum 13.6Ap Lophophytum (parasitic plant)
Lotononis 14.2t Lotononis
Lotus 12.2A Bird's foot trefoil, Trefoil
Luffa 8.1t, 9.1A, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Ao, 13.1t, 13.4At, 13.4Ht, 13.5P, 13.8Jt
Luffa, Sponge gourd
Lunaria 3.2Bo, 3.3Do, 6.3o, 6.4a Honesty, Lunaria
Lupinus 3.1Aa, 3.1Ba, 3.2Bp, 3.3Aa, 3.3Bp, 3.3C, 4.1Ep, 4.2a, 4.3Aa, 4.3Ca, 4.5A, 4.5C, 5.1Ap, 5.5Bo, 5.5Da, 7.3Ap, 7.3Cp, 8.1p, 8.1t, 8.3Cp, 9.3Gp, 9.3Gt, 9.7p, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 13.8Mt, 13.8Yt
Lupine
Lychnis 7.4t, 9.1A, 11.1Gt Campion, Catchfly
Lychnophora 7.3At Lychnophora
Lycium 13.1a, 14.2t Desert thorn

- Lycopersicon* 3.1Aa, 3.2Bt, 3.3Ea, 5.5Da, 5.6a, 5.8La, 6.3o, 6.4a, 6.5a, 7.3Ao, 7.3Bo, 9.3Ap, 10.2a, 10.4o, 10.5a, 11.1It, 11.2Ct, 11.2It, 12.1p, 12.2B, 12.2C, 12.2D, 12.2E, 12.3t, 12.4D, 12.4E, 13.3, 13.5A, 13.5D, 13.5K, 13.5N, 13.5O, 13.7Ha, 13.8F, 13.8U, 13.8W, 14.1Ao, 14.2a, 14.6a Tomato
- Lycopodium* 3.1Aa, 3.1Ba, 6.1G, 6.2a, 6.4a, 10.2a Clubmoss
- Lycopus* 7.2B, 13.8ZF, 14.5p Bugleweed
- Lycoris* 3.1Aa, 6.4a, 9.2a, 9.7a, 13.8O Lycoris, Red spider lily, Resurrection lily
- Lygos* 14.6a Retama
- Lysimachia* 13.8V Loosestrife
- Lysionotus* 14.5p Lysionotus
- Maackia* 12.2A, 13.5E Maackia
- Machilus* 3.3Da Machilus
- Macleaya* 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 6.1A, 6.1B Macleaya, Plume poppy
- Maclura* 4.1Ep, 8.1p, 12.2B Maclura, Osage orange
- Macrocystis* 11.2E Kelp
- Macrotomia* 9.3Fp Arnebia
- Macrotyloma* 13.5G Horsegtram, Macrotyloma
- Magnolia* 3.1Ba, 3.2Bp, 4.4Aa, 4.4Ap, 5.2Aa, 5.2Ba, 5.3Aa, 5.7C, 5.7Gp, 7.3Ap, 8.1p, 9.3Ga, 10.1p, 10.4p, 11.1E, 12.1p, 14.1Ap Magnolia, Umbrella tree
- Mahonia* 3.1Ba, 3.2Ba, 3.4Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.3Ca, 5.5Da, 6.1B, 6.4a, 7.1a, 9.3Aa, 9.3Fa, 9.5Ba, 12.1a, 14.1Aa Barberry
- Mallotus* 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 9.3Dp, 9.5Bp, 13.1p, 13.4Ap, 13.6Bp Kamala tree, Mallotus
- Malus* 5.5Dp, 5.8J, 6.4t, 8.1p, 8.1t, 8.3Cp, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Bt, 9.7t, 10.2p, 10.3o, 10.4o, 10.4p, 10.4t, 10.5t, 10.6o, 10.6p, 10.6t, 11.1Hp, 11.1Ip, 11.1It, 11.2Ct, 11.2Gp, 12.4E, 13.4At, 13.4Ht, 13.6Ap, 13.7Ep, 13.7I, 13.8Jt, 14.1Ao, 14.1At, 14.2o, 14.2p, 14.2t, 14.5p Apple, Crabapple
- Malva* 6.5p Mallow
- Mammea* 8.1p, 10.3o Mammea, Mammypapple
- Mandragora* 3.1Ba, 5.2Ba Mandrake
- Mangifera* 10.2p, 10.3o, 13.4Ip, 13.8Jp, 14.2p, 14.6p Mango
- Manihot* 3.3Ao, 9.1A, 10.2o, 13.6Bo Cassava, Manihot, Tapioca
- Mappia* 9.3Fa, 12.1a Mappia
- Maprounea* 9.3Ct, 9.5Bt Aegopricum, Maprounea
- Marchantia* 11.2Gp, 14.1Ap, 14.2p Marchantia
- Marrubium* 10.2t Horehound
- Marsilia drummondii* 13.8ZK Nardoo
- Matricaria* 3.2Ap, 5.1Ap, 13.8ZOp, 14.1At, 14.5p Chamomile
- Matteuccia* 14.5p, 14.6p Matteuccia
- Maytenus* 5.3Co, 6.2p, 6.3o, 7.3At, 9.2t, 9.3At, 9.6Eo, 11.2E, 12.1t, 13.7Ht, 14.1At Mayten
- Medicago* 7.4p, 8.1o, 8.1p, 8.2p, 8.3Cp, 10.3o, 11.1Gp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2It, 12.2A, 13.3, 13.4Hp, 13.5G, 14.1Ap, 14.2t, 14.6t Alfalfa, Medick
- Melaleuca* 6.4t, 8.1t, 10.4t, 10.6t, 12.1p Cajeput, Melaleuca, Teatree
- Melampodium* 10.6t Blackfoot
- Melampyrum* 10.1o Cowwheat
- Melastoma* 7.3Ap, 7.3Bp Melastoma, Melastome
- Melia* 4.4At, 5.8R, 7.3Ba China berry tree, Melia
- Melicope* 5.5Da Melicope
- Melilotus* 13.4Hp, 13.8X Sweet clover
- Melissa* 7.2B, 9.5Ap, 10.4t, 10.5t, 10.6t, 11.2Gp, 13.4Hp, 14.1Ap, 14.2p, 14.5p Balm
- Melodinus* 4.2a Melodinus
- Menispermum* 3.1Ba, 3.2Bt, 3.3Dt, 4.4Aa, 5.7Ga, 7.1a Moonseed
- Mentha* 4.5A, 4.5C, 5.1Ap, 5.6t, 7.2B, 7.3Ap, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.3Cp, 9.5Ap, 10.4t, 10.6o, 10.6t, 11.1Hp, 11.2Gp, 13.4Hp, 13.8ZF, 14.1Ap, 14.2p, 14.5p Mint, Spearmint
- Menyanthes* 10.2t Buckbean
- Mesembryanthemum* 9.1A Iceplant
- Metasequoia* 7.2Co, 8.1p Dawn redwood
- Methysticodendron* 5.2Ba Methysticodendron, Culebra-borrachero, Intoxicant of the snake
- Mezoneuron* 14.2p Caesalpinia, Mezoneuron, Uhiuhi
- Michelia* 5.5Dt, 5.7C, 6.2t, 7.3At, 8.1t 10.4o, 10.4t, 10.5o, 14.1At Michelia
- Microcitrus* 10.2p Australian lime, Microcitrus
- Micromeria* 10.4o, 14.1Ap Savory
- Microtea* 5.1Ap Jumpy pepper
- Millettia* 7.4p Millettia
- Mimosa* 5.3Bp, 5.3Cp, 5.5Da, 9.3Ao, 12.1o, 14.3Bo Mimosa, Sensitive plant
- Mimusops* 10.1o Mimusops, Spanish cherry
- Mirabilis* 9.1A Four o'clock
- Mitracarpus* 10.5t, 10.6o Mitracarpus
- Mitragyna* 5.6a, 14.2p, 14.6p Kratom
- Mnium* 11.2Bo, 14.1Ao Calcareous moss
- Momordica* 5.8F, 5.8K, 9.1A, 9.5Ao, 12.2B, 12.4C, 13.5N, 13.5P, 14.6o Balsam pear, Momordica
- Monarda* 10.4t, 10.4o Beebalm, Horsemint
- Mondia* 6.1F Mondia, White's ginger
- Monechma* 5.8Q Monechma, Skaapbloubossie
- Monimia* 8.1a Monimia
- Monochasma* 10.2p, 14.1Ap, 14.5p, 14.5t Monochasma
- Monopteryx* 12.1p Ormosia, Tento
- Montanoa* 5.8Q Montanoa, Tree daisy
- Montezuma* 4.1At, 7.1t, 8.1t, 9.3Dt, 14.1At, 14.2p Puerto Rico hibiscus

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- Morinda* 8.1p, 8.3Hp, 9.3Gp, 9.5Ap, 12.1p, 13.6Dp Indian mulberry, Morinda
Morus 5.8B, 5.8H, 6.5p, 7.3Ap, 7.4p, 8.1p, 8.2p, 9.3Cp, 9.3Dp, 9.7p, 10.3o, 10.4o, 10.6o, 11.1Gt, 11.1Hp, 11.1Ip, 11.2Fp, 13.1a, 13.4Ap, 13.6Ap, 13.6Cp, 13.8Qp, 13.8Yp, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p, 14.5p, 14.6o, 14.6p Mulberry
Mosla 10.4o, 10.4t, 10.6o, 10.6t Miniature beefsteak plant, Mosla
Mucuna 3.1Aa, 3.3Ea, 5.5Da, 5.8La, 6.5a, 10.5a, 13.8F, 14.1Ap, 14.6a Cowitch, Mucuna
Murraya 5.5Da, 9.3Fa, 9.3Ga, 12.1a, 14.1Aa, 14.2a Curryleaf tree, Murraya
Musa 3.1Aa, 3.3Ea, 5.3Ap, 5.3Ba, 5.3Bp, 5.3Ca, 5.3Cp, 5.4a, 5.4p, 5.5Da, 5.6a, 5.7Ea, 5.8F, 5.8O, 7.4p, 8.2p, 10.3o, 10.4o, 10.4p, 10.4t, 10.5a, 10.6o, 11.2Jp, 12.2D, 12.2E, 12.4E, 13.6Ba, 13.8F, 13.8Qp, 14.1Ap, 14.6a, 14.6p Banana, Plantain
Mussaia 7.4p Mussatia (liana)
Myoporum 14.2p Myoporum, Ngaio tree
Myrcia 7.4p, 9.5Ap, 10.4p, 10.4t, 10.6t, 13.1p, 14.5p Rodwood
Myrica 4.1Cp, 5.8H, 7.3Cp, 8.1p, 9.3Cp, 9.3Dp, 9.3Gp, 9.5, 9.5Ap, 9.5Bp, 9.7p, 11.1Bp, 11.1Hp, 11.1Jp, 11.2Fp, 13.1p, 13.4Ap, 13.4Fp, 13.6Ap, 13.8Yp, 13.8ZB, 14.1Ap, 14.5p Sweetgale
Myristica 6.1F, 6.5p, 10.4o, 10.4p, 10.4t, 11.2Bo, 12.1p, 13.8Qp, 14.1Ap Nutmeg
Myroxylon 8.1p, 10.2p, 10.4t Balsam of Peru, Myroxylon
Myrsine 8.1p, 8.4p, 9.3Ap, 9.3Gp, 12.1p Colic wood
Myrtus 10.4t, 10.6t Myrtle, Myrtus

Nandina 3.1Ba, 5.2Ba, 5.3Aa, 5.3Ba, 5.3Ca, 5.5Da, 6.1B, 6.4a, 9.3Aa, 9.5Ba, 12.1a Nandina, Sacred bamboo
Narcissus 3.1Aa, 6.4a, 9.2a, 9.7a, 10.1o, 10.4p, 12.2B, 13.8O Daffodil, Jonquil, Narcissus
Nardostachys 8.3M Nard, Spikenard
Nectandra 5.7Gp, 10.4a Sweetwood
Nelumbo 3.3Aa, 5.5Da, 5.4a, 7.3Aa, 14.5p Lotus, Sacred lotus
Nemuaron 12.1p Nemuaron
Neolitsea 4.4Aa, 7.3Aa White bolly gum
Neonauclea 9.3Gp Neonauclea
Nepenthes 5.7Ea Pitcher plant
Nepeta 5.6t, 10.5o, 10.6t Catmint
Nephelium 10.4o, 10.4p, 10.4t, 14.2p Nephelium, Rambutan
Nerium 4.1Ct, 6.4t, 7.3Aa, 7.3Ap, 8.1t, 14.5p Oleander
Nicotiana 3.1Aa, 3.1Ba, 3.2Aa, 5.8La, 5.8U, 6.1G, 6.2a, 6.5a, 6.5o, 7.2Co, 8.2t, 9.7o, 10.2a, 10.4o, 10.5a, 10.5o, 10.6o, 11.1It, 11.1Ja, 11.2It, 12.1a, 12.2C, 12.2D, 12.2E, 12.4A, 12.4B, 12.4D, 12.4E, 13.5N, 13.5O, 13.8W, 14.1Aa, 14.1At, 14.3Bo, 14.3Bn Tobacco
Nigella 10.4a, 14.1Ap Nigella, Spanish fennel
Nolina 7.4t Beargrass, Nolina
Nothapodytes 3.2Ap Stinking tree
Nothofagus 5.8H, 6.5p, 7.3Ap, 8.1p, 9.3Dp, 9.7p, 11.1Ip, 13.6Ap, 13.6Cp, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p Nothofagus
Notholaena 14.5p Cloak fern
Notholirion 6.4a, 8.1a False lily
Notopterygium 14.1Ao, 14.1Ap Notopterygium, Qlang ho
Nuphar 4.1Bp, 13.1p, 13.6Bp, 13.8ZOp Pond lily
Nymphaea 3.3Aa, 5.4a Blue lotus, Egyptian lotus, Waterlily

Ochrocarpus 8.1p African mammy apple, Mammia
Ochrosia 9.3Aa, 9.3Ba, 9.3Ga, 12.1a Yellowwood
Ocimum 5.2At, 5.7Et, 6.1F, 7.2B, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 9.5Ap, 10.4p, 10.4t, 10.5t, 10.6t, 11.2Gp, 12.1p, 13.4Ap, 13.4Hp, 13.7Hp, 13.8C, 13.8Qp, 14.1Ap, 14.2p, 14.5p, 14.6p Basil
Ocotea 5.7Gp, 9.3Fa, 10.4p, 12.1p, 14.1Ap Sweetwood
Oenanthe 7.3Ao, 8.1p, 10.4t, 14.1Ao Water dropwort
Oenothera 4.1Cp, 4.5A, 5.1Ap, 5.5Da, 5.6t, 6.1B, 6.1D, 7.1p, 7.3Ap, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.2p, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 11.1Bp, 11.1E, 11.1Gp, 11.1Hp, 11.1Jp, 11.1Kp, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap, 13.7Hp, 13.8Jp, 13.8Kp, 13.8Qp, 13.8X, 13.8Yp, 13.8ZE, 14.1Ap, 14.2p, 14.5p, 14.6o, 14.6p Evening primrose
Olea 4.2a, 7.4p, 8.1p, 8.3Cp, 9.2p, 9.7p, 14.1Ap, 14.2p, 10.2t, 10.3o, 10.4o, 10.6o, 11.1Bo, 12.2E, 13.4At, 13.4Ht, 13.4Ip, 13.8Jt, 13.8Kp, 13.8S, 13.8ZOp, 13.8ZP, 14.1Ap, 14.1At, 14.2o, 14.2p, 14.2t Olive
Omphalea 13.1a Cobnut
Onobrychis 11.1Ip, 12.2A Sainfoin
Ononis 14.1Ap Restharrow
Onosma 5.7C, 9.3Fp, 9.3Gp Onosma
Oonopsis 9.7o, 14.2o, 14.3Bo False goldenweed
Ophrys 10.5t Twayblade
Oplopanax 5.7C, 7.3Ao Devil's club
Opuntia 5.7Ea Prickly pear
Origanum 4.5A, 4.5C, 5.1Ap, 5.2At, 6.1F, 6.4t, 7.2B, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 10.2p, 10.4p, 10.4t, 10.5t, 10.6p, 11.2Fp, 13.4Hp, 13.4Ip, 13.8Qp, 14.1Ap, 14.2p, 14.5p, 14.6p Marjoram, Oregano
Orixa 3.1Ba, 5.5Da Orixa
Ormosia 3.1Aa Peronia, Ormosia

- Ornithogalum* 4.1Ct Star of Bethlehem
Oroxylum 3.2Ap, 5.7C, 5.7J, 8.1p, 9.2p, 9.3Ap, 9.3Gp, 9.5Ap, 9.5Bp, 9.7p, 11.1Jp, 12.1p, 14.1Ap Trumpet flower
Orthodon 4.3Co, 6.5p, 10.4o, 12.1p
 Orthodontium moss
Oryza 4.4E, 4.5A, 5.6o, 5.7C, 8.3Co, 8.4o, 10.4a, 10.5t, 12.2B, 12.2C, 12.2D, 12.4B, 12.4D, 12.4E, 13.2, 13.5B, 13.5F, 13.5K, 13.5Q, 13.7C, 14.2p Rice
Osbeckia 7.3Bp, 13.6Bp Osbeckia, Wideleaf osbeckia
Otholobium 14.6t Otholobium
Ougeimia 14.1Ap Sandan
Ouretea 14.5p Amarillo, Ouratea
Oxalis 7.1o, 10.3o Oxalis, Wood sorrel
Oxytropis 13.1a Locoweed
- Pachygone* 5.3Aa, 5.3Ba, 13.4Da Pachygone
Pachyrhizus 13.6Bp Yam bean
Paeollia 8.1p, 13.1p, 13.6Bp, 13.8Zop Paconia, Peony
Paeonia 4.1Bp, 4.1Cp, 4.3Ap, 4.4Ap, 5.1Ap, 5.3Bp, 5.4p, 5.6p, 11.1C, 11.1D, 11.1F, 11.1Ip, 11.2Gp, 13.1p, 13.1t, 13.6Bp, 13.8ZOp, 14.6o Peony
Palicourea 3.3Da, 6.5a, 6.5p, 13.8A Cappel
Pandanus 14.6p Pandanus, Screwpine
Panax 3.1Bt, 3.2Bt, 4.4At, 5.2Bt, 5.5Dt, 5.6t, 5.7C, 5.7Et, 5.7F, 5.8E, 5.8R, 5.8V, 5.9, 6.1G, 6.2t, 7.2Ct, 7.3Ao, 7.3Bo, 7.3Bt, 8.3M, 9.7n, 9.7t, 10.3o, 11.1It, 14.1Ao, 14.1B, 14.6o Ginseng
Pancreatium 3.1Aa, 6.4a, 9.2a, 14.1Ap
 Pancreatium, Spiderlily
Panda 14.1Ap Panda
Papaver 3.1Aa, 3.1Ba, 3.2Ba, 3.3Aa, 3.3Da, 3.4Aa, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.3Ca, 5.4a, 5.5Da, 5.6a, 5.8Xa, 6.1A, 6.1B, 6.4a, 7.4a, 8.1a, 9.2p, 9.3Aa, 9.3Ca, 9.5Ba, 10.1p, 10.3o, 13.8ZOp, 5.4a, 12.1a, 14.1Aa, 14.1Ap, 14.2p Opium poppy, Poppy
Paratecoma 5.8R, 14.6p White peroba
Parmelia 13.6Cp Shield lichen
Parthenium 9.7t, 10.6t, 12.1t Feverfew
Parthenocissus 12.2D Creeper, Virginia creeper
Passiflora 3.2Aa, 3.2Ap, 3.3Aa, 4.1Ca, 4.2a, 4.4Aa, 5.3Aa, 5.3Ba, 5.5Da, 5.8La, 5.9, 6.2a, 6.5a, 8.1p, 10.4o, 11.1Ip, 12.1a, 13.1a Passionflower
Pastinaca 3.2Ap, 6.5p, 7.3Bp, 7.3Bt, 8.1p, 9.3Ap, 10.4o, 10.4t, 10.5t, 12.1p Parsnip
Paullinia 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 10.2a Bread and cheese, Guarana
Pausinystalia 4.2a, 5.3Aa, 5.3Ba, 5.4Aa, 5.5Da, 5.8D, 5.8La, 11.1Ha Yohimbe
Pavonia 10.6o Rock rose
Peganum 3.2Aa, 3.3Aa, 4.1Ca, 4.2a, 4.4Aa, 5.3Aa, 5.3Ba, 5.5Da, 5.8La, 5.9, 6.2a, 6.4a, 6.5a, 9.3Gt, 12.1a, 13.1a Peganum
Pelargonium 6.5p, 10.3o, 10.4t, 14.1Ap, 14.5p
 Geranium, Pelargonium
Pelea 10.1p, 10.4p Melicope
Pelvetia 10.1o Channelled wrack (brown alga)
Pennisetum 7.1o, 11.2Fp, 13.5B Fountain grass, Kikuyu grass, Pearl millet
Penstemon 4.4Ap, 8.1p Beardtongue, Penstemon
Pentadiplandra 10.1o J'oublie
Pera 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp Jiqi, Pera
Pergularia 9.2a, 9.4Aa, 9.4Ba Pergularia, Sandspurry
Periandra 10.1t Clitoria, Periandra
Perilla 9.3Do, 10.1n, 14.1Ap, 14.5o, 14.5p, 14.5t
 Beefsteak plant, Perilla
Periploca 5.7C Silkvine, Periploca
Perriera 13.8W Perriera
Persea 4.4At, 7.3Ao, 7.3Bo, 10.1o, 11.1Bo, 12.2B, 12.2D, 14.1Ao Avocado, Bay
Petasites 4.4At, 5.7Gt, 10.6t Butterbur, Dock
Petilium 5.2Ba Petilium
Petrocoptis 9.1A Lychnis, Petrocoptis
Petrocosmea 11.2Gp Petrocosmea
Petroselinum 6.5p, 7.3Ao, 7.3Ap, 7.3Bp, 7.3Bt, 7.4p, 8.1p, 8.3Cp, 8.3D, 8.3F, 8.3Hp, 9.3Ap, 10.4o, 10.4t, 10.5p, 11.1Hp, 11.1Ip, 12.1p, 13.4Ap, 13.6Ap, 13.7Hp, 13.8C, 13.8Yp, 14.1Ap, 14.5p Parsley
Petunia 12.2D, 12.4A, 12.4B, 12.4D Petunia
Peucedanum 4.4Ap, 5.7Gp, 5.8W, 7.3Bp, 7.4p, 14.1Ap Biscuitroot, Dogfennel, Peucedanum
Peumus 3.1Aa, 8.1a, 14.2a Boldo, Peumus
Pfaffia 11.1Gt Jojo, Pfaffia
Phalaris 5.5Da, 10.6a, 10.6p, 13.8F, 14.6a
 Canarygrass
Pharbitis 12.2C, 13.1p, 14.2a Morning glory
Phaseolus 3.2Bp, 3.2Bo, 4.2a, 4.5A, 4.5C, 5.1Ap, 5.3Bp, 5.3Cp, 5.5A, 5.5Bo, 5.5Da, 5.7C, 5.8La, 6.1D, 6.2a, 6.5a, 7.3Ap, 7.3Cp, 7.4a, 8.1p, 8.3Co, 8.3Cp, 10.6t, 11.1Gp, 11.1Ip, 11.1It, 11.1Jp, 11.1Kp, 11.2Fp, 12.1a, 12.2A, 12.2D, 12.2E, 12.4B, 12.4E, 13.3, 13.5E, 13.5G, 13.5J, 13.5K, 13.5L, 13.5R, 13.8ZI, 14.2t, 14.6o Bean
Phebalium 6.5p, 8.1p, 9.3Ap, 12.1p Phebalium, Waxflower
Phellandrium 10.4t Water dropwort
Phellodendron 3.1Ba Cork tree
Phleum 5.7C Timothy
Phlomis 10.1t Jerusalem sage
Phoebe 5.3Ca Avispillo
Phoenix 3.1Aa, 3.2Bo, 3.3Ea, 5.5A, 10.1p, 11.1It, 11.1M, 12.3t Date palm
Phoradendron 9.1B, 12.2B, 12.4F Mistletoe

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- Phycanthus* 5.4a Phycanthus
Phyllanthus 3.2Ba, 4.3Ap, 4.3Bp, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p, 8.1p, 8.1t, 9.3Dp, 9.3Gt, 9.5Bp, 10.2p, 13.4Ap, 13.4Ht, 13.8Mt, 13.8Yt, 14.5p Leaf flower
Phyllarthron 7.3Cp, 9.3Fp, 9.5Bp, 9.7p Zahana
Phyllocladus 8.1p Celery-top pine, Phyllocladus
Physalis 7.3Bt, 13.1a, 14.2t Ground cherry
Physena 9.7t Physena
Physostigma 3.1Aa, 6.4a Calabar bean, Physostigma
Phytelphas 10.1o Yarina
Phytolacca 6.1A, 9.1A, 12.2C, 14.1Ao Pokeweed
Picea 5.8Q, 7.3Ap, 8.1p, 8.3M, 10.4t, 10.5t, 10.6t, 12.2D, 13.4Ip, 13.6Ap, 14.1Ap, 14.2p Spruce
Picalima 5.6a Picalima
Picrasma 10.2t Quassia
Picrodendron 3.2Bt Jamaica walnut
Picrorhiza 5.8R, 8.3M, 10.2p, 13.4Ip Kharbagechindi, Picrorhiza
Pieris 4.2t, 5.8J, 8.1p, 8.3Cp, 10.2p, 11.1Hp, 11.1Ip, 11.2Gp, 13.6Ap, 13.7Ep, 13.7I Lily of the valley bush, Pieris
Pierreodendron 9.2t Mannia, Pierreodendron
Pilocarpus 3.1Ba, 5.2Aa Pilocarpus
Pimelea 5.1Ap, 7.4p, 8.1p, 8.2t, 8.3Cp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ap, 13.7Hp, 14.1Ap Riceflower
Pimenta 10.4p, 12.1p Pimenta, Pimentus
Pimentum 6.1F, 10.4p, 13.8Qp, 14.1Ap Pimentum
Pimpinella 7.3Bp, 7.3Bt, 9.3Ap, 12.1p, 10.1p, 10.4p, 10.5p, 11.1Bp, 14.5p Burnet, Saxifrage
Pinus 3.2Ap, 5.7C, 5.8H, 5.8Q, 5.8R, 6.4t, 6.5p, 7.3Ap, 7.3Bp, 7.4p, 8.1p, 9.3Dp, 9.7p, 10.4o, 10.4p, 10.4t, 10.5p, 10.5t, 10.6t, 11.1At, 11.1Hp, 11.1Ip, 11.1It, 11.1Jp, 11.1Kp, 11.1Kt, 11.2Fp, 11.2It, 12.1p, 12.2D, 12.4B, 13.6Ap, 13.6Cp, 13.7Hp, 13.8W, 13.8Yp, 13.8ZN, 13.8ZOp, 14.1Ap, 14.1At, 14.2p, 14.5p Pine
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Piptadenia 5.5Da, 5.8La, 6.5a Carbonero, Piptadenia
Piptanthus 3.1Aa, 4.2a, 4.3Aa, 4.3Ca Evergreen laburnum
Pistacia 8.1t, 10.3o, 11.1Ip, 13.4Dp Pistache, Pistachio
Pisum 3.1Ao, 3.2Bo, 3.3Bo, 5.2Ao, 5.3Bp, 5.3Cp, 5.5A, 7.4a, 7.4p, 8.1p, 8.3Cp, 9.1A, 10.3o, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 12.2A, 12.2E, 12.4A, 12.4E, 13.5G, 14.1Ao, 14.2t, 14.6p Pea
Pithecolobium 9.3Aa Manila tamarind
Pityrogramma 3.2Ap, 8.1Ao, 8.1p, 13.7Hp, 13.8R, 14.5p Goldback fern
Plagiobothrys 9.3Fp Popcorn flower
Plantago 3.2Ap, 5.2Bo, 5.7C, 5.7I, 7.4p, 8.1p, 8.3Cp, 8.4t, 9.7t, 10.1o, 10.2t, 10.6t, 11.1Jp, 13.1p, 13.8Kp, 14.1Ap, 14.1At, 14.2p, 14.2t, 14.5p, 14.6o Isphagula, Plantain, Ribwort
Platanus 7.4p, 8.1p Maple, Planetree, Sycamore
Platycapnos 4.1Aa, 4.1Ca, 4.3Aa, 4.3Ba, 4.4Aa Platycapnos
Platycara 8.1p Dyetree
Platycodon 5.8D Balloon flower, Platycodon
Plectranthus 3.2Bt, 10.2t, 10.4o Mexican mint, Plectranthus
Plocama 6.6A Balo
Plumbago 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp, 14.5p Leadwort
Plumeria 9.3Ct Graveyard flower, Plumeria
Podanthus 14.2t Footflower, Mitique, Podanthus
Podocarpus 3.2Ap, 5.3Cp, 5.4p, 6.5p, 7.4p, 8.1p, 8.3Hp, 9.5Bp, 10.2p, 10.5t, 11.1Gt, 13.4Ip, 14.1Ap, 14.5p, 14.6p Plum pine, Podocarpus, Yellowwood
Podachaenium 7.3At Giant tree daisy, Podochaenium
Podophyllum 4.1Cp, 4.5A, 5.1Ap, 7.1p, 7.3Ap, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.2p, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.6Ep, 11.1E, 11.1Gp, 11.1Hp, 14.6p Mayapple
Pogonopus 9.2a, 9.3Aa, 12.1a Pogonopus
Pogostemon 10.4p, 10.4t Patchouli, Pogostemon
Polianthes 9.2a Tuberose, Polianthes
Polygala 5.7B, 5.8V, 13.7Et, 14.6t Milkwort, Polygala
Polygonatum 6.3o, 9.1B, 9.7t, 14.6t, 12.2B, 13.8Z Solomon's seal
Polygonum 4.1Ap, 5.1Ap, 5.8H, 5.9, 6.5p, 7.3Aa, 7.3Ap, 7.4p, 8.1p, 8.4p, 9.3Ap, 9.3Dp, 9.7p, 10.6t, 11.1Ip, 11.2An, 12.1p, 13.4Ap, 13.4Dp, 13.6Ap, 13.6Cp, 13.8Jp, 13.8ZN, 13.8ZOp, 14.1Aa, 14.1Ap, 14.2p, 14.5p Knotweed, Smartweed
Polypodium 5.7Go, 7.4t, 10.1t, 11.1Gt Polypody
Poncirus 8.1p, 14.2p, 14.5p Hardy orange, Poncirus
Populus 3.2Ap, 4.3Co, 6.5p, 7.3Ap, 7.4p, 8.1p, 9.7p, 9.5Ap, 10.4o, 10.4t, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 12.2D, 13.5K, 13.7Hp, 13.8Yp, 14.1Ap, 14.2p, 14.5p Aspen, Cottonwood, Poplar
Portulaca 5.3Bp, 5.3Cp, 14.6t Purslane
Potentilla 4.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.6p, 7.3Bp, 13.6Bp, 13.8ZA, 14.5p Cinqufoil
Pothomorphe 9.3Fp Caapeba
Prangos 5.8W, 7.3Bp, 14.1Ap Prangos

- Prestonia* 5.5Da Babeira, *Prestonia*
Primula 4.1Cp, 5.1Ap, 7.3Cp, 7.4p, 8.1p, 8.3Cp,
 9.3Cp, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.7p,
 10.1o, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp,
 11.2Ap, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap,
 13.7Hp, 13.8Yp, 13.8ZB, 14.1Ap Primrose
Pristimera 7.3At, 14.1At *Pristimera*
Prosopis 5.5Da, 5.8La, 6.5a, 10.1o, 13.5K, 14.2p
 Mesquite
Protea 10.5p *Protea*
Prunella 6.4t, 7.2B, 8.1t, 9.3Ct, 9.3Dt, 9.3Ft,
 9.3Gt, 9.5Bt, 9.7t, 11.2Gp, 13.4At, 13.4Ht,
 13.8Jt, 14.1Ap, 14.1At, 14.2p, 14.5p
 Selfheal
Prunus 3.2Ap, 3.2Bp, 4.2p, 4.5A, 4.5C, 5.1Ap,
 5.5Dp, 5.7C, 5.8O, 7.3Ap, 7.3Cp, 8.1p,
 8.3Cp, 9.3Do, 9.3Gp, 9.7p, 10.1o, 10.2o,
 10.3o, 10.4o, 10.4t, 10.5o, 10.5t, 10.6o, 10.6t,
 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2E, 12.4E,
 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C,
 13.8D, 14.1Ap, 14.2p, 14.2t, 14.5o, 14.5p
 Almond, Apricot, Cherry, Nectarine, Peach,
 Plum
Psacalium 14.6o, 14.6t Indian bush
Pseudocinchona 11.1Ha *Corynanthe*,
Pseudocinchona
Psedotsuga 8.1p, 12.4E Douglas fir
Pseudoxandra 5.4a, 5.5Da *Crematosperma*,
Unonopsis
Psidium 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.6p, 7.3Bp,
 8.1p, 9.3Fp, 9.3Gp, 9.5Ap, 11.2Gp, 12.1p
 Guava
Psophocarpus 4.3At, 6.1B, 6.1D, 8.1t, 9.3Dt,
 9.3Ft, 12.2A, 13.4At, 13.4C, 13.5K, 14.1At
Psophocarpus, Winged bean
Psoralea 3.2Bp, 6.5p, 7.3Ap, 7.3Cp, 8.1p, 9.3Ap,
 9.3Dp, 9.3Gp, 9.7p, 11.1Ip, 12.1p, 13.6Bp,
 14.6t Babchi, Breadroot, Scurfpea
Psorospermum 8.1p, 8.4p, 9.3Ap, 9.3Gp, 12.1p
Psorospermum
Psychotria 4.4Ao, 5.7C, 5.7F, 5.8U, 8.3Ca, 8.3K,
 8.3P, 9.2a, 9.3Aa, 12.1a Wild coffee
Psidium 7.4t, 9.3Do, 12.1o, 14.5o, 14.5p
 Bracken fern
Pteridophyllum 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 5.3Aa,
 5.3Ba, 5.5Da, 5.8Xa, 6.1A, 6.1B, 6.4a, 8.1a,
 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 14.1Aa Brake
 fern
Pteris 8.1Ao, 11.1Gt, 13.8R, 14.5p Cretan
 brake
Pterocarpus 5.3Cp, 5.4p, 5.8R, 6.5p, 6.6A, 7.3Ap,
 7.4p, 8.1p, 8.3Cp, 8.3Hp, 10.2p, 13.4Ip,
 13.8C, 14.5p, 14.6p Dragon's blood tree,
Pterocarpus
Pterocarya 10.1t Chinese wingnut, *Pterocarya*
Pterotaberna 5.2Ba, 5.7Ea *Pterotaberna*,
Tabernaemontana
Ptilota 12.2B *Ptilota* (red alga)
- Pueraria* 3.2Bp, 4.5A, 7.3Ap, 7.3Cp, 8.1p, 9.3Gp,
 11.1Ip, 11.1It, 11.2Fp, 13.4Ap, 13.6Ap, 14.5p
 Kudzu, Kwao keur
Pulicaria 9.5Bp, 14.5p False fleabane
Punica 7.3Ap, 7.3Bp, 8.1t, 9.5Bp, 10.2p, 11.1Bo,
 11.1It, 13.8Ip, 13.8Jp, 13.8ZJ, 14.2p, 14.5p
 Pomegranate
Putterlickia 9.6Eo *Putterlickia*
Pycnanthus 14.6t Ilomba
Pycnarrhena 7.1a *Batania*, *Pycnarrhena*
Pyralaria 4.4Ao, 7.2Ao, 12.4F Buffalo nut,
Pyralaria
Pyrus 6.4t, 8.1t, 9.3Ct, 9.3Dt, 9.3Ft,
 9.3Gt, 9.5Bt, 9.7t, 10.3o, 10.4t, 10.5t,
 12.4E, 13.3, 13.4At, 13.4Ht, 13.4Ip, 13.8Jt,
 14.1At Pear
Quassia 10.2p, 10.2t, 13.8W *Quassia*
Quercus 4.1Bp, 4.3Ap, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p,
 5.5Dp, 5.6p, 7.3Ap, 7.3Bp, 7.4p, 8.1p, 8.1t,
 8.3Cp, 9.5Ap, 9.5Bp, 10.1o, 10.4o, 10.6o,
 13.1p, 13.4Dp, 13.4Ip, 13.6Ap, 13.6Bp,
 13.8Jp, 13.8Qp, 13.8ZB, 13.8ZJ, 13.8ZO, p,
 14.1Ap, 14.5p Oak
Quisqualis 3.3Ba, 3.3C, 5.5Ba Rangoon creeper
Ranunculus 10.2o, 14.3Bo Buttercup
Raphanus 7.1o, 10.4o, 10.6o, 12.4A, 12.4B,
 12.4C, 14.4A Radish
Rauwolfia 3.4Aa, 4.2a, 4.4Aa, 5.3Aa, 5.3Ba,
 5.4a, 5.5Da, 5.8D, 5.8La, 6.3a, 6.4a, 7.4a,
 9.3Aa, 9.3Ga, 9.6Ea, 11.1Ha, 12.1a, 13.7Ha
Rauwolfia
Reboulia 14.2p *Reboulia*
Rehmannia 3.2Bo, 5.5A, 7.3Do, 10.1o, 10.2t,
 12.2D, 12.4E, 14.1Ap Chinese foxglove,
Rehmannia
Reineckia 7.4t *Reineckia*
Relbunium 8.1p, 9.5Ap *Relbunium*
Remijia 4.2a, 4.3Ca, 6.5a, 10.2a, 11.1Ha,
 13.7Ha, 13.8Qa *Cuprea*
Renealmia 10.4t Narciso colorado, *Renealmia*
Retama 9.3Gp Bridal broom
Retanilla 8.1a *Retanilla*, *Trevoa*
Rhagodia 11.1Gt Climbing saltbush, Coastal
 saltbush
Rhamnus 5.1Ap, 5.7D, 7.4p, 8.1p, 8.3B, 8.4p,
 9.3Ap, 9.3Gp, 12.1p, 14.2p Buckthorn
Rhaponticum 11.1Gt Globe thistle, *Rhaponticum*
Rheum 7.1o, 7.3Ap, 7.3Bp, 8.1p, 8.3Cp, 8.4p,
 9.2p, 9.3Ap, 9.3Gp, 9.5Ap, 10.3o, 12.1p,
 13.1p, 13.4Dp, 13.4Fp, 13.4Ip, 13.6Dp,
 13.8ZJ *Rhubarb*
Rhinanthus 13.8ZP Yellow rattle
Rhodiola 13.4Ip, 13.4It *Stoncrop*
Rhododendron 4.2t, 4.3At, 5.1Ap, 5.8J,
 7.3Ap, 7.3Bp, 7.3Bt, 8.1p, 8.1t, 8.3Cp,
 9.3Dt, 9.3Ft, 9.3Gt, 9.7t, 10.2p, 11.1Hp,
 11.1Ip, 11.2Gp, 13.4At, 13.4At, 13.4C,

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- 13.6Ap, 13.7Ep, 13.7I, 13.8Jt Azalea,
Rhododendron
- Rhus* 3.2Ap, 4.1Bp, 4.1Cp, 6.1F, 7.4p, 8.1p,
9.5Ap, 9.5Bp, 9.7p, 11.2Fp, 13.1p, 13.4Ap,
13.4Fp, 13.6Bp, 13.8ZOp, 14.1Ap, 14.5p
Poison ivy, Sumac
- Ribes* 3.2Bo, 5.1Ap, 6.3o, 8.1p, 10.3o, 14.6o
Blackcurrant, Currant, Gooseberry
- Richadella* 13.5K Miracle berry, Synsepalum
- Ricinus* 3.2Aa, 3.3Aa, 5.8Lo, 7.1o, 9.1B, 9.7o,
10.3o, 12.2B, 12.4B, 12.4C, 14.1Ao Castor
bean, Ricinus
- Rivea* 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 8.3O
Christmas vine, Elephant creeper
- Robinia* 4.1Cp, 7.3Co, 7.4p, 8.1p, 8.3Cp, 10.4o,
10.4p, 10.6o, 11.1Bp, 12.2A, 13.4Ap, 14.1Ap,
14.5p Locust
- Rollinia* 13.6Bo Amazon custard apple,
Rollinia
- Rosa* 4.1Bp, 4.3Ap, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p,
5.6p, 5.7A, 5.7Ep, 5.8R, 6.1F, 8.1p, 9.7t,
10.4o, 10.4p, 10.4t, 10.5t, 10.6t, 11.2Ct,
13.1p, 13.6Bp, 13.8Qp, 13.8ZOp, 13.8ZJ,
14.1Ap, 14.2o Rose
- Rosmarinus* 3.2Bt, 5.1Ap, 5.2At, 7.2B, 7.3Bp,
7.3Bt, 7.3Cp, 7.4p, 8.1p, 8.1t, 9.3Ct, 9.3Dt,
9.3Ft, 9.3Gt, 9.5Ap, 9.5Bt, 10.4t, 10.5t,
11.2Gp, 13.1t, 13.4At, 13.4Hp, 13.4Ht,
13.7Ho, 13.8Jt, 13.8Yp, 14.1Ap, 14.1At,
14.2p, 14.2t, 14.5p Rosemary
- Rubia* 8.1p, 9.5Ap, 12.1p, 13.6Dp Madder, Rubia
- Rubus* 4.3Ap, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp,
5.6p, 5.7Ep, 7.3Bp, 8.1t, 10.1o, 10.1t, 10.3o,
10.4o, 13.3, 13.6Bp Blackberry, Drewberry,
Raspberry, Rubus
- Rudua* 14.2t Bean, Phaseolus
- Rumex* 8.1p, 8.4p, 9.3Ap, 9.3Gp, 12.1p, 14.6p
Dock, Sorrel
- Ruscus* 13.4Ht Butcher's broom, Jew's myrtle,
Knee Holly, Pettigree, Sweet broom
- Ruta* 4.4Aa, 5.1Aa, 5.5Da, 5.8R, 5.9, 7.3Bp,
8.1p, 8.2p, 9.3Ap, 10.4o, 10.4p, 10.5p, 12.1a,
12.1p, 13.4Ap, 13.6E, 13.6F, 13.6G, 13.8Jp,
14.1Ap, 14.2p, 14.5p Rue
- Ryania* 4.4Aa, 4.4E Ryania
- Saccharum* 10.1o, 10.3o Plume grass, Sugar cane
- Salacia* 13.1o, 14.5t Salacia
- Salix* 5.1Ap, 5.5Dp, 7.4p, 8.1p, 8.3N, 10.2p,
11.1It, 11.2Gp, 12.2E, 13.5K, 13.8ZA,
14.1Ap, 14.2p, 14.5p Willow
- Salpianthus* 5.2Ao Salpianthus
- Salsola* 11.1E Russian thistle
- Salvia* 3.2At, 3.2Bt, 4.1Bp, 4.4Ap, 5.1Ap, 5.2At,
5.7C, 5.8C, 5.8M, 6.1F, 6.4t, 7.2B, 7.3Bt,
8.1t, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Ap, 9.5Bt,
10.4t, 11.1Jt, 11.2Gp, 13.1t, 13.4At, 13.4Hp,
13.4Ht, 13.8Jt, 13.8Yp, 13.8ZF, 14.1Ap,
14.1At, 14.2p, 14.2t, 14.5p, 14.5t, 14.6o,
14.6p Sage
- Samanea* 5.3Bp, 5.3Cp Raintree
- Sambucus* 3.1Aa, 9.1A, 9.1B, 10.4o, 10.4t, 12.2B,
12.2C, 12.2D, 12.4E, 14.5o Elderberry
- Sanguinaria* 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 5.3Aa,
5.3Ba, 5.5Da, 5.8Xa, 6.1A, 6.1B, 6.4a, 7.4a,
8.1a, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 14.1Aa
Bloodroot
- Sanguisorba* 5.7C, 5.7Gp, 9.3Fp, 9.3Gp, 13.6Bp
Burnet bloodwort, Greater burnet
- Sanicula* 7.2B, 9.5Ap, 11.2Gp, 13.4Hp, 14.1Ap,
14.2p, 14.5p Blacksnake root, Sanicle
- Santalum* 3.2Bo, 5.4t, 5.5Dt, 5.6t, 10.4t
Sandalwood
- Sapium* 8.2t, 14.1Ap Milktree
- Saponaria* 9.1A, 9.5Ao Soapwort
- Saposhnikovia* 7.3Ao, 7.3Bo, 7.3Bt Saposhnikovia
- Saraca* 9.7o, 12.2B Saraca
- Sarcococca* 6.4a Sarcococca
- Sargassum* 3.1Aa, 4.2a, 4.3Aa, 4.3Ca, 5.8H,
14.5p Sargassum
- Sarothamnus* 3.1Aa, 4.2a, 4.3Ca, 14.5p Broom,
Cytisus
- Sarracenia* 3.1Aa, 5.7Ea Pitcher plant
- Sassafras* 3.2Bp, 6.1F, 7.3Ap, 8.1a, 8.1p, 10.4p,
11.1E, 12.1p, 13.8Qp, 14.1Ap, 14.2a
Sassafras
- Satureja* 5.7Gt, 14.1Ap, 14.6o Savory
- Sauromatum* 10.4a, 10.5p, 14.1Ap, 14.3A
Sauromatum
- Saussurea* 5.7C, 7.3At, 7.3Bt, 8.2t, 13.8Mt
Costus, Sawwort
- Scaphyglottis* 7.3Bp Hexisea, Scaphyglottis
(orchid)
- Schaefferia* 7.3At, 9.2t, 9.3At, 12.1t, 14.1At
Florida boxwood, Schaefferia
- Schefflera* 4.4Ao, 5.2At, 5.2Bo, 5.4t, 5.5Do,
5.5Dt, 7.3Ao, 14.1Ao Matchwood, Schefflera
- Schinopsis* 7.4p, 8.1p Quebracho, Scinopsis
- Schinus* 4.1Bp, 13.1p, 13.6Bp, 13.8ZOp, 14.1Ap
Peppertree
- Schisandra* 9.5Bp, 9.5Bt Schizandra
- Schizobium* 13.5K Brazilian firetree
- Schoenocaulon* 4.2a, 12.3t Feathershank
- Schoepfia* 12.1o Schoepfia
- Sciadotenia* 3.1Ba Sciadotenia
- Scilla* 4.1Ct Scilla, Squill
- Sclerocarya* 6.1F Sclerocarya
- Scelopendrium* 11.2Bo, 14.1Ao Hart's tongue fern
- Scoparia* 13.1t Broomwort, Licorice root
- Scopolia* 3.1Ba, 5.2Ba, 13.1a Scopolia
- Scorzonera* 5.8R Scorzonera
- Scrophularia* 10.2t Figwort
- Scutellaria* 3.2Ap, 5.7C, 5.7J, 7.3Ap, 8.1p, 9.3Gp,
9.5Ap, 9.5Bp, 9.7p, 11.1Jp, 13.1p, 13.8Kp,
14.1Ap, 14.5p Skullcap
- Sebastiania* 14.1Ap Mexican jumping bean

- Secale* 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 8.1p, 8.3O, 11.1Jp, 12.4E, 13.2, 13.5Q Rye
Sechium 9.1A Chayote, Sechium
Securidaca 3.2Ba, 10.2o Easter flower, Securidaca
Securinega 3.2Ba Securinega
Sedum 3.1Aa, 3.1Ba, 6.1G, 6.2a, 10.2a Stonecrop
Selaginella 7.4p, 9.5Bp, 13.8ZD Spike moss
Selenicereus 3.1Ba Queen of the night cactus
Selinum 9.3Ap, 12.1p Selinum
Selliguea 10.1p, 10.1t Selliguea (fern)
Senecio 10.5a, 10.6t Ragwort
Senna 5.7Ea, 8.1p, 8.4p, 9.3Ap, 10.1o, 12.1p Senna
Senra 7.3Ap, 14.1Ap Senra
Sequoia 7.3Ap Redwood
Serenoa 11.1At, 11.1Bo Saw palmetto, Serenoa
Serratula 11.1Gt Saw wort
Sesamum 3.3Ao, 5.3Ba, 5.8Lo, 14.1Ap, 14.2o Sesame
Sesei 8.2p Sesei
Seseli 7.4p, 7.4t, 9.3Ap, 10.4t, 10.5t, 12.1p Moon carrot, Seseli
Setaria 7.1o, 13.5F Bristlegrass
Shepherdia 9.5Bp Buffalo berry
Shorea 8.1t Sal tree, Shorea
Sickingia 3.2Aa, 4.4Aa, 5.3Aa, 5.5Da, 5.8La, 5.9, 6.2a, 6.5a, 12.1a Simira
Sida 6.4a Fan petals
Sideritis 7.3At, 7.3Bp, 14.1Ap, 14.1At, 14.5p, 14.6p Ironwort
Silybum 7.3Bp, 8.1p, 13.7Hp, 14.1Ap, 14.2p, 14.5p, 14.6p Milk thistle
Sinapis 5.5Bo, 5.8V, 7.1o, 10.4p, 12.4A, 12.4C, 13.5I, 13.5M Mustard
Sinomenium 5.1Aa, 7.3Ba, 8.3J, 8.3Q Orient vine
Siphocampylus 5.6a Siphocampylus
Siratia 10.1t Siratia
Sisymbrium 10.4p Flixweed, Hedge mustard
Sisyrinchium 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp Blue-eyed grass, Grass widows
Skimmia 5.5Da, 8.2t, 12.1a Skimmia
Smilax 7.4p, 7.4t, 10.2p, 10.2t, 12.3t Carrion flower, Green brier, Sarsaparilla, Smilax
Solanum 3.2Aa, 3.2An, 3.3Ea, 4.3At, 4.4E, 5.3Bp, 5.3Cp, 5.7F, 5.8D, 5.8La, 5.8R, 6.4a, 6.4o, 6.5a, 8.1a, 8.1t, 8.3Co, 10.6o, 10.2a, 10.3o, 10.4o, 10.4t, 10.5a, 10.5t, 10.6o, 10.7, 11.1It, 11.2It, 12.2B, 12.2C, 12.2D, 12.2E, 12.4A, 12.4D, 13.3, 13.5A, 13.5B, 13.5D, 13.5G, 13.5K, 13.5N, 13.5O, 13.6Ao, 13.7Ha, 13.8W, 14.2p, 14.5p, 14.6o Eggplant, Horse nettle, Huckleberry, Nightshade, Potato, Tomato
Solenostemma 14.5p Argel
Solidago 10.4p, 13.4Ht Goldenrod
Sophora 3.1Aa, 3.1Ba, 3.2Bp, 4.4Ap, 4.5A, 4.5C, 5.1Ap, 5.6a, 5.9, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Gp, 9.7p, 10.5a, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2A, 13.4Ap, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 14.1Ap, 14.5p, 14.6a Necklace pod, Sophora
Sorbus 8.1p, 8.3Cp, 10.1o Mountain ash
Sorghum 10.1o, 12.4A, 13.5B, 13.2 Sorghum
Soymda 4.1Cp, 7.3Cp, 7.4p, 8.1p, 9.3Cp, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.7p, 11.1Bp, 11.1Hp, 11.1Jp, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap, 13.8Yp, 13.8ZB, 14.1Ap, 14.5p, 14.6p Indian mahogany
Sparaxis 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp Wandflower
Spartina 12.4D Cordgrass
Spartium 3.1Aa, 3.2Ap, 4.2a, 4.3Aa, 4.3Ca, 14.6a Broom
Spinacia 3.1Ao, 3.3Ao, 5.2Ao, 5.7Ea, 5.8U, 7.1o, 9.1A, 10.3o, 10.5t, 11.1Gp, 11.1Gt, 11.1Ip, 11.1Jp, 11.1Kp, 12.4B, 10.3o, 13.4Ht Spinach
Spiraea 5.8R, 7.3Bt Meadowsweet, Spiraea
Spirogyra 13.1p Spirogyra
Spondias 5.3Ap Jewish plum, Mombin, Spondias
Stachys 10.2p, 14.1Ap, 14.2p, 14.5p Betony, Woundwort
Stachyurus 4.3Ap, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.6p, 7.3Bp, 13.6Bp Stachyurus
Stanleya 14.2o Prince's plume
Stauranthus 13.6E, 13.6F, 13.6G Stauranthus
Staurogyne 10.1t Staurogyne
Stellera 8.2t Stellera
Stemmadenia 3.2Aa, 3.3Aa, 3.4Aa, 4.2a, 5.6a Cojon de toro
Stemodia 13.8Yp Cenizo
Stephania 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.7Ga, 7.1a, 9.7a, 13.4Da Stephania
Sterculia 13.8N Sterculia
Stevia 4.4At, 8.2t, 8.3Ht, 10.1t, 10.2a, 11.1Jt, 14.6t Candyleaf
Stipa 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 8.3O Needlegrass
Stirlingia 4.3Co, 10.4o Stirlingia
Stizolobium 3.3Ba Cowitch
Strobilanthes 7.3Aa, 11.2Aa, 14.1Aa Persian shield
Strophanthus 4.1Ct Strophanthus
Strychnos 3.1Ba, 3.3Da, 5.2Aa, 5.2Ba, 5.3Aa, 9.3Aa, 9.3Ga, 9.7a, 10.2a, 10.2t, 12.1a Strychnine tree, Strychnos
Stylosanthes 14.2t Pencil flower
Styrax 10.1t Snowbell
Sullivantia 14.1Ap Corlwort
Swainsona 13.1a Sturt's desert pea
Swertia 5.2At, 5.2Ba, 5.2Bt, 9.3Ap, 9.3Cp, 9.3Ft, 9.5Bp, 10.2t, 12.1p, 13.4At, 13.4Ht, 13.8Jt, 14.6p Fräsera, Swertia
Symphonia 8.1p Chewstick
Symphytum 5.8R, 7.2B, 9.5Ap, 11.2Gp, 13.4Hp, 14.1Ap, 14.2p, 14.5p Comfrey
Symplocos 3.2Aa, 4.4Aa, 5.3Aa, 5.5Da, 5.8J, 5.8La, 5.9, 6.2a, 6.5a, 8.1p, 8.3Cp, 10.2p,

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- 11.1Hp, 11.1Ip, 11.2Gp, 12.1a, 13.6Ap,
13.7Ep, 13.7I Sweetleaf
Synsepalum 10.1o Miraculous berry, Synsepalum
Syzygium 4.3Ap, 4.3At, 5.2At, 5.3Ap, 5.3Bp,
5.4p, 5.5Dt, 5.6p, 5.8R, 6.1E, 7.3Bp, 8.1p,
8.1t, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.7t, 10.4p,
10.5p, 13.1t, 13.4At, 13.4C, 13.4Ht, 13.8Jt,
13.8Qp, 13.8ZJ, 14.1Ap, 14.1At, 14.2p Clove,
Syzygium
Tabebuia 7.3Ap, 7.3Cp, 9.3Fp, 9.3Gp, 9.5Bp,
9.7p, 14.6p Trumpet tree
Tabernaemontana 3.2Aa, 3.3Aa, 3.4Aa, 4.2a,
5.1Aa, 5.6a Milkwood
Tabernanthe 3.2Aa, 3.3Aa, 3.3Ea, 3.4Aa, 4.2a,
5.1Aa, 5.2Aa, 5.3Aa, 5.4a, 5.5Da, 5.6a, 6.3a
Bittergrass, Iboga, Leaf of God
Tagetes 4.1Cp, 8.1o, 8.1p, 9.3Dp, 9.3Gp, 9.5Ap,
9.5Bp, 10.4o, 10.4p, 10.4t, 12.1p, 13.6Ap,
14.1Ap Marigold
Tamarindus 5.5Da, 10.3o Tamarind
Tamarix 5.1Ap, 5.7C, 7.4p, 10.1o, 14.6p Tamarisk
Tanacetum 3.2Bt, 4.2t, 5.5Dt, 5.7C, 5.8C, 5.8N,
5.8O, 6.2t, 7.3At, 7.3Bp, 7.3Bt, 8.1t, 10.4t,
10.6t, 14.1Ap, 14.1At Feverfew, Pyrethrum,
Tansy
Taraxacum 8.2t, 9.2p 9.5Ap, 13.4Ht, 13.8ZOp,
14.1Ap, 14.2p Dandelion
Taxillus 14.5p Taxillus
Taxodium 3.2Bt, 8.1p Bald cypress
Taxus 4.4Aa, 5.3Co, 7.3Ao, 7.4p, 9.7o, 9.6Eo,
13.7Ha, 14.1Ap Yew
Teclea 5.1Aa Achacha, Ng bamu
Tecoma 10.4a Yellow bells, Yellow trumpet flower
Tectona 7.3Cp, 8.1p, 9.2p, 9.3Ap, 9.3Fp, 9.3Gp,
9.5B, 9.7p, 12.1p Teak, Tectona
Telekia 5.7C Yellow oxeye
Tellima 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.6p, 8.1p,
13.8ZJ Tellima
Telosma 10.1t, 10.2t Telosma
Teramnus 14.6p Blue wiss, Teramnus
Terminalia 4.1p, 9.3Fp, 9.5Bp, 10.3o, 13.1p,
13.6Bp, 13.8Ip, 13.8Jp, 13.8ZOp, 14.2p
Terminalia, Tropical almond
Tessaria 10.1p Arrowweed pluchea, Marsh
fleabane
Tetracera 9.3Dt, 9.3Ft Tetracera
Tetraclinis 7.3Ap Sandarac tree
Tetragonolobus 12.2A Tetragonolobus, Winged
bean
Teucrium 7.2B, 9.5Ap, 9.7p, 10.2t, 10.6t, 11.2Gp,
13.4Hp, 14.1Ap, 14.2p, 14.5p Germander,
Woodsage
Thalictrum 3.1Ba, 3.3Da, 4.4Aa, 5.1Ap, 5.2Ba,
5.3Aa, 5.3Ba, 5.4a, 5.5Da, 6.1B, 6.4a, 7.4p,
9.3Aa, 9.5Ba, 12.1a, 13.7Ha Maid of the
mist, Meadow rue
Thapsia 4.1At, 8.2t, 10.5t Drias
Thaumatococcus 10.1o, 12.4E Miracle fruit,
Thaumatococcus
Theobroma 3.3Ea, 3.4Bo, 4.3Ba, 5.1Aa, 5.3Ba,
5.3Ca, 5.4a, 5.5Da, 5.6a, 5.8F, 7.4a, 10.5a,
13.5K, 13.6Ba, 13.8F, 14.5p, 14.6a Cacao,
Cocoa, Theobroma
Thermopsis 3.1Aa, 3.1Ba Golden banner
Thesium 4.1Ct Flaxleaf, Thesium
Thespesia 4.1Ap, 7.1t, 7.4p, 8.1p, 8.1t, 8.3Cp,
9.3Dt, 11.1E, 11.1Hp, 14.1At, 14.2p, 14.6p
Portia tree, Seaside mahoe
Thevetia 4.1Ct Lucky nut, Thevetia
Thladiantha 10.1t Manchu tuber gourd,
Thladiantha
Thuja 3.2Bt, 5.8C, 8.1p, 10.4p, 10.4t, 13.4Gt,
14.1At Arborvitae, Red cedar
Thujopsis 3.2Bt, 5.8C, 8.1p, 10.4p, 10.4t, 13.4Gt,
14.1At Asahi, Hiba arborvitae
Thymelea 8.2t Thymelea
Thymus 3.1Bt, 4.5A, 4.5C, 5.1Ap, 5.2At, 7.2B,
7.3Ap, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.1t, 8.3Cp,
9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Bt, 10.4t, 10.5t,
11.1Hp, 13.1t, 14.1Ap, 14.5p, 14.6p, 14.6t
Thyme
Tilia 3.2Ap, 7.4p, 8.1p, 8.3Cp, 13.8S, 14.5p
Basswood, Linden
Tillandsia 14.6o Airplant, Needleleaf, Spanish
moss
Tinomisium 3.2Bt, 3.3Dt Tinomisium
Toddalia 3.1Ba, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da,
6.1B, 6.4a, 9.3Aa, 9.5Ba, 12.1a Toddalia
Tonduzia 4.2a Alstonia, Madera del diablo
Torilis 8.3G, 8.3R Hedge parsley
Torresea 13.5G Torresea
Toxicodendron 14.1Ap Poison ivy, Poison oak
Trachelospermum 5.8R, 7.4p Climbing dogbane,
Trachelospermum
Trema 14.5p False lobelia, Trema, Tremotodon
moss
Tribulus 3.2Aa, 4.2a, 4.4Aa, 5.3Aa, 5.5Da,
5.8La, 5.9, 6.2a, 6.5a, 11.1At, 12.1a Puncture
vine
Trichilla 9.6Et, 10.2t Abre camino, Siguaraya,
Path opener
Trichocereus 5.3Bp, 5.5Dp, 6.3p, 6.5p Echinopsis,
Trichocereus, San Pedro Cactus
Trichosanthes 7.3Bo, 9.1A, 9.5Ao, 9.5Bt, 9.7t,
13.5P, 14.6o Snake gourd, Trichosanthes
Trifolium 3.2Bp, 4.1Cp, 4.2p, 4.5A, 4.5C, 5.1Ap,
5.7C, 5.8H, 6.5p, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp,
9.3Dp, 9.3Gp, 9.5Ap, 9.7p, 10.4t, 11.2Fp,
11.1Gp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp,
12.2A, 13.4Ap, 13.4Fp, 13.4Ht, 13.6Ap,
13.6Cp, 13.7Ep, 13.7Hp, 13.8C, 13.8ZN,
13.8ZOp, 14.1Ap, 14.2p, 14.5p, 14.6p Clover
Trigonella 7.4p, 14.1Ap, 14.6o Fenugreek

- Tripterospermum* 5.7B, 5.8V Tripterospermum
Tripterygium 7.3At, 9.5Bt Three wing nut,
 Thunder god vine
Triteleia 7.4t Triteleia
Triticum 3.2Aa, 3.2An, 5.5Da, 5.6o, 5.7C, 6.4p,
 7.2Ao, 8.1o, 8.3Co, 8.3Ho, 9.1A, 9.2o, 10.6a,
 11.1It, 11.2It, 12.2B, 12.2C, 12.2E, 12.4A,
 12.4B, 12.4E, 12.4F, 13.2, 13.4Hp, 13.5C,
 13.5E, 13.5F, 13.5K, 13.5Q, 13.8S, 14.2o,
 14.2t, 14.6o, 14.6t Wheat
Tsuga 5.7C, 7.3Ap, 8.1p, 13.6Ap, 14.2p Douglas
 fir
Tulipa 12.2B Tulip
Turraea 11.1Gt Turraea
Tussilago 4.4At, 5.7Gt, 7.3Bt, 8.2t, 14.2p, 14.5p
 Coltsfoot
Tylecodon 4.1Ct Tylecodon
Tylophora 9.2a Indian ipecac
- Ulex* 3.1Aa, 3.1Ba, 3.2Bp, 4.2p, 4.5A, 4.5C,
 5.1Ap, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Dp,
 9.3Gp, 9.7p, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp,
 12.2A, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp,
 13.8C, 14.1Ap, 14.6a Gorse
Umbellularia 10.4t California bay laurel
Uncaria 5.3Aa, 5.5Da, 8.3Cp, 10.3o, 13.8ZD,
 14.2p Gambir, Uncaria
Ungernia 3.1Aa, 6.4a Ungernia
Uragoga 9.2a Cephaelis, Ipecac
Urginea 4.1Ct Liverseed grass, Red squill
Urtica 3.1Aa, 3.1Ao, 3.3Ea, 4.3Co, 5.2Ao,
 5.5Da, 5.7Ea, 10.1o, 10.3o, 10.4o, 10.5a,
 10.5o, 10.6o, 12.2C, 12.2D, 13.5E, 13.8F,
 14.6a Nettle, Stinging nettle
Usnea 13.6Cp Beard lichen
Uvaria 4.1Aa, 4.1Ca, 4.3Aa, 4.3Ba, 4.4Aa
 Ilang-ilang
- Vaccaria* 9.1A, 11.1Io Soapwort
Vaccinium 4.1Cp, 6.4t, 7.3Cp, 8.1p, 8.1t, 9.3Cp,
 9.3Ct, 9.3Dp, 9.3Ct, 9.3Ft, 9.3Gp, 9.3Gt,
 9.5Ap, 9.5Bp, 9.5Bt, 9.7p, 9.7t, 9.3Gt, 9.5Ap,
 10.3o, 10.5p, 11.1Hp, 11.1Jp, 11.2Fp,
 13.4Ap, 13.4At, 13.4Fp, 13.4Ht, 13.4Hp,
 13.4Ip, 13.6Ap, 13.8Jt, 13.8Yp, 13.8ZB,
 14.1At, 14.2t, 14.5p Bilberry, Blueberry,
 Cranberry
Valeriana 3.2Ap, 3.2Bo, 5.5A, 5.6p, 6.4a, 6.6A,
 10.4o, 10.4t, 10.5o, 10.6o Valerian
Vanilla 5.8R, 10.4p, 10.5p, 14.2p Vanilla
Vanillosmopsis 7.3At Vanillosmopsis
Vatairea 12.2A Bitter angelim
Ventilago 8.1p, 8.4p, 9.3Ap, 9.3Gp, 12.1p
 Ventilago
Veratrum 4.2a, 5.8H, 6.4a, 6.5p, 7.3Ap, 8.1a,
 8.1p, 9.3Dp, 9.7p, 11.1Ip, 13.6Ap, 13.6Cp,
 13.7Ha, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p
 False hellebore
- Verbascum* 8.1p, 8.3Cp, 10.2p, 14.1Ap, 14.2p,
 14.5p Mullein
Verbena 10.4t, 10.5t, 10.6t, 14.5p Verbena,
 Vervain
Vermonia 7.3At, 10.2t, 10.6t Ironweed, Santa
 Maria
Veronica 10.2t, 10.6t Speedwell, Veronica
Vestia 14.1Ap Vestia
Vetiveria 5.8Xt, 10.4t Vetivergrass
Vexibia 5.6a Vexibia
Viburnum 3.2Ap, 7.4p, 14.1Ap, 14.5p
 Arrowwood, Viburnum
Vicia 3.2Bo, 3.3Ao, 5.5A, 8.1p, 8.3Cp, 11.1M,
 12.2A, 12.3t, 12.4A, 13.5A, 13.5G, 13.5N,
 13.6Ap, 13.8Qp, 13.8ZP, 14.1Ap, 14.2t, 14.6p
 Vetch
Vigna 3.2Bp, 7.3Ap, 7.3Cp, 9.5Ao, 9.5Bo, 10.1o,
 10.7o, 11.1Bp, 11.1Gp, 11.1Ip, 11.1Jp,
 11.1Kp, 12.2A, 12.4A, 13.4Ap, 13.5G, 13.5N,
 14.2t, 14.5p, 14.6o Cowpea, Mung bean
Vinca 6.3a, 9.6Ea, 13.4Ap, 13.7Ha, 14.5p
 Periwinkle
Vincetoxicum 9.2a Milkvine, Swallow wort
Viola 5.9, 8.1t, 10.4p, 13.4Ap, 13.8Jp, 14.1Ap
 Violet
Virola 5.5Da, 5.7Gp, 8.1p, 8.3Cp, 11.1Ip, 11.1Jp,
 11.1Kp, 11.2Bo, 11.2Fp, 13.6Ap, 13.8ZG
 Virola
Viscum 4.4Ao, 5.3Bp, 6.3p, 6.5p, 9.1B, 9.6Bn,
 9.7o, 10.1o, 12.2B, 12.2C, 12.4F, 13.4At,
 13.4Ht, 13.5E, 13.8Jt Mistletoe
Vitex 5.4t, 9.6Bt, 9.7p, 9.7t, 11.1At, 11.1Gt,
 11.2Fp, 14.5p Chaste tree
Vitis 4.1Cp, 5.8H, 6.5p, 7.3Ap, 7.3Bp, 8.1p,
 9.3Dp, 9.6C, 9.7p, 9.7t, 10.3o, 10.4a, 10.4o,
 10.4p, 10.4t, 10.5o, 10.5p, 10.5t, 10.6o, 10.6t,
 11.1Gp, 11.1Ip, 11.1It, 12.4D, 12.4E, 13.6Ap,
 13.6Cp, 13.8Kp, 13.8ZN, 13.8ZOp, 13.6Ap,
 13.8Qp, 14.1Ap, 14.2a, 14.2p, 14.6p Grape
Voacanga 3.3Aa, 3.3Ea, 3.4Aa, 4.2a, 5.1Aa,
 5.2Aa, 5.3Aa, 5.4a, 5.5Da, 5.6a, 6.3a
 Voacanga
Vriesea 14.5p Flaming sword, Painted feather
- Warburgia* 3.4Bt, 10.6t, 13.8ZP Fever tree,
 Warburgia
Wasabia 14.4A Wasibi, Wasibia
Wedelia 14.1Ap Creeping oxeye
Wikstroemia 8.2p, 8.2t False ohelo
Wisteria 12.2A, 13.5B, 14.2t Wisteria
Withania 5.3Bt Withania
Woodfordia 9.3Gp Dhai, Phool
- Xanthium* 10.5p, 10.6t Cocklebur
Xanthoceras 13.4Ap, 13.4At, 13.4Ht, 13.8Jt
 Yellowhorn
Xanthocercis 13.1a, 14.6o Mashatu tree, Nyala
 tree

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- Xanthorrhea* 9.2p, 9.3Ap, 9.3Gp, 12.1p Grasstree
Xanthoxylum 6.5p, 8.1p, 9.3Ap, 12.1p, 14.1Ap
Prickly ash
Xeranthemum 10.6t Immortelle
Ximenia 14.5o Fallow wood, Ximenia
Xylopia 3.3Da, 5.3Aa, 9.7t, 10.4o, 10.4p, 10.4t,
10.5t, 10.6t, 14.2p Ethiopian pepper
Xylorrhiza 14.2o Woody aster
Xynis 8.1p, 9.3Ap, 9.3Gp, 12.1p Yelloweyed grass
- Zaluzania* 7.3At, 10.6t Zaluzania
Zamia 7.4p, 14.1Ap Coontie, Zamia
Zanthoxylum 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba,
5.3Aa, 5.3Ba, 5.5Da, 5.7D, 5.8Xa, 6.1A,
6.1B, 6.4a, 7.3Bp, 7.4a, 8.1a, 8.3B, 9.3Aa,
9.3Ca, 9.5Ba, 12.1a, 14.1Aa, 14.6p Hercules'
club, Prickly ash
- Zea* 4.2o, 4.4E, 4.4Fn, 5.5Da, 5.8La, 6.5a, 7.4a,
8.3L, 10.2o, 10.3o, 10.4a, 10.4o, 10.4t, 10.6a,
10.6o, 10.6t, 11.1In, 11.1Io, 11.1It, 11.1Kp,
11.2Ct, 12.1a, 12.2D, 12.2E, 12.4B, 12.4E,
13.2, 13.5B, 13.5C, 13.5F, 13.5N, 13.5Q,
13.5R, 14.2t, 14.5p, 14.6o, 14.6p Corn,
Maize, Teosinte
Zephyranthes 9.2a Atamasco lily
Zingiber 3.4Bp, 4.1Ap, 4.2a, 4.3Cp, 5.7C, 6.1F,
7.3Ap, 7.3Bt, 8.1p, 9.7p, 10.1p, 10.4p, 10.4t,
10.6o, 10.6t, 13.6Ap, 14.1Ap Ginger
Zinnia 3.1Aa, 7.3At, 10.5a Zinnia
Ziziphus 10.1t Jujube, Lotebush
Zizyphusspina 14.6t Crown of thorns jujube
Zollikoferia 3.1Aa, 10.5a Zollikoferia
Zygophyllum 3.2Aa, 4.4Aa, 5.3Aa, 5.5Da, 5.8La,
5.9, 6.2a, 6.5a, 12.1a Beancaper

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- Aaronsohnia, *Aaronsohnia* 14.1Ao
Abo, *Hannoa* 10.2t
Abre camino, *Trichilla* 9.6Et, 10.2t
Acacia, *Acacia* 3.3Bo, 4.1Cp, 4.3Ap, 5.1Ap, 5.5Da, 6.3o, 7.4p, 8.1p, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.7t, 9.7p, 10.1o, 10.4p, 11.2Fp, 12.3t, 13.4Ap, 13.4Fp, 13.5K, 13.6Ap, 13.8H, 13.8Z, 14.1Ap, 14.5o, 14.5p
Acanthosicyos, *Acanthosicyos* 10.2t
Achacha, *Teclea* 5.1Aa
Adhatoda, *Adhatoda* 6.4a, 8.1p, 10.2p, 11.2Fp, 14.5p
Adiscanthus, *Adiscanthus* 4.4Aa, 12.1a
Aegopricum, *Maprounea* 9.3Ct, 9.5Bt
Aeolanthus, *Aeolanthus* 3.1Bt
African daisy, *Arctotis* 5.5Dt, 5.7C, 6.2t, 7.3At, 8.1t, 14.1At
African mammy apple, *Ochrocarpus* 8.1p
African teak, *Chlorophora* 7.4p, 8.1p, 9.3Cp, 11.1Hp, 13.4Ap, 13.6Ap, 13.8Qp, 13.8Yp, 14.1Ap, 14.2p, 14.5p
Agapanthus, *Agapanthus* 7.4t
Aglaiia, *Aglaiia* 5.7Gp
Agrimony, *Agrimonia* 5.5Dp, 7.4p, 8.1p, 10.2p, 13.8ZA, 14.1Ap, 14.2p, 14.5p
Airplant, *Tillandsia* 14.6o
Ajania, *Ajania* 13.8Zop
Akee, *Blighia* 13.8D
Akichouji, *Isodon* 7.3At, 10.2t, 10.5t, 10.6t, 11.1Jt
Alangium, *Alangium* 3.1Aa, 9.2a, 9.3Aa, 9.4Aa, 9.4Ba, 9.5Ba, 10.5a, 12.1a, 13.8L
Albizia, *Albizia* 5.3Bp, 5.3Cp, 9.5Bt, 13.5K, 13.8H, 14.1Aa
Albizzia, *Albizia* 5.3Bp, 5.3Cp, 9.5Bt, 13.5K, 13.8H, 14.1Aa
Alchornea, *Alchornea* 9.3Gp
Alchornea, *Bleekeria* 9.3Aa, 9.3Ba, 9.3Ga, 12.1a
Alder, *Alnus* 5.8R, 7.3Ap, 8.1p, 11.1Gt, 14.1Ap
Alexandrian laurel, *Calophyllum* 9.5Bp
Alfalfa, *Medicago* 7.4p, 8.1o, 8.1p, 8.2p, 8.3Cp, 10.3o, 11.1Gp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2It, 12.2A, 13.3, 13.4Hp, 13.5G, 14.1Ap, 14.2t, 14.6t
Alkanna, *Alkanna* 9.3Fp
Allanblackia, *Allanblackia* 8.1p
Almond, *Prunus* 3.2Ap, 3.2Bp, 4.2p, 4.5A, 4.5C, 5.1Ap, 5.5Dp, 5.7C, 5.8O, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Do, 9.3Gp, 9.7p, 10.1o, 10.2o, 10.3o, 10.4o, 10.4t, 10.5o, 10.5t, 10.6o, 10.6t, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2E, 12.4E, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 13.8D, 14.1Ap, 14.2p, 14.2t, 14.5o, 14.5p
Aloe, *Aloe* 3.1Aa, 5.8R, 7.3Bo, 9.2p, 9.3Ap, 9.3Gp, 9.7o, 10.2p, 10.4o, 10.6o, 11.1M, 12.1p, 12.2B, 12.3t, 14.6o
Alp lily, *Lloydia* 11.1Gt
Alphitonia, *Alphitonia* 14.1Ap, 14.1At
Alpine coltsfoot, *Homogyne* 10.6t
Alpinia, *Alpinia* 3.2Ap, 4.1Cp, 5.1Ap, 6.4t, 6.1F, 7.4p, 8.1p, 10.4p, 10.4t, 11.1Jp, 11.2Ap, 13.7Hp, 13.8B, 13.8C, 14.1Ap, 14.5p
Alsophila, *Alsophila* 13.8ZOp
Alstonia, *Alstonia* 3.2Ba, 3.3Da, 8.1t, 9.3Gt, 13.4At, 13.4Gt, 13.4Ht, 13.8Mt, 13.8Yt
Alstonia, *Tonduzia* 4.2a
Alumroot, *Heuchera* 12.4A
Amaranth, *Amaranthus* 9.1A, 12.2C, 13.2, 13.5N
Amarillo, *Ouatea* 14.5p
Amaryllis, *Brunsvigia* 9.2a
Amazon custard apple, *Rollinia* 13.6Bo
Amazone vine, *Banisteria* 3.2Aa, 3.3Aa, 4.1Ca, 4.2a, 4.4Aa, 5.3Aa, 5.3Ba, 5.5Da, 5.8La, 5.9, 6.5a, 12.1a, 13.1a
Ammi, *Ammi* 3.2Ap, 4.4Ap, 5.1Ap, 5.5Dt, 7.3Bp, 7.3Cp, 7.3Bt, 7.4p, 8.1p, 8.3Cp, 9.3Ap, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ap, 12.1p, 13.7Hp, 13.8Yp, 14.1Ap, 14.5p
Amorphophallus, *Amorphophallus* 10.4a
Anabasia, *Anabasis* 3.1Aa, 10.5a
Anabasis, *Anabasis* 3.1Aa, 10.5a
Ancistrocladus, *Ancistrocladus* 9.5Ba
Andira, *Andira* 14.1Ap
Anemarrhena, *Anemarrhena* 7.4p, 11.1Ip, 14.6p, 14.6t
Anemone, *Anemone* 10.2o, 14.3Bo
Aneura (liverwort), *Aneura* 10.6t
Angelica, *Angelica* 3.2Ap, 5.8R, 5.8W, 7.3Ao, 7.3Ap, 7.3Bo, 7.3Bp, 7.3Bt, 7.4p, 8.2p, 9.3Ap, 10.2p, 10.4o, 12.1p, 13.4Da, 13.5C, 14.1Ao, 14.1Ap

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- Angelica, *Archangelica* 3.1Ba, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 9.3Aa, 9.5Ba, 12.1a
Angophora, *Angophora* 6.5p
Angylocalyx, *Angylocalyx* 13.1a
Aniba, *Aniba* 12.1p
Anise tree, *Illicium* 3.2Bt, 5.7Gp, 6.1A, 8.3M, 10.1p, 10.3o, 10.4p, 10.4p, 12.1p, 13.8Qp
Anisochilus, *Anisochilus* 7.3Ap
Anodendron, *Anodendron* 7.3Ap, 14.1Ap
Anthocephalus, *Anthocephalus* 14.5p
Anthocercis, *Anthocercis* 5.2Ba
Apple, *Malus* 5.5Dp, 5.8J, 6.4t, 8.1p, 8.1t, 8.3Cp, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Bt, 9.7t, 10.2p, 10.3o, 10.4o, 10.4p, 10.4t, 10.5t, 10.6o, 10.6p, 10.6t, 11.1Hp, 11.1Ip, 11.1It, 11.2Ct, 11.2Gp, 12.4E, 13.4At, 13.4Ht, 13.6Ap, 13.7Ep, 13.7I, 13.8Jt, 14.1Ao, 14.1At, 14.2o, 14.2p, 14.2t, 14.5p
Apricot, *Prunus* 3.2Ap, 3.2Bp, 4.2p, 4.5A, 4.5C, 5.1Ap, 5.5Dp, 5.7C, 5.8O, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Do, 9.3Gp, 9.7p, 10.1o, 10.2o, 10.3o, 10.4o, 10.4t, 10.5o, 10.5t, 10.6o, 10.6t, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2E, 12.4E, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 13.8D, 14.1Ap, 14.2p, 14.2t, 14.5o, 14.5p
Araliopsis, *Araliopsis* 3.4Ba, 4.4Aa, 5.5Da
Arariba, *Arariba* 3.2Aa
Araucaria, *Araucaria* 7.3Ap, 7.4p, 9.5Bp, 11.1Ip, 14.5p
Arborvitae, *Biota* 5.1Ap, 5.7Gt
Arborvitae, *Thuja* 3.2Bt, 5.8C, 8.1p, 10.4p, 10.4t, 13.4Gt, 14.1At
Areca, *Areca* 5.2Aa, 6.3a, 12.1p, 13.4Dp, 14.6a
Argel, *Solenostemma* 14.5p
Argyreia, *Argyreia* 3.1Ba, 5.3Ba, 5.4a
Aristea, *Aristea* 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp
Arnebia, *Macrotomia* 9.3Fp
Arnica, *Arnica* 4.4B, 7.2B, 8.1p, 8.1t, 8.2t, 11.1Jt, 13.6Dt, 13.8Yp
Arrowweed pluchea, *Tessaria* 10.1p
Arrowwood, *Viburnum* 3.2Ap, 7.4p, 14.1Ap, 14.5p
Artichoke, *Cynara* 14.2p
Arum, *Arum* 10.4a, 12.2B, 13.8ZA
Asahi, *Thujopsis* 3.2Bt, 5.8C, 8.1p, 10.4p, 10.4t, 13.4Gt, 14.1At
Ash, *Fraxinus* 5.8R, 7.3Ap, 10.1o, 13.8ZOp, 14.1Ap, 14.1Ap, 14.2p, 14.5p
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- Cactus, Giant cactus, *Carnegiae* 5.3Ap, 5.4p, 11.2Jp
- Caesalpinia, *Mezoneuron* 14.2Bp
- Cajeput, *Melaleuca* 6.4t, 8.1t, 10.4t, 10.6t, 12.1p
Melaleuca, *Melaleuca* 6.4t, 8.1t, 10.4t, 10.6t, 12.1p
- Calabar bean, *Physostigma* 3.1Aa, 6.4a
- Calamint, *Calamintha* 10.2p
- Calcareous moss, *Mnium* 11.2Bo, 14.1Ao
- Calendula, *Calendula* 8.2t, 14.1Ao
- California bay laurel, *Umbellularia* 10.4t
- California poppy, *Eschscholtzia* 3.1Aa, 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba, 5.5Da, 5.6a, 5.8Xa, 6.1A, 6.1B, 7.4a, 8.1a, 9.3Ca, 12.1a
- Calophyllum, *Calophyllum* 9.5Bp
- Calotropis, *Calotropis* 4.1Ct
- Calumba, *Jateorrhiza* 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 9.3Aa, 9.3Fa, 9.5Ba, 10.2t, 12.1a
- Camass, *Camassia* 9.7t, 10.2t
- Camel's foot, *Bauhinia* 12.2A, 13.5E, 13.5K
- Camellia, *Camellia* 4.1Bp, 4.1Cp, 4.3Aa, 4.3Ap, 4.3Ba, 4.3Ca, 4.4Aa, 4.4D, 4.4E, 5.1Aa, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p, 6.1B, 6.1F, 6.1G, 6.2o, 6.5p, 7.3Ap, 7.3Bp, 7.3Cp, 7.4a, 7.4p, 8.1p, 8.2t, 8.3Cp, 8.3D, 8.3I, 8.3L, 8.3N, 8.3R, 9.3Cp, 9.3Dp, 9.3Fp, 9.3Gp, 9.5Ap, 9.5Bp, 9.7p, 9.7t, 10.2a, 10.2p, 10.4a, 10.4o, 10.4p, 10.4t, 10.5p, 10.5t, 10.6t, 11.1Ap, 11.1Bp, 11.1Hp, 11.1Gt, 11.1Ip, 11.1Jp, 11.2Fp, 12.3t, 13.1p, 13.4Ap, 13.4Fp, 13.4Gp, 13.4Hp, 13.4Ip, 13.6Ap, 13.6Bp, 13.7Ho, 13.7Hp, 13.7I, 13.8Qp, 13.8Yp, 13.8ZB, 13.8ZJ, 13.8ZO, 14.1Ao, 14.1Ap, 14.2a, 14.2p, 14.5p, 14.6p
- Camelthorn, *Alhagi* 5.5Dp, 9.2p
- Camphor tree, *Cinnamomum* 4.4Ap, 5.7K, 6.1F, 6.5p, 7.3Ap, 8.3Hp, 9.1A, 9.1B, 10.1p, 10.4p, 10.4t, 10.6t, 12.1p, 12.2B, 13.4Ip, 13.8Mp, 13.8Qp, 14.1Ap, 14.6p
- Campion, *Lychnis* 7.4t, 9.1A, 11.1Gt
- Campotheca, *Campotheca* 9.3Fa, 12.1a, 14.5p
- Camwood, *Baphia* 13.1a
- Canarygrass, *Phalaris* 5.5Da, 10.6a, 10.6p, 13.8F, 14.6a
- Candyleaf, *Stevia* 4.4At, 8.2t, 8.3Ht, 10.1t, 10.2a, 11.1Jt, 14.6t
- Candytuff, *Iberis* 11.1D, 11.1Gt
- Cannabis, *Cannabis* 5.7Ep, 5.8C, 6.3p, 11.1Ap, 13.6Bp
- Cannonball tree, *Couroupita* 7.3Aa, 11.2Aa, 14.1Aa
- Canola, *Brassica* 3.3Aa, 3.3Bp, 3.3C, 5.5Bo, 5.6a, 6.1C, 7.1o, 7.4p, 10.2a, 10.4o, 10.4p, 10.5o, 10.6o, 10.6t, 10.7, 11.1Gp, 11.1Gt, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Bo, 11.2E, 11.2Go, 12.2E, 12.4B, 12.4C, 13.5I, 13.5J, 13.5K, 13.5M, 13.5O, 13.7F, 13.8ZM, 14.1Ao, 14.2t, 14.4A, 14.6p
- Cape ash, *Ekebergia* 5.2At
- Caper, *Capparis* 10.1o
- Cappel, *Palicourea* 3.3Da, 6.5a, 6.5p, 13.8A
- Carambola, *Averrhoa* 10.3o, 14.1Ao
- Caraway, *Carum* 6.1F, 7.3Ao, 10.4t
- Carbonero, *Piptadenia* 5.5Da, 5.8La, 6.5a
- Cardamom, *Amomum* 10.4p, 14.1Ap
- Cardamom, *Elettaria* 5.7Et, 10.4t, 10.6t
- Carica, *Carica* 3.1Aa, 12.2D, 13.5B, 13.5K
- Carnation, *Dianthus* 9.1A, 10.4o, 10.5o, 10.6o, 11.1Jp, 11.1Kp, 11.2Gp
- Carpesium, *Carpesium* 7.3At
- Carrion flower, *Smilax* 7.4p, 7.4t, 10.2p, 10.2t, 12.3t
- Carrot, *Daucus* 3.2Ap, 4.5A, 4.5C, 5.1Ap, 6.5p, 7.3Ao, 7.3Bo, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.3Cp, 10.1o, 10.2p, 10.3o, 10.4p, 10.4t, 11.1Hp, 11.1Jp, 11.1Kp, 11.2Cn, 11.2Ct, 12.1p, 12.4B, 12.4E, 13.5B, 14.1Ao, 14.5p
- Carum, *Carum* 6.1F, 7.3Ao, 10.4t

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- Caryopteris, *Caryopteris* 10.2t, 10.6t
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Cassava, *Manihot* 3.3Ao, 9.1A, 10.2o, 13.6Bo
Cassia, *Cassia* 4.1Ca, 5.8H, 6.1F, 6.2a, 6.5p, 7.3Ap, 8.1p, 9.3Dp, 9.7p, 9.2p, 9.3Ap, 9.3Gp, 9.7p, 10.1o, 10.4p, 10.4t, 11.1Ip, 12.1p, 12.4A, 12.4B, 13.5J, 13.6Ap, 13.6Cp, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p
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Catalpa, *Catalpa* 5.7C, 10.2t, 10.6t, 13.8ZOp, 14.6p
Catchfly, *Lychnis* 7.4t, 9.1A, 11.1Gt
Catha, *Catha* 5.3Co, 6.2p, 6.3o, 7.3At, 11.2E, 13.1p, 14.1At
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Cauliflower, *Brassica* 3.3Aa, 3.3Bp, 3.3C, 5.5Bo, 5.6a, 6.1C, 7.1o, 7.4p, 10.2a, 10.4o, 10.4p, 10.5o, 10.6o, 10.6t, 10.7, 11.1Gp, 11.1Gt, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Bo, 11.2E, 11.2Go, 12.2E, 12.4B, 12.4C, 13.5I, 13.5J, 13.5K, 13.5M, 13.5O, 13.7F, 13.8ZM, 14.1Ao, 14.2t, 14.4A, 14.6p
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Cedar, *Chamaecyparis* 7.4p, 11.1Ip
Cedar, *Cupressus* 5.7Gt, 7.4p, 9.5Bp, 10.4t, 14.1At
Ceiba, *Ceiba* 14.1Ap
Celandrine, *Chelidonium* 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 5.8Xa, 6.1A, 6.1B, 6.4a, 6.6B, 7.4a, 8.1a, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 13.5B, 14.1Aa
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Centaur, *Erythraea* 10.2t
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Cephaelis, *Uragoga* 9.2a
Cephalotaxus, *Cephalotaxus* 7.3Ao, 9.2a, 9.7a
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Ceylon spinach, *Basella* 9.1A
Chaff flower, *Achyranthes* 11.1Gt
Chameleon, *Houttuynia* 14.5p
Chamomile, *Anthemis* 9.2p, 13.8ZOp, 14.1Ap, 14.2p
Chamomile, *Matricaria* 3.2Ap, 5.1Ap, 13.8ZOp, 14.1At, 14.5p
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Chaste tree, *Vitex* 5.4t, 9.6Bt, 9.7p, 9.7t, 11.1At, 11.1Gt, 11.2Fp, 14.5p
Chau wu tong, *Clerodendron* 4.3Ao, 4.3At, 5.1Ap, 5.2Ao, 9.5Ap, 11.1Jp, 11.1Kp, 13.7Hp, 13.8C
Chaulmoogra, *Hydnocarpus* 14.6p
Chayote, *Sechium* 9.1A
Cheesebush, *Hymenoclea* 9.7t, 10.6t
Cherry, *Prunus* 3.2Ap, 3.2Bp, 4.2p, 4.5A, 4.5C, 5.1Ap, 5.5Dp, 5.7C, 5.8O, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Do, 9.3Gp, 9.7p, 10.1o, 10.2o, 10.3o, 10.4o, 10.4t, 10.5o, 10.5t, 10.6o, 10.6t, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2E, 12.4E, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 13.8D, 14.1Ap, 14.2p, 14.2t, 14.5o, 14.5p
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Chewstick, *Symphonia* 8.1p
Chick pea, *Cicer* 7.4p, 8.1p, 8.3Cp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2A, 12.4E, 13.6Ap, 13.8ZI, 14.2t
Chickory, *Cichorium* 3.2Aa, 5.3Ba, 5.5Da, 6.5a, 9.5Ap, 10.1o, 10.2t, 10.4o, 14.5p
Chilean lantern plant, *Crinodendron* 10.2t, 11.1Gt
Chimaphila, *Chimaphila* 8.1p, 8.3Cp, 13.4Ip, 14.5p
China berry tree, *Melia* 4.4At, 5.8R, 7.3Ba
Chinchona, *Cinchona* 4.2a, 4.3Ca, 5.5Da, 6.5a, 8.1p, 9.2p, 9.3Ap, 9.3Gp, 6.5a, 10.2a, 11.1Ha, 12.1p, 13.7Ha, 13.8Qa, 13.8ZOp, 14.1Ap, 14.2p
Chinese arborvitae, *Biota* 5.1Ap, 5.7Gt
Chinese foxglove, *Rehmannia* 3.2Bo, 5.5A, 7.3Do, 10.1o, 10.2t, 12.2D, 12.4E, 14.1Ap
Chinese wingnut, *Pterocarya* 10.1t
Chinquapin, *Castanopsis* 9.3Ap, 12.1p
Chionodoxa, *Chionodoxa* 7.4t
Chirita, *Chirita* 11.2Gp
Chondria (red alga), *Chondria* 3.3Ba
Chondrodendron, *Chondrodendron* 3.1Aa, 3.1Ba, 3.2Ba, 3.3Ea
Christmas berry, *Crossopetalum* 9.2t, 9.3At, 12.1t, 13.7Ht
Christmas box tree, *Bursaria* 14.1Ap, 14.5p
Christmas vine, *Rivea* 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 8.3O
Chrysanthemum, *Chrysanthemum* 4.2t, 5.5Dt, 5.7C, 5.8N, 5.8O, 6.2t, 7.3At, 7.3Bo, 7.3Bp,

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- Chrysophyllum, *Chrysophyllum* 6.1B
- Cicer, *Cicer* 7.4p, 8.1p, 8.3Cp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2A, 12.4E, 13.6Ap, 13.8ZI, 14.2t
- Cinnamon, *Cinnamomum* 4.4Ap, 5.7K, 6.1F, 6.5p, 7.3Ap, 8.3Hp, 9.1A, 9.1B, 10.1p, 10.4p, 10.4t, 10.6t, 12.1p, 12.2B, 13.4Ip, 13.8Mp, 13.8Qp, 14.1Ap, 14.6p
- Cinnamosma, *Cinnamosma* 3.4Bt
- Cinquoil, *Potentilla* 4.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.6p, 7.3Bp, 13.6Bp, 13.8ZA, 14.5p
- Cissampelos, *Cissampelos* 4.4Aa, 5.7Ga, 7.1a, 9.7a, 13.4Da
- Cistanchis, *Cistanche* 14.2p
- Clarisa, *Clarisa* 8.1p
- Clausenia, *Clausenia* 5.8W, 7.3Bp, 10.1p, 10.4p, 14.1Ap
- Cleistanthus, *Cleistanthus* 9.7p
- Clematis, *Clematis* 10.2o, 14.3Bo
- Climbing dogbane, *Trachelospermum* 5.8R, 7.4p
- Climbing fumitory, *Adlumia* 3.1Ba, 3.2Ba
- Climbing saltbush, *Rhagodia* 11.1Gt
- Clitoria, *Periandra* 10.1t
- Clitoris flower, *Clitoria* 12.4A
- Cloak fern, *Notholaena* 14.5p
- Clove, *Caryophyllus* 13.4It
- Clove, *Syzygium* 4.3Ap, 4.3At, 5.2At, 5.3Ap, 5.3Bp, 5.4p, 5.5Dt, 5.6p, 5.8R, 6.1F, 7.3Bp, 8.1p, 8.1t, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.7t, 10.4p, 10.5p, 13.1t, 13.4At, 13.4C, 13.4Ht, 13.8Jt, 13.8Qp, 13.8ZJ, 14.1Ap, 14.1At, 14.2p
- Clover, *Trifolium* 3.2Bp, 4.1Cp, 4.2p, 4.5A, 4.5C, 5.1Ap, 5.7C, 5.8H, 6.5p, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Dp, 9.3Gp, 9.5Ap, 9.7p, 10.4t, 11.2Fp, 11.1Gp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2A, 13.4Ap, 13.4Fp, 13.4Ht, 13.6Ap, 13.6Cp, 13.7Ep, 13.7Hp, 13.8C, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p, 14.5p, 14.6p
- Clubmoss, *Huperzia* 6.4a
- Clubmoss, *Lycopodium* 3.1Aa, 3.1Ba, 6.1G, 6.2a, 6.4a, 10.2a
- Clusterpea, *Dioclea* 7.3Bp, 9.7o, 12.2A, 13.5G
- Coastal saltbush, *Rhagodia* 11.1Gt
- Cobnut, *Omphalea* 13.1a
- Coca, *Erythroxylum* 3.2Ba, 4.2a, 5.2Ba, 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.8E, 5.9, 6.3a, 6.4a, 8.1t, 13.4Ap, 13.4At, 13.4Gt, 13.4Ht, 13.8Jp, 13.8Yt
- Cocklebur, *Xanthium* 10.5p, 10.6t
- Cocoa, *Theobroma* 3.3Ea, 3.4Bo, 4.3Ba, 5.1Aa, 5.3Ba, 5.3Ca, 5.4a, 5.5Da, 5.6a, 5.8F, 7.4a, 10.5a, 13.5K, 13.6Ba, 13.8F, 14.5p, 14.6a
- Coconut palm, *Cocos* 5.2Bo, 10.1o, 10.5o, 10.6o, 11.1Bo, 11.2Bo
- Coffee, *Coffea* 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 9.2p, 10.2a, 10.2t, 10.4a, 10.4o, 10.4p, 10.4t, 13.8ZOp, 14.1Ap, 14.2p, 14.5p
- Cohoba, *Anadenanthera* 5.5Da
- Cohosh, *Caulophyllum* 3.1Aa
- Cojon de toro, *Stemmadenia* 3.2Aa, 3.3Aa, 3.4Aa, 4.2a, 5.6a
- Cola, *Cola* 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 10.2a
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- Colic wood, *Myrsine* 8.1p, 8.4p, 9.3Ap, 9.3Gp, 12.1p
- Coltsfoot, *Tussilago* 4.4At, 5.7Gt, 7.3Bt, 8.2t, 14.2p, 14.5p
- Columbine, *Aquilegia* 14.1Ao
- Comfrey, *Symphytum* 5.8R, 7.2B, 9.5Ap, 11.2Gp, 13.4Hp, 14.1Ap, 14.2p, 14.5p
- Coneflower, *Echinacea* 8.1p, 8.3Cp, 9.5Ap, 14.1Ao, 14.1Ap, 14.2p, 14.5p
- Coontie, *Zamia* 7.4p, 14.1Ap
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- Coralbead, *Cocculus* 3.1Ba
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- Corchorus, *Corchorus* 4.1Ct
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- Coriaria, *Coriaria* 3.2Bt, 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 8.1p, 13.4Ap, 13.8ZJ
- Cork tree, *Phellodendron* 3.1Ba
- Corlwort, *Sullivantia* 14.1Ap
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- Corncockle, *Agrostemma* 9.1A, 9.7o
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- Cornflower, *Centaurea* 7.4p, 10.2p, 11.1E, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.8Kp, 13.8Yp, 14.1Ao, 14.5p
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- Costus, *Saussurea* 5.7C, 7.3At, 7.3Bt, 8.2t, 13.8Mt
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- Cowparsnip, *Heracleum* 3.1Ba, 7.3Bp, 7.3Bt, 9.3Ap, 12.1p, 14.5p
- Cowpea, *Vigna* 3.2Bp, 7.3Ap, 7.3Cp, 9.5Ao, 9.5Bo, 10.1o, 10.7o, 11.1Bp, 11.1Gp, 11.1Ip, 11.1Jp, 11.1Kp, 12.2A, 12.4A, 13.4Ap, 13.5G, 13.5N, 14.2t, 14.5p, 14.6o
- Cowwheat, *Melampyrum* 10.1o
- Crabapple, *Malus* 5.5Dp, 5.8J, 6.4t, 8.1p, 8.1t, 8.3Cp, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Bt, 9.7t, 10.2p, 10.3o, 10.4o, 10.4p, 10.4t, 10.5t, 10.6o, 10.6p, 10.6t, 11.1Hp, 11.1Ip, 11.1It, 11.2Ct, 11.2Gp, 12.4E, 13.4At, 13.4Ht, 13.6Ap, 13.7Ep, 13.7I, 13.8Jt, 14.1Ao, 14.1At, 14.2o, 14.2p, 14.2t, 14.5p
- Crabgrass, *Digitaria* 4.5A, 4.5C, 5.1Ap, 7.1o, 7.3Ap, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.3F, 8.3Hp, 9.5Ap, 9.7p, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.2Fp, 13.4Ap, 13.6Ap, 13.8Yp, 14.5p
- Crambe, *Crambe* 10.4p, 12.4F
- Cranberry, *Vaccinium* 4.1Cp, 6.4t, 7.3Cp, 8.1p, 8.1t, 9.3Cp, 9.3Ct, 9.3Dp, 9.3Ft, 9.3Gp, 9.3Gt, 9.5Ap, 9.5Bp, 9.5Bt, 9.7p, 9.7t, 10.3o, 10.5p, 11.1Hp, 11.1Jp, 11.2Fp, 13.4Ap, 13.4At, 13.4Fp, 13.4Ht, 13.4Hp, 13.4Ip, 13.6Ap, 13.8Jt, 13.8Yp, 13.8ZB, 14.1At, 14.2t, 14.5p
- Crape myrtle, *Lagerstroemia* 14.1Aa
- Cratylia, *Cratylia* 12.2A
- Creepier, *Parthenocissus* 12.2D
- Creeping oxeye, *Wedelia* 14.1Ap
- Crematosperma, *Pseudoxandra* 5.4a, 5.5Da
- Creosote bush, *Larrea* 4.3Cp, 4.4Ap, 14.1Ap, 14.6p
- Cress, *Arabidopsis* 8.1o, 12.2B, 12.2C, 12.2E, 12.4A, 12.4B, 12.4D, 12.4E, 13.3, 13.5I, 13.5K, 13.5O
- Cretan brake, *Pteris* 8.1Ao, 11.1Gt, 13.8R, 14.5p
- Crocus, *Crocus* 7.3Ao, 8.1p, 8.1t, 10.2p, 10.4t, 12.2B, 14.1At, 14.2t
- Crossopetalum, *Crossopetalum* 9.2t, 9.3At, 12.1t, 13.7Ht
- Croton, *Croton* 3.1Ba, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.8I, 5.8S, 8.2t, 10.1o, 10.3o, 10.4p, 12.1p, 13.4Gt, 13.7C, 14.6t
- Crown of thorns jujube, *Zizyphus spina* 14.6t
- Crownvetch, *Coromilla* 6.5p, 8.1p, 9.3Ap, 12.1p
- Cryptolepis, *Cryptolepis* 5.2Ba, 9.3Aa, 9.3Ga, 9.7a, 12.1a, 14.6a
- Cucumber, *Cucumis* 5.8La, 6.5a, 10.2t, 10.4o, 10.5o, 10.6o, 11.1Bo, 11.1Gt, 11.2Bo, 12.2D, 13.5P, 14.1Ao, 14.6o
- Culebra-borrachero, *Methysticodendron* 5.2Ba
- Cumin, *Cuminum* 6.1F, 7.3Bp, 7.3Cp, 7.3Do, 7.4p, 8.1p, 10.4p, 10.4t, 10.5t
- Cuprea, *Remijia* 4.2a, 4.3Ca, 6.5a, 10.2a, 11.1Ha, 13.7Ha, 13.8Qa
- Curare, *Chondrodendron* 3.1Aa, 3.1Ba, 3.2Ba, 3.3Ea
- Curatella, *Curatella* 14.5p
- Curculigo, *Curculigo* 10.1o
- Curjun, *Dipterocarpus* 8.1t
- Currant, *Ribes* 3.2Bo, 5.1Ap, 6.3o, 8.1p, 10.3o, 14.6o
- Curroria, *Cryptolepis* 5.2Ba, 9.3Aa, 9.3Ga, 9.7a, 12.1a, 14.6a
- Curryleaf tree, *Murraya* 5.5Da, 9.3Fa, 9.3Ga, 12.1a, 14.1Aa, 14.2a
- Curupay, *Anadenanthera* 5.5Da
- Custard apple, *Annona* 3.2Bo, 4.2a, 4.4Aa, 5.2Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.3Ca, 5.4a, 5.5Da, 5.6a, 5.8F, 7.3Aa, 7.4a, 9.5Bt, 10.5o, 13.6Bo
- Cyamopsis, *Cyamopsis* 14.6o
- Cycad, *Cycas* 3.2Ap, 3.3Bo, 5.5Bo, 6.3o, 7.4p, 8.3A, 8.3M, 9.5Bp, 12.1o, 13.7I, 14.1Ap, 14.5p
- Cyclamen, *Cyclamen* 12.3t
- Cydonia, *Cydonia* 10.1o
- Cymbidium, *Cymbidium* 12.2B
- Cynara, *Cynara* 14.2p
- Cyphomandra, *Cyphomandra* 13.8U
- Cypress pine, *Callitris* 9.3Gp, 9.6Ep
- Cypress, *Cupressus* 5.7Gt, 7.4p, 9.5Bp, 10.4t, 14.1At
- Cytisus, *Sarothamnus* 3.1Aa, 4.2a, 4.3Ca, 14.5p
- Daffodil, *Narcissus* 3.1Aa, 6.4a, 9.2a, 9.7a, 10.1o, 10.4p, 12.2B, 13.8O
- Dahlia, *Dahlia* 5.8R, 7.3Ap, 7.4p, 8.1p, 8.3D, 8.3F, 8.3Hp, 10.2p, 10.4p, 10.5p, 11.1E, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.4A, 13.4Ap, 13.6Ap, 13.6Cp, 13.7Hp, 13.8C, 13.8Kp, 13.8Yp, 14.1Ap, 14.2p, 14.5p
- Daisy, *Chrysanthemum* 4.2t, 5.5Dt, 5.7C, 5.8N, 5.8O, 6.2t, 7.3At, 7.3Bo, 7.3Bp, 7.3Bt, 7.3Cp, 7.4p, 8.1t, 9.7t, 10.4t, 10.6t, 11.1Jt, 13.4Ht, 13.7D, 14.1At, 14.5o, 14.5p, 14.5t
- Daisy, *Gerbera* 10.2o, 12.4B
- Damnacanthus, *Damnacanthus* 12.1p
- Dandelion, *Taraxacum* 8.2t, 9.2p, 9.5Ap, 13.4Ht, 13.8ZOp, 14.1Ap, 14.2p
- Daphne, *Daphne* 8.2p, 8.2t, 9.2t
- Daphniphyllum, *Daphniphyllum* 8.4t, 14.2p, 14.5p
- Date palm, *Phoenix* 3.1Aa, 3.2Bo, 3.3Ea, 5.5A, 10.1p, 11.1It, 11.1M, 12.3t

- Datisca, *Datisca* 5.1Ap, 7.4p, 13.7Hp, 13.8C, 14.1Ap
- Datura, *Datura* 3.1Ba, 5.2Ba, 12.2A, 13.5E
- Davidson's plum, *Davidsonia* 5.3Cp, 5.4p, 5.6p, 6.1B, 6.1G, 7.3Ap, 7.3Bp, 8.1p, 8.3Cp, 8.3D, 8.3I, 8.3N, 8.3R, 9.3Fp, 9.3Gp, 9.5Bp, 9.7p, 11.1Ap, 11.1Bp, 11.1Ip, 13.4Gp, 13.4Hp, 13.4Ip, 13.6Ap, 13.6Bp, 13.7Hp, 13.7I, 13.8ZJ, 13.8ZOp, 14.1Ap, 14.2p
- Dawn redwood, *Metasequoia* 7.2Co, 8.1p
- Deadly nightshade, *Atropa* 3.1Ba, 5.2Ba, 7.3Ap, 14.5p
- Dead man's fingers (green alga), *Codium* 12.2A
- Deadnettle, *Lamium* 10.2t, 11.1Gt
- Decodon, *Decodon* 14.1Aa
- Delphinium, *Delphinium* 3.1At, 3.1Ba, 4.2a, 4.5A, 6.5p, 8.1p, 8.3Cp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.7Ht, 13.8C, 13.8Jp, 14.5p
- Dendrodium (orchid), *Dendrodium* 4.1Ca
- Derris, *Derris* 8.1p, 13.1a
- Desert lime, *Eremocitrus* 10.2p
- Desert marigold, *Baileya* 13.8ZP
- Desert thorn, *Lycium* 13.1a, 14.2t
- Devil's backbone, *Bryophyllum* 10.3o
- Devil's claw, *Harpagophytum* 10.2t
- Devil's club, *Ophlopanax* 5.7C, 7.3Ao
- Devil's gut, *Cassytha* 5.3Aa
- Devil's tongue, *Amorphophallus* 10.4a
- Deviltree, *Alstonia* 3.2Ba, 3.3Da, 8.1t, 9.3Gt, 13.4At, 13.4Gt, 13.4Ht, 13.8Mt, 13.8Yt
- Dhai, *Woodfordia* 9.3Gp
- Dicranum moss, *Dicranum* 14.1Aa
- Dictamnus, *Dictamnus* 4.4Aa, 4.4At, 5.5Da, 9.6Et, 10.2t, 10.4p, 12.1a
- Dill, *Anethum* 4.4Ap, 5.1Ap, 7.2B, 7.4p, 8.1p, 8.3Cp, 9.5Ap, 10.4o, 10.4t, 10.6t, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ap, 11.2Gp, 13.4Hp, 13.7Hp, 14.1Ap, 14.2p, 14.5p
- Dillenia, *Dillenia* 13.7Hp
- Dioclea, *Dioclea* 7.3Bp, 9.7o, 12.2A, 13.5G
- Dionysia, *Dionysia* 5.1Ap, 7.4p, 8.1p, 8.3Cp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ap, 13.7Hp, 14.1Ap
- Dioscoreophyllum, *Dioscoreophyllum* 10.1o
- Diosma, *Diosma* 13.8Yp
- Diospyros, *Diospyros* 4.3At, 6.5p, 7.3Ap, 8.1p, 8.1t, 9.3Ap, 9.3Fp, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp, 14.5p
- Diploclisia, *Diploclisia* 11.1Gt, 11.1Ht
- Dipteryx, *Dipteryx* 8.1p, 10.2p, 10.4p
- Distaff thistle, *Carthamus* 4.4Ap, 14.1Ao
- Dock, *Petasites* 4.4At, 5.7Gt, 10.6t
- Dock, *Rumex* 8.1p, 8.4p, 9.3Ap, 9.3Gp, 12.1p, 14.6p
- Dodder, *Cuscuta* 4.5A, 6.5p, 8.1p, 8.3Cp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.8C, 13.8Jp, 14.6p
- Dogbane, *Apocynum* 3.2Aa, 4.1Ct
- Dogfennel, *Chamaemelum* 7.4p, 14.5p
- Dogfennel, *Peucedanum* 4.4Ap, 5.7Gp, 5.8W, 7.3Bp, 7.4p, 14.1Ap
- Doghobble, *Leucothoe* 4.2t
- Dogwood, *Cornus* 7.3At
- Doryphora, *Doryphora* 10.4p
- Douglas fir, *Pseudotsuga* 8.1p, 12.4E
- Douglas fir, *Tsuga* 5.7C, 7.3Ap, 8.1p, 13.6Ap, 14.2p
- Draba, *Draba* 10.4p
- Dracaena, *Dracaena* 11.1Ip, 11.1Kp, 13.8Kp, 14.1Ap, 14.2p
- Dracunculus, *Dracunculus* 10.4a
- Dragon tree, *Dracaena* 11.1Ip, 11.1Kp, 13.8Kp, 14.1Ap, 14.2p
- Dragon's blood tree, *Pterocarpus* 5.3Cp, 5.4p, 5.8R, 6.5p, 6.6A, 7.3Ap, 7.4p, 8.1p, 8.3Cp, 8.3Hp, 10.2p, 13.4Ip, 13.8C, 14.5p, 14.6p
- Pterocarpus, *Pterocarpus* 5.3Cp, 5.4p, 5.8R, 6.5p, 6.6A, 7.3Ap, 7.4p, 8.1p, 8.3Cp, 8.3Hp, 10.2p, 13.4Ip, 13.8C, 14.5p, 14.6p
- Dragon's blood, *Draconis* 14.1Ap
- Drewberry, *Rubus* 4.3Ap, 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 7.3Bp, 8.1t, 10.1o, 10.1t, 10.3o, 10.4o, 13.3, 13.6Bp
- Drias, *Thapsia* 4.1At, 8.2t, 10.5t
- Duckweed, *Lemna* 5.8U
- Dudiho, *Euclea* 9.3Fp
- Dunbaria, *Dunbaria* 14.2t
- Durian, *Durio* 10.4o
- Durio, *Durio* 10.4o
- Dutchman's pipe, *Aristolochia* 3.1Ba, 5.2Ba, 5.2Ba, 8.1o, 10.5o
- Dwarf apple, *Angophora* 6.5p
- Dyeteer, *Platycaea* 8.1p
- Dysophila, *Eusteralis* 10.5t
- Easter flower, *Securidaca* 3.2Ba, 10.2o
- Echinacea, *Echinacea* 8.1p, 8.3Cp, 9.5Ap, 14.1Ao, 14.1Ap, 14.2p, 14.5p
- Echinocystis, *Echinocystis* 13.5P
- Echinopsis, *Trichocereus* 5.3Bp, 5.5Dp, 6.3p, 6.5p
- Eclipta, *Eclipta* 14.1Ap
- Eggplant, *Solanum* 3.2Aa, 3.2An, 3.3Ea, 4.3At, 4.4E, 5.3Bp, 5.3Cp, 5.7F, 5.8D, 5.8La, 5.8R, 6.4a, 6.4o, 6.5a, 8.1a, 8.1t, 8.3Co, 10.6o, 10.2a, 10.3o, 10.4o, 10.4t, 10.5a, 10.5t, 10.6o, 10.7, 11.1It, 11.2It, 12.2B, 12.2C, 12.2D, 12.2E, 12.4A, 12.4D, 13.3, 13.5A, 13.5B, 13.5D, 13.5G, 13.5K, 13.5N, 13.5O, 13.6Ao, 13.7Ha, 13.8W, 14.2p, 14.5p, 14.6o
- Egyptian lotus, *Nymphaea* 3.3Aa, 5.4a
- Ekebergia, *Ekebergia* 5.2At
- Elderberry, *Sambucus* 3.1Aa, 9.1A, 9.1B, 10.4o, 10.4t, 12.2B, 12.2C, 12.2D, 12.4E, 14.5o
- Elephant creeper, *Argyria* 3.1Ba, 5.3Ba, 5.4a
- Elephant creeper, *Rivea* 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 8.3O

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- Elephant tree, *Bursera* 3.1Bt, 10.4t, 10.5t
 Elettaria, *Elettaria* 5.7Et, 10.4t, 10.6t
 Eleutherococcus, *Eleutherococcus* 14.1Ap
 Engelhardtia, *Engelhardtia* 7.4p, 14.1Ap, 14.5p
 Enterolobium, *Enterolobium* 13.5K
 Epinetrum, *Epinetrum* 3.1Ba
 Eremanthus, *Eremanthus* 7.3At
 Eremocitrus, *Eremocitrus* 10.2p
 Erigeron, *Erigeron* 6.5p, 7.3Ap, 8.1p, 8.3D, 8.3F, 8.3Hp, 11.1Hp, 11.1Ip, 13.4Ap, 13.6Ap, 13.7Hp, 13.8C, 13.8Yp, 14.1Ap, 14.5p
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 Erythrina, *Erythrina* 3.1Ba, 4.1Ep, 5.3Aa, 5.3Ba, 5.3Ca, 5.5Da, 12.2A, 13.5G, 13.5K
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 Ethiopian pepper, *Xylopia* 3.3Da, 5.3Aa, 9.7t, 10.4o, 10.4p, 10.4t, 10.5t, 10.6t, 14.2p
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 Falcaria, *Falcaria* 7.3Ao, 14.1Ao
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 False daisy, *Eclipta* 14.1Ap
 False fleabane, *Pulicaria* 9.5Bp, 14.5p
 False goat's beard, *Astilbe* 5.1Ap, 8.1p, 14.5p
 False goldenweed, *Oenopsis* 9.7o, 14.2o, 14.3Bo
 False hellebore, *Veratrum* 4.2a, 5.8H, 6.4a, 6.5p, 7.3Ap, 8.1a, 8.1p, 9.3Dp, 9.7p, 11.1Ip, 13.6Ap, 13.6Cp, 13.7Ha, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p
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 False ohelo, *Wikstroemia* 8.2p, 8.2t
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 False waterwillow, *Andrographis* 10.2t, 13.4Ht
 False willow, *Baccharis* 3.2Ap, 5.1Ap, 7.4p, 8.1p, 10.1p, 10.2p, 10.4p, 11.1E, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.7Hp, 13.8Kp, 13.8S, 13.8Yp, 14.5p
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 Fescue, *Lolium* 4.3Ba, 4.4B, 5.2Ba, 5.3Ba, 6.3p, 6.5p, 7.4a, 9.7o, 10.4o, 13.8ZG
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 Feverfew, *Chrysanthemum* 4.2t, 5.5Dt, 5.7C, 5.8N, 5.8O, 6.2t, 7.3At, 7.3Bo, 7.3Bp, 7.3Bt, 7.3Cp, 7.4p, 8.1t, 9.7t, 10.4t, 10.6t, 11.1Jt, 13.4Ht, 13.7D, 14.1At, 14.5o, 14.5p, 14.5t
 Feverfew, *Parthenium* 9.7t, 10.6t, 12.1t
 Feverfew, *Tanacetum* 3.2Bt, 4.2t, 5.5Dt, 5.7C, 5.8C, 5.8N, 5.8O, 6.2t, 7.3At, 7.3Bp, 7.3Bt, 8.1t, 10.4t, 10.6t, 14.1Ap, 14.1At
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 Figwort, *Scrophularia* 10.2t
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 Fir, *Abies* 5.8Q, 5.8R, 8.2t, 10.1o, 10.4o, 10.4t, 10.5t
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- Fleabane, *Erigeron* 6.5p, 7.3Ap, 8.1p, 8.3D, 8.3F, 8.3Hp, 11.1Hp, 11.1Ip, 13.4Ap, 13.6Ap, 13.7Hp, 13.8C, 13.8Yp, 14.1Ap, 14.5p
- Flemingia, *Flemingia* 14.2t
- Flixweed, *Sisymbrium* 10.4p
- Florida boxwood, *Schaefferia* 7.3At, 9.2t, 9.3At, 12.1t, 14.1At
- Footflower, *Podanthus* 14.2t
- Forsythia, *Forsythia* 7.4p, 8.1p, 8.3Cp, 10.2p, 14.1Ap, 14.2p, 14.5p, 14.5p
- Fountain grass, *Pennisetum* 7.1o, 11.2Fp, 13.5B
- Four o'clock, *Mirabilis* 9.1A
- Foxglove, *Digitalis* 3.2Ap, 4.1Ct, 5.1Ap, 8.1p, 9.2a, 9.2p, 9.2t, 9.5Bp, 4.1Ct, 10.2a, 10.3o, 10.5t, 12.3t, 13.8ZOp, 14.1Ap, 14.2p, 14.5p
- Fragrant orchid, *Gymnadenia* 5.8R, 10.4p, 10.5p, 14.2p
- Frankincense, *Boswellia* 9.3Ft, 9.3Gt, 10.4t, 13.4Ht, 14.1At
- Fraseria, *Sweetia* 5.2At, 5.2Ba, 5.2Bt, 9.3Ap, 9.3Cp, 9.3Ft, 9.5Bp, 10.2t, 12.1p, 13.4At, 13.4Ht, 13.8Jt, 14.6p
- Fritillary, *Fritillaria* 5.2Ba
- Frullania (liverwort), *Frullania* 8.2t, 14.1Ap
- Fuchsia, *Fuchsia* 4.1Bp, 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 8.1p, 13.1p, 13.4Ap, 13.6Bp, 13.8ZJ, 13.8ZOp
- Fumewort, *Corydalis* 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.3Ca, 5.5Da, 5.7Ga, 6.1B, 6.4a, 7.4a, 8.1a, 9.3Aa, 9.5Ba, 12.1a, 14.1Aa, 14.5a
- Fumitory, *Fumaria* 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 5.8Xa, 6.1A, 6.1B, 6.4a, 7.4a, 8.1a, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 14.1Aa
- Fungus root (parasitic plant), *Balanophora* 8.1t, 13.4At, 13.4Gt, 13.4Ht, 13.8Yt
- Galbulimima, *Himantandra* 5.2Ba
- Gambir, *Uncaria* 5.3Aa, 5.5Da, 8.3Cp, 10.3o, 13.8ZD, 14.2p
- Garcinia, *Garcinia* 4.1Ap, 5.5Dp, 5.7Ep, 6.1A, 7.4p, 8.1p, 9.5Bp, 11.1Ip, 13.4Ap, 13.8ZC, 14.2p, 14.5p, 14.6p
- Gardenia, *Gardenia* 7.3At, 8.1t, 14.1Ap
- Garlic, *Allium* 4.1Ct, 4.1Cp, 4.5A, 5.1Ap, 7.1p, 7.3Ao, 7.3Ap, 7.3Bo, 7.3Do, 7.4p, 7.4t, 8.1p, 8.3Cp, 8.4p, 9.2p, 9.3Gp, 9.5Ap, 9.5Bp, 9.7o, 10.1o, 10.3o, 10.4o, 10.7o, 11.1E, 11.1Gp, 11.1Hp, 12.2B, 12.3o, 13.4Ip, 14.1Ao, 14.2o, 14.6o, 14.6p
- Gasplant, *Dictamnus* 4.4Aa, 4.4At, 5.5Da, 9.6Et, 10.2t, 10.4p, 12.1a
- Geigeria, *Geigeria* 13.6Dt
- Genipa, *Genipa* 7.3At
- Gentian, *Gentiana* 5.2Ba, 5.2At, 9.3Ft, 10.2t, 14.6p
- Geranium, *Geranium* 4.1Bp, 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 13.1p, 13.4Ap, 13.6Bp, 13.8Zop, 14.1Ap
- Geranium, *Pelargonium* 6.5p, 10.3o, 10.4t, 14.1Ap, 14.5p
- Gerbera, *Gerbera* 10.2o, 12.4B
- Germander, *Teucrium* 7.2B, 9.5Ap, 9.7p, 10.2t, 10.6t, 11.2Gp, 13.4Hp, 14.1Ap, 14.2p, 14.5p
- Geronggang, *Cratogeomys* 8.1p
- Giant milkweed, *Calotropis* 4.1Ct
- Giant reed, *Arundo* 5.5Da, 10.6a
- Giant tree daisy, *Podachaenium* 7.3At
- Gie nambo, *Desmos* 8.1a, 8.1p, 8.3Cp
- Ginger, *Zingiber* 3.4Bp, 4.1Ap, 4.2a, 4.3Cp, 5.7C, 6.1E, 7.3Ap, 7.3Bt, 8.1p, 9.7p, 10.1p, 10.4p, 10.4t, 10.6o, 10.6t, 13.6Ap, 14.1Ap
- Ginkgo, *Ginkgo* 3.2Ap, 3.2At, 3.3At, 5.2At, 5.7Gt, 7.3Ap, 7.3At, 7.4p, 8.1p, 8.3Cp, 8.3E, 8.3R, 9.7t, 10.2t, 10.5t, 10.6t, 11.1M, 13.8ZC, 14.1Ap, 14.2t, 14.5P
- Ginseng, *Panax* 3.1Bt, 3.2Bt, 4.4At, 5.2Bt, 5.5Dt, 5.6t, 5.7C, 5.7Et, 5.7F, 5.8F, 5.8R, 5.8V, 5.9, 6.1G, 6.2t, 7.2Ct, 7.3Ao, 7.3Bo, 7.3Bt, 8.3M, 9.7n, 9.7t, 10.3o, 11.1It, 14.1Ao, 14.1B, 14.6o
- Gladiolus, *Gladiolus* 6.5p, 14.5p
- Glechoma, *Glechoma* 5.7Ho, 8.1t
- Gliciridia, *Gliciridia* 7.4p
- Globe artichoke, *Cynara* 14.2p
- Globe thistle, *Rhaponticum* 11.1Gt
- Glory of the snow, *Chionodoxa* 7.4t
- Glycosmis, *Glycosmis* 4.4Aa, 5.1Aa, 5.5Da, 12.1a
- Goatbush, *Castela* 10.2t, 13.8W
- Goebelia, *Goebelia* 5.6a
- Goldback fern, *Pityrogramma* 3.2Ap, 8.1Ao, 8.1p, 13.7Hp, 13.8R, 14.5p
- Golden banner, *Thermopsis* 3.1Aa, 3.1Ba
- Golden raintree, *Koelreuteria* 4.1Cp, 4.5A, 5.1Ap, 6.5p, 7.1p, 7.3Ap, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.2p, 9.3Dp, 9.3Gp, 9.5Bp, 11.1E, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap, 13.7Hp, 13.8C, 13.8Jp, 13.8X, 13.8Yp
- Golden weed, *Haplopappus* 4.1Cp, 7.3Cp, 7.4p, 8.1p, 9.3Cp, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.7p, 11.1Bp, 11.1Hp, 11.1Ip, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap, 13.8P, 13.8Yp, 13.8ZB, 14.1Ap, 14.5p, 14.6p
- Goldenchain tree, *Laburnum* 3.1Aa, 3.1Ba, 4.1Ep, 7.3Ap, 8.1p, 12.2A, 13.6Ap, 14.2p, 14.6a
- Goldenrod, *Solidago* 10.4p, 13.4Ht
- Goldenseal, *Hydrastis* 3.1Ba, 3.2Ba, 3.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 9.3Aa, 9.5Ba, 12.1a
- Goldthread, *Coptis* 3.1Ba, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 7.3Bp, 9.3Aa, 9.3Fa, 9.3Ga, 9.5Ba, 12.1a, 14.1Aa

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- Goniothalamus, *Goniothalamus* 9.7o, 12.1a, 13.6Bo
- Gooseberry, *Ribes* 3.2Bo, 5.1Ap, 6.3o, 8.1p, 10.3o, 14.6o
- Goosefoot, *Chenopodium* 5.8N, 5.8O, 7.1o, 7.3Bp, 7.3Bt, 9.1A, 10.2t, 10.3o, 10.4o, 10.4t, 10.5o, 11.1Gt
- Goosegrass, *Eleusine* 12.4B, 13.2, 13.5L, 13.5Q
- Gordonia, *Gordonia* 9.7p
- Gorse, *Ulex* 3.1Aa, 3.1Ba, 3.2Bp, 4.2p, 4.5A, 4.5C, 5.1Ap, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Dp, 9.3Gp, 9.7p, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2A, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 14.1Ap, 14.6a
- Gourd, *Cucurbita* 9.1A, 10.1o, 12.2B, 12.4C, 13.5A, 13.5N, 13.5P, 13.5R, 14.6o
- Grape, *Vitis* 4.1Cp, 5.8H, 6.5p, 7.3Ap, 7.3Bp, 8.1p, 9.3Dp, 9.6C, 9.7p, 9.7t, 10.3o, 10.4a, 10.4o, 10.4p, 10.4t, 10.5o, 10.5p, 10.5t, 10.6o, 10.6t, 11.1Gp, 11.1Ip, 11.1It, 12.4D, 12.4E, 13.6Ap, 13.6Cp, 13.8Kp, 13.8ZN, 13.8ZOp, 13.8Qp, 14.1Ap, 14.2a, 14.2p, 14.6p
- Grapefruit, *Citrus* 3.1Bt, 3.2Ap, 4.5A, 5.1Ap, 5.3Ap, 5.3Bp, 5.5Da, 5.8R, 5.8W, 6.3p, 6.4t, 6.5p, 7.3Bp, 7.3Bt, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.3Ap, 9.5Ap, 9.5Bp, 9.6Bt, 9.6Et, 9.7p, 9.7t, 10.1n, 10.2p, 10.2t, 10.3o, 10.4a, 10.4o, 10.4p, 10.4t, 10.5o, 10.5p, 10.5t, 10.6o, 10.6t, 11.1E, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ct, 11.2Fp, 12.1p, 12.2B, 12.2C, 13.4Gp, 13.5K, 13.6Ap, 13.7Hp, 13.8C, 13.8Jp, 13.8Kp, 13.8Qp, 13.8Yp, 13.8ZOp, 14.1Ap, 14.2o, 14.2p, 14.2t, 14.5p, 14.6p
- Grapple plant, *Harbagophytum* 10.2t
- Grass pea, *Lathyrus* 3.3Ao, 3.3Bo, 5.3Ba, 5.8Lo, 6.3o, 8.3A, 8.3M, 12.2A, 13.8Z, 14.1Ap
- Grass widows, *Sisyrinchium* 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp
- Grasree, *Xanthorrhoea* 9.2p, 9.3Ap, 9.3Gp, 12.1p
- Graveyard flower, *Plumeria* 9.3Ct
- Great arum, *Amorphophallus* 10.4a
- Greater burnet, *Sanguisorba* 5.7C, 5.7Gp, 9.3Fp, 9.3Gp, 13.6Bp
- Green brier, *Smilax* 7.4p, 7.4t, 10.2p, 10.2t, 12.3t
- Grevillea, *Grevillea* 14.1Ap
- Grey milkwood, *Cerbera* 4.1Ct, 14.2p
- Griffonia, *Bandeiraea* 12.2A
- Griffonia, *Griffonia* 12.2A
- Ground cherry, *Physalis* 7.3Bt, 13.1a, 14.2t
- Ground ivy, *Glechoma* 5.7Ho, 8.1t
- Ground lily, *Anmocharis* 9.2a
- Groundnut, *Apios* 14.2t
- Guaiacum, *Guaiacum* 4.3Bp, 4.3Cp, 4.4Ap, 10.4p, 10.4t, 10.5p, 14.1Ap, 14.6p, 14.1Ap
- Guarana, *Paullinia* 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 10.2a
- Gutteria, *Gutteria* 3.1Ba, 4.2a, 4.4Aa, 5.2Aa, 5.2Ba, 5.3Aa, 5.5Da, 7.4a, 9.3Fa
- Guava, *Psidium* 4.3Ap, 5.3Ap, 5.3Bp, 5.4p, 5.6p, 7.3Bp, 8.1p, 9.3Fp, 9.3Gp, 9.5Ap, 11.2Gp, 12.1p
- Guayatil Colorado, *Arariba* 3.2Aa
- Guiera, *Guiera* 9.3Dp
- Gum bully, *Bumelia* 14.6t
- Gumtree, *Eucalyptus* 3.3Ep, 4.3Ap, 4.4At, 5.3Ap, 5.3Bp, 5.4p, 5.6p, 5.8H, 6.4t, 6.1F, 6.5p, 7.3Ap, 7.3Bp, 7.4p, 8.1p, 9.3Dp, 9.5Bp, 9.7p, 10.4t, 10.5t, 10.6t, 11.1Bp, 11.1Ip, 11.1Jp, 13.4Ip, 13.6Ap, 13.6Bp, 13.6Cp, 13.8Jp, 13.8ZE, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p, 14.5p
- Gumweed, *Grindelia* 13.8P
- Gymnadenia, *Gymnadenia* 5.8R, 10.4p, 10.5p, 14.2p
- Gymnema, *Gymnema* 5.8J, 10.1o, 10.1t, 10.2t, 13.7Et, 14.6t
- Gymnostemma, *Gymnostemma* 4.1Ct, 9.7t
- Haematoxylum, *Haematoxylum* 4.3Ap, 4.3Bp
- Handelia, *Handelia* 10.6t
- Hannoa, *Quassia* 10.2t
- Haplophyllum, *Haplophyllum* 4.4Aa, 5.5Da, 5.8W, 7.3Bp, 9.5Bp, 12.1a, 14.1Ap
- Hardenbergia, *Hardenbergia* 12.4A
- Hardwickia, *Hardwickia* 9.3Dt
- Hardy orange, *Poncirus* 8.1p, 14.2p, 14.5p
- Harrisonia, *Harrisonia* 9.6Et, 10.2t
- Hart's tongue fern, *Scolopendrium* 11.2Bo, 14.1Ao
- Hawksbeard, *Crepis* 14.1Ao
- Hawthorn, *Crataegus* 4.3Cp, 5.3Cp, 5.4p, 5.5Dp, 6.5p, 7.4p, 8.1p, 8.1t, 8.3Hp, 10.2p, 13.4At, 13.4Ip, 13.8Jt, 14.1Ap, 14.5p, 14.6p
- Heart leaf, *Bergenia* 5.1Ap, 13.4Ip
- Heath, *Erica* 5.8R, 13.4Ip
- Heather, *Calluna* 9.7t, 14.1At
- Hebe, *Hebe* 14.5p
- Hedge mustard, *Sisymbrium* 10.4p
- Hedge parsley, *Torilis* 8.3G, 8.3R
- Hedgehyssop, *Gratiola* 11.1D
- Heimia, *Heimia* 14.1Aa
- Heisteria, *Heisteria* 14.1Ao
- Helianthella, *Iostephane* 4.4At
- Heliotrope, *Heliotropium* 10.4p
- Helleborine orchid, *Epipactis* 12.2B
- Hemlock, *Conium* 3.1Aa, 7.3Ao, 9.2p, 10.1o, 13.8ZOp, 14.1Ap, 14.2p
- Hemp, *Cannabis* 5.7Ep, 5.8C, 6.3p, 11.1Ap, 13.6Bp
- Henbane, *Hyoscyamus* 3.1Ba, 5.2Ba
- Hercules' club, *Zanthoxylum* 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 5.7D, 5.8Xa, 6.1A, 6.1B, 6.4a, 7.3Bp, 7.4a, 8.1a, 8.3B, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 14.1Aa, 14.6p
- Hermidium, *Hermidium* 5.3Ap, 5.3Cp, 5.4p, 11.2Jp Four o'clock

- Heterophragma, *Haplophragma* 7.3Cp, 9.3Fp, 9.5Bp, 9.7p
- Hexisea, *Scaphyglottis* 7.3Bp
- Hiba arborvitae, *Thujaopsis* 3.2Bt, 5.8C, 8.1p, 10.4p, 10.4t, 13.4Gt, 14.1At
- Hibiscus, *Hibiscus* 7.4p, 9.7p, 10.3o, 13.4Ap, 13.4Ip, 13.8N, 14.1Ap, 14.5p
- Hickory, *Carya* 8.1p, 11.1Hp, 13.8Kp
- Himatanthus, *Himatanthus* 6.5p
- Hippomane, *Hippomane* 3.1Aa, 6.4a, 8.2t, 14.1Ap
- Hiptage, *Hiptage* 14.6p
- Hogpeanut, *Amphicarpaea* 14.2t
- Hogpeanut, *Amphicarpea* 12.2A
- Hollow heart, *Acnistus* 5.3Bt
- Holly, *Ilex* 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 10.2a, 14.2p
- Honesty, *Lumaria* 3.2Bo, 3.3Do, 6.3o, 6.4a
- Honeycomb head, *Balduina* 8.1t, 11.1Jt, 13.6Dt, 13.8Qt
- Honeysuckle, *Lonicera* 5.8R, 8.1t, 9.3Ct, 9.3Ft, 9.3Gt, 13.1t, 13.4At, 14.1At, 14.5p, 14.6t
- Hong Kong arborescent fern, *Boweringia* 12.2A
- Hops, *Humulus* 6.3p, 10.2p, 10.4o, 10.4t, 10.6o, 11.1Ip, 11.1It, 11.2Gp, 14.5p, 14.6t
- Horehound, *Ballota* 14.1Ap, 14.2p
- Horehound, *Marrubium* 10.2t
- Hornpoppy, *Glaucium* 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ca, 5.8Xa, 6.1A, 6.1B, 7.4a, 8.1a, 10.3o, 14.1Ao
- Horse chestnut, *Billia* 13.8D
- Horse nettle, *Solanum* 3.2Aa, 3.2An, 3.3Ea, 4.3At, 4.4E, 5.3Bp, 5.3Cp, 5.7F, 5.8D, 5.8La, 5.8R, 6.4a, 6.4o, 6.5a, 8.1a, 8.1t, 8.3Co, 10.6o, 10.2a, 10.3o, 10.4o, 10.4t, 10.5a, 10.5t, 10.6o, 10.7, 11.1It, 11.2It, 12.2B, 12.2C, 12.2D, 12.2E, 12.4A, 12.4D, 13.3, 13.5A, 13.5B, 13.5D, 13.5G, 13.5K, 13.5N, 13.5O, 13.6Ao, 13.7Ha, 13.8W, 14.2p, 14.5p, 14.6o
- Horsegram, *Macrotyloma* 13.5G
- Horsemint, *Monarda* 10.4t, 10.4o
- Horsetail, *Equisetum* 3.1Aa, 3.1Ba, 6.1G, 6.2a, 10.2a
- Horseweed, *Conyza* 9.3Ft, 13.4Ht, 13.8ZOp
- Hortia, *Hortia* 3.4Ba, 14.1Aa
- Hovenia, *Hovenia* 10.1t
- Huang Qi, *Astragalus* 7.2Co, 7.4p, 9.7o, 10.3o, 13.1a, 14.2o, 14.3Bo, 14.5p
- Huckleberry, *Solanum* 3.2Aa, 3.2An, 3.3Ea, 4.3At, 4.4E, 5.3Bp, 5.3Cp, 5.7F, 5.8D, 5.8La, 5.8R, 6.4a, 6.4o, 6.5a, 8.1a, 8.1t, 8.3Co, 10.6o, 10.2a, 10.3o, 10.4o, 10.4t, 10.5a, 10.5t, 10.7, 11.1It, 11.2It, 12.2B, 12.2C, 12.2D, 12.2E, 12.4A, 12.4D, 13.3, 13.5A, 13.5B, 13.5D, 13.5G, 13.5K, 13.5N, 13.5O, 13.6Ao, 13.7Ha, 13.8W, 14.2p, 14.5p, 14.6o
- Hunteria, *Hunteria* 3.2Ba, 3.3Da
- Huon pine, *Dacrydium* 7.4p
- Hyacinth, *Hyacinthus* 10.4p, 13.1a
- Hyacinth bean, *Lablab* 8.1p, 8.3Cp, 11.1Ip, 13.2
- Hyacinthoides, *Hyacinthoides* 13.1a
- Hydrangea, *Hydrangea* 10.1p, 10.2t, 14.5p
- Hydrastis, *Hydrastis* 3.1Ba, 3.2Ba, 3.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 6.1B, 6.4a, 9.3Aa, 9.5Ba, 12.1a
- Hypoestes, *Hypoestes* 7.3At, 8.1t
- Hypolaena, *Hypolaena* 14.1Ap
- Hyssop, *Agastache* 8.1p, 8.3Cp, 9.5Ap, 10.4p, 12.1p, 13.4At, 13.7Hp, 14.1Ap, 14.5p
- Hyssop, *Hyssopus* 8.1p, 10.4t, 14.2p, 14.5p
- Iboga, *Tabernanthe* 3.2Aa, 3.3Aa, 3.3Ea, 3.4Aa, 4.2a, 5.1Aa, 5.2Aa, 5.3Aa, 5.4a, 5.5Da, 5.6a, 6.3a
- Iceland moss, *Cetraria* 9.3Co, 9.5Bo, 9.5Bt
- Iceland pea, *Christia* 14.2t
- Iceplant, *Mesembryanthemum* 9.1A
- Ifil, *Intsia* 5.8H, 6.5p, 7.3Ap, 8.1p, 9.3Dp, 9.7p, 11.1Ip, 13.6Ap, 13.6Cp, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p
- Ilang-ilang, *Cananga* 10.4o, 10.4p, 10.4t, 10.5o, 10.6o
- Ilang-ilang, *Uvaria* 4.1Aa, 4.1Ca, 4.3Aa, 4.3Ba, 4.4Aa
- Ilomba, *Pycnanthus* 14.6t
- Immortelle, *Helichrysum* 11.2Gp, 14.2p, 14.5p
- Immortelle, *Xeranthemum* 10.6t
- Indian bael, *Aegle* 4.4Aa, 7.3Bp, 7.3Bt, 12.1a, 12.1p, 14.5p
- Indian bush, *Psacalium* 14.6o, 14.6t
- Indian ipecac, *Tylophora* 9.2a
- Indian mahogany, *Soymida* 4.1Cp, 7.3Cp, 7.4p, 8.1p, 9.3Cp, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.7p, 11.1Bp, 11.1Hp, 11.1Jp, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap, 13.8Yp, 13.8ZB, 14.1Ap, 14.5p, 14.6p
- Indian mulberry, *Morinda* 8.1p, 8.3Hp, 9.3Gp, 9.5Ap, 12.1p, 13.6Dp
- Indian plantain, *Cacalia* 10.6t
- Indicus cocculus, *Anamirta* 3.2Bt, 3.3Dt
- Indigo, *Indigofera* 7.3Co, 13.8G, 14.2t
- Intoxicant of the snake, *Methysticodendron* 5.2Ba
- Ipecac, *Cephaelis* 9.2a, 9.3Aa, 9.5Ba, 12.1a
- Ipecac, *Uragoga* 9.2a
- Iporuru, *Bleekeria* 9.3Aa, 9.3Ba, 9.3Ga, 12.1a
- Iris, *Iris* 3.2Bo, 3.3Do, 6.3o, 8.2t, 9.1A, 10.4t, 11.1Gp, 11.2Bo, 14.1Ap, 14.2p
- Ironweed, *Vernonia* 7.3At, 10.2t, 10.6t
- Ironwood, Myrtle, *Bachhousia* 10.1p, 10.4p
- Ironwort, *Sideritis* 7.3At, 7.3Bp, 14.1Ap, 14.1At, 14.5p, 14.6p
- Isphagula, *Plantago* 3.2Ap, 5.2Bo, 5.7C, 5.7I, 7.4p, 8.1p, 8.3Cp, 8.4t, 9.7t, 10.1o, 10.2t, 10.6t, 11.1Jp, 13.1p, 13.8Kp, 14.1Ap, 14.1At, 14.2p, 14.2t, 14.5p, 14.6o
- Ivy, *Hedera* 7.3Ao, 8.1t, 9.2a, 9.3Aa, 12.1a, 12.3t, 13.1t, 13.4Ht, 13.8Jt, 13.8Mt, 14.1Ao, 14.6t

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- J'oublie, *Pentadiplandra* 10.1o
Jacaranda, *Jacaranda* 14.1Ao
Jackbean, *Canavalia* 7.3Co, 9.7o, 9.6D, 12.2A, 12.2C, 13.5G, 13.5K, 13.5N, 13.8E, 13.8Z, 13.8ZL, 14.1Ao, 14.2t
Jackfruit, *Artocarpus* 5.8H, 6.5p, 7.3Ap, 7.4p, 8.1p, 9.3Cp, 9.3Dp, 9.7p, 11.1Bp, 11.1Hp, 11.1Ip, 12.2B, 13.4Ap, 13.6Ap, 13.6Cp, 13.7B, 13.8Qp, 13.8Yp, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p, 14.5p
Jamaica walnut, *Picodendron* 3.2Bt
Japanese cedar, *Cryptomeria* 10.6p
Japanese raisin tree, *Hovenia* 10.1t
Jasmine, *Jasminum* 5.7Et, 10.4a, 10.4o, 10.5o, 10.6o, 13.4Dt
Jequirity bean, *Abrus* 5.7B, 5.8V, 8.1p, 9.1B, 9.7o, 10.1t, 12.2A, 14.5p
Jerusalem sage, *Phlomis* 10.1t
Jewish plum, *Spondias* 5.3Ap
Jew's myrtle, *Ruscus* 13.4Ht
Jimsonweed, *Datura* 3.1Ba, 5.2Ba, 12.2A, 13.5E
Jiqi, *Pera* 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp
Job's tears, *Cotix* 13.2, 13.5F
Joint vetch, *Aeschynomene* 14.2t
Jointfir, *Ephedra* 5.3Co
Jojo, *Puffia* 11.1Gt
Jonquil, *Narcissus* 3.1Aa, 6.4a, 9.2a, 9.7a, 10.1o, 10.4p, 12.2B, 13.8O
Jopoy, *Esenbeckia* 4.4Aa, 5.5Da, 12.1a
Jujube, *Ziziphus* 10.1t
Jumbie bean, *Leucaena* 9.3Ao, 11.2Fa, 11.2Fp, 12.1o, 14.3Bo
Jumpy pepper, *Microtea* 5.1Ap
Juniper, *Juniperus* 4.4At, 5.7Gt, 6.4t, 7.4p, 9.3Gp, 9.5Bp, 9.6Ep, 10.1p, 10.4t, 12.1p, 14.1At, 14.5t
Jurinia, *Jurinea* 10.6t, 14.1At
Jute, *Corchorus* 4.1Ct

Kachana, *Iostephane* 4.4At
Kadsura, *Kadsura* 5.7Gp
Kaempferia, *Kaempferia* 5.8Q, 10.4t
Kamala tree, *Mallotus* 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 9.3Dp, 9.5Bp, 13.1p, 13.4Ap, 13.6Bp
Kandelia (mangrove), *Kandelia* 13.6Bp
Kapok tree, *Ceiba* 14.1Ap
Kapur, *Dryobalanops* 10.4t
Karwinskia, *Karwinskia* 9.3Gp, 9.7p
Katbo, *Lophopetalum* 13.8Mt
Katsura tree, *Cercidiphyllum* 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 13.4Ap
Kauri, *Agathis* 7.4p, 9.5Bp
Kelp, *Laminaria* 10.1o
Kelp, *Macrocystis* 11.2E
Keruing, *Dipterocarpus* 8.1t
Kharbagehindi, *Picrorhiza* 5.8R, 8.3M, 10.2p, 13.4Ip

Khat, *Catha* 5.3Co, 6.2p, 6.3o, 7.3At, 11.2E, 13.1p, 14.1At
Kikuyu grass, *Pennisetum* 7.1o, 11.2Fp, 13.5B
King's spear, *Asphodeline* 9.5Bp, 14.5p
Kiwi, *Actinidia* 10.3o, 13.4Ip
Knapweed, *Centaurea* 7.4p, 10.2p, 11.1E, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.8Kp, 13.8Yp, 14.1Ao, 14.5p
Knee Holly, *Ruscus* 13.4Ht
Knight's spur, *Consolida* 3.1Ba
Knotweed, *Polygonum* 4.1Ap, 5.1Ap, 5.8H, 5.9, 6.5p, 7.3Aa, 7.3Ap, 7.4p, 8.1p, 8.4p, 9.3Ap, 9.3Dp, 9.7p, 10.6t, 11.1Ip, 11.2An, 12.1p, 13.4Ap, 13.4Dp, 13.6Ap, 13.6Cp, 13.8Jp, 13.8ZN, 13.8ZOp, 14.1Aa, 14.1Ap, 14.2p, 14.5p
Kohlrabi, *Brassica* 3.3Aa, 3.3Bp, 3.3C, 5.5Bo, 5.6a, 6.1C, 7.1o, 7.4p, 10.2a, 10.4o, 10.4p, 10.5o, 10.6o, 10.6t, 10.7, 11.1Gp, 11.1Gt, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Bo, 11.2E, 11.2Go, 12.2E, 12.4B, 12.4C, 13.5I, 13.5J, 13.5K, 13.5M, 13.5O, 13.7E, 13.8ZM, 14.1Ao, 14.2t, 14.4A, 14.6p
Kratom, *Mitragyna* 5.6a, 14.2p, 14.6p
Kudzu, *Pueraria* 3.2Bp, 4.5A, 7.3Ap, 7.3Cp, 8.1p, 9.3Gp, 11.1Ip, 11.1It, 11.2Fp, 13.4Ap, 13.6Ap, 14.5p
Kunzea, *Kunzea* 10.4t
Kwao keur, *Pueraria* 3.2Bp, 4.5A, 7.3Ap, 7.3Cp, 8.1p, 9.3Gp, 11.1Ip, 11.1It, 11.2Fp, 13.4Ap, 13.6Ap, 14.5p

Lablab, *Lablab* 8.1p, 8.3Cp, 11.1Ip, 13.2
Labrador tea, *Ledum* 10.4t
Laburnum, *Laburnum* 3.1Aa, 3.1Ba, 4.1Ep, 7.3Ap, 8.1p, 12.2A, 13.6Ap, 14.2p, 14.6a
Ladybells, *Adenophora* 13.1a
Ladyfern, *Athyrium* 14.6p
Lagenaria, *Lagenaria* 13.5P
Lagenaria, *Lagerstroemia* 14.1Aa
Lambsquarters, *Chenopodium* 5.8N, 5.8O, 7.1o, 7.3Bp, 7.3Bt, 9.1A, 10.2t, 10.3o, 10.4o, 10.4t, 10.5o, 11.1Gt
Lancepod, *Lonchocarpus* 12.2A, 13.1a, 13.5G, 13.6Bp
Lantern tree, *Crinodendron* 10.2t, 11.1Gt
Larch, *Larix* 5.8R, 10.1o, 10.4o
Larkspur, *Delphinium* 3.1At, 3.1Ba, 4.2a, 4.5A, 6.5p, 8.1p, 8.3Cp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.7Ht, 13.8C, 13.8Jp, 14.5p
Laser, *Laser* 10.6t
Laurel, *Laurus* 5.7C, 7.3At, 7.3Bt, 13.7D, 13.8Mt
Lavender, *Lavandula* 3.1Bt, 5.2At, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.1t, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Bt, 10.4o, 10.4p, 10.4t, 10.5t, 10.6t, 13.1t
Lawsonia, *Lawsonia* 14.1Ap, 14.2p

- Lead tree, *Leucaena* 9.3Ao, 11.2Fa, 11.2Fp, 12.1o, 14.3Bo
- Leadwort, *Plumbago* 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp, 14.5p
- Leaf flower, *Phyllanthus* 3.2Ba, 4.3Ap, 4.3Bp, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 5.6p, 8.1p, 8.1t, 9.3Dp, 9.3Gt, 9.5Bp, 10.2p, 13.4Ap, 13.4Ht, 13.8Mt, 13.8Yt, 14.5p
- Leaf of God, *Tabernanthe* 3.2Aa, 3.3Aa, 3.3Ea, 3.4Aa, 4.2a, 5.1Aa, 5.2Aa, 5.3Aa, 5.4a, 5.5Da, 5.6a, 6.3a
- Lemon, *Citrus* 3.1Bt, 3.2Ap, 4.5A, 5.1Ap, 5.3Ap, 5.3Bp, 5.5Da, 5.8R, 5.8W, 6.3p, 6.4t, 6.5p, 7.3Bp, 7.3Bt, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.3Ap, 9.5Ap, 9.5Bp, 9.6Bt, 9.6Et, 9.7p, 9.7t, 10.1n, 10.2p, 10.2t, 10.3o, 10.4a, 10.4o, 10.4p, 10.4t, 10.5o, 10.5p, 10.5t, 10.6o, 10.6t, 11.1E, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ct, 11.2Fp, 12.1p, 12.2B, 12.2C, 13.4Gp, 13.5K, 13.6Ap, 13.7Hp, 13.8C, 13.8Jp, 13.8Kp, 13.8Qp, 13.8Yp, 13.8ZOp, 14.1Ap, 14.2o, 14.2p, 14.2t, 14.5p, 14.6p
- Lemongrass, *Cymbopogon* 10.4t, 10.5t, 12.1p
- Lentil, *Lens* 12.2A, 13.8ZI, 14.2t
- Lespedeza, *Lespedeza* 13.4Dp
- Lethedon, *Lethedon* 9.3Fp
- Lettuce, *Lactuca* 9.5Ap, 10.2t
- Levisticum, *Levisticum* 6.5p, 7.2B, 7.3Bp, 7.3Bt, 8.1p, 9.3Ap, 9.5Ap, 11.2Gp, 12.1p, 13.4Hp, 14.1Ap, 14.2p, 14.5p
- Lichen, *Cetraria* 9.3Co, 9.5Bo, 9.5Bt
- Lignum vitae, *Guaiacum* 4.3Bp, 4.3Cp, 4.4Ap, 10.4p, 10.4t, 10.5p, 14.1Ap, 14.6p, 14.1Ap
- Lily, *Lilium* 7.4t, 14.2t
- Lily of the valley, *Convallaria* 4.1Ct
- Lily of the valley bush, *Pteris* 4.2t, 5.8J, 8.1p, 8.3Cp, 10.2p, 11.1Hp, 11.1Ip, 11.2Gp, 13.6Ap, 13.7Ep, 13.7I
- Lim panas, *Goniothalamus* 9.7o, 12.1a, 13.6Bo
- Lime, *Citrus* 3.1Bt, 3.2Ap, 4.5A, 5.1Ap, 5.3Ap, 5.3Bp, 5.5Da, 5.8R, 5.8W, 6.3p, 6.4t, 6.5p, 7.3Bp, 7.3Bt, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.3Ap, 9.5Ap, 9.5Bp, 9.6Bt, 9.6Et, 9.7p, 9.7t, 10.1n, 10.2p, 10.2t, 10.3o, 10.4a, 10.4o, 10.4p, 10.4t, 10.5o, 10.5p, 10.5t, 10.6o, 10.6t, 11.1E, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ct, 11.2Fp, 12.1p, 12.2B, 12.2C, 13.4Gp, 13.5K, 13.6Ap, 13.7Hp, 13.8C, 13.8Jp, 13.8Kp, 13.8Qp, 13.8Yp, 13.8ZOp, 14.1Ap, 14.2o, 14.2p, 14.2t, 14.5p, 14.6p
- Linden, *Tilia* 3.2Ap, 7.4p, 8.1p, 8.3Cp, 13.8S, 14.5p
- Lippia, *Lippia* 10.1t, 10.2p, 10.4t, 14.1Ap
- Lipstick tree, *Bixa* 8.1t
- Liquidambar, *Liquidambar* 7.3Bp, 10.4p, 13.6Bp
- Liquirice, *Glycyrrhiza* 4.1Ct, 4.4Aa, 5.8K, 7.4p, 8.1p, 8.1t, 8.2t, 10.1t, 10.4o, 11.1C, 11.1D, 11.1E, 11.1F, 11.1Ip, 11.1It, 11.1Jp, 11.1Kt, 13.4Ht, 13.4Ip, 13.6Cp, 13.8N, 13.8Qp, 13.8ZC, 14.1Ap, 14.3A, 14.5p, 14.6t
- Liquirice root, *Ligusticum* 4.4Aa, 7.4p
- Liquorice root, *Scoparia* 13.1t
- Liverseed grass, *Urginea* 4.1Ct
- Livingrock, *Ariocarpus* 10.6p
- Lobelia, *Lobelia* 3.1Aa, 3.1Ba, 6.2t, 13.1a, 13.4Gt
- Locoweed, *Oxytropis* 13.1a
- Locust, *Gleditsia* 7.4p
- Locust, *Robinia* 4.1Cp, 7.3Co, 7.4p, 8.1p, 8.3Cp, 10.4o, 10.4p, 10.6o, 11.1Bp, 12.2A, 13.4Ap, 14.1Ap, 14.5p
- Logwood, *Haematoxylon* 5.1Ap
- Lomatia, *Lomatia* 8.1p, 11.1Hp, 13.8Kp
- Loosestrife, *Lysimachia* 13.8V
- Lophophora, *Lophophora* 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 6.3p, 6.5p, 11.2Jp
- Lophophytum (parasitic plant), *Lophophytum* 13.6Ap
- Lotebush, *Ziziphus* 10.1t
- Lotononis, *Lotononis* 14.2t
- Lotus, *Nelumbo* 3.3Aa, 5.5Da, 5.4a, 7.3Aa, 14.5p
- Lovage, *Levisticum* 6.5p, 7.2B, 7.3Bp, 7.3Bt, 8.1p, 9.3Ap, 9.5Ap, 11.2Gp, 12.1p, 13.4Hp, 14.1Ap, 14.2p, 14.5p
- Lucky nut, *Thevetia* 4.1Ct
- Luffa, *Luffa* 8.1t, 9.1A, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Ao, 13.1t, 13.4At, 13.4Ht, 13.5P, 13.8Jt
- Lunaria, *Lunaria* 3.2Bo, 3.3Do, 6.3o, 6.4a
- Luo guo di, *Hemsleya* 10.1t, 10.2t
- Lupine, *Lupinus* 3.1Aa, 3.1Ba, 3.2Bp, 3.3Aa, 3.3Bp, 3.3C, 4.1Ep, 4.2a, 4.3Aa, 4.3Ca, 4.5A, 4.5C, 5.1Ap, 5.5Bo, 5.5Da, 7.3Ap, 7.3Cp, 8.1p, 8.1t, 8.3Cp, 9.3Gp, 9.3Gt, 9.7p, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 13.8Mt, 13.8Yt
- Lychee, *Litchi* 9.7t, 10.4o, 10.4p, 10.4t, 13.8D, 13.8ZA, 14.2p
- Lychnis, *Petrocoptis* 9.1A
- Lychnophora, *Lychnophora* 7.3At
- Lycoris, *Lycoris* 3.1Aa, 6.4a, 9.2a, 9.7a, 13.8O
- Lysionotus, *Lysionotus* 14.5p
- Maackia, *Maackia* 12.2A, 13.5E
- Machilus, *Machilus* 3.3Da
- Macleaya, *Macleaya* 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 6.1A, 6.1B
- Maclura, *Maclura* 4.1Ep, 8.1p, 12.2B
- Macrotyloma, *Macrotyloma* 13.5G
- Madagascar Periwinkle, *Catharanthus* 4.2a, 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 5.6a, 5.8D, 6.3a, 9.3Ga, 10.2t, 12.1a, 13.7Ha
- Madder, *Rubia* 8.1p, 9.5Ap, 12.1p, 13.6Dp
- Madera del diablo, *Tonduzia* 4.2a
- Madrone, *Arbutus* 10.5p

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- Magnolia, *Galbulimima* 5.2Ba
Magnolia, *Himantandra* 5.2Ba
Magnolia, *Magnolia* 3.1Ba, 3.2Bp, 4.4Aa, 4.4Ap, 5.2Aa, 5.2Ba, 5.3Aa, 5.7C, 5.7Gp, 7.3Ap, 8.1p, 9.3Ga, 10.1p, 10.4p, 11.1E, 12.1p, 14.1Ap
Mahogany, *Azelia* 14.1Ao, 14.6p
Maid of the mist, *Thalictrum* 3.1Ba, 3.3Da, 4.4Aa, 5.1Ap, 5.2Ba, 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 6.1B, 6.4a, 7.4p, 9.3Aa, 9.5Ba, 12.1a, 13.7Ha
Maidenhair fern, *Adiantum* 8.1p, 10.2p, 11.2Fp
Maidenhair tree, *Ginkgo* 3.2Ap, 3.2At, 3.3At, 5.2At, 5.7Gt, 7.3Ap, 7.3At, 7.4p, 8.1p, 8.3Cp, 8.3E, 8.3R, 9.7t, 10.2t, 10.5t, 10.6t, 11.1M, 13.8ZC, 14.1Ap, 14.2t, 14.5P
Maize, *Zea* 4.2o, 4.4E, 4.4Fn, 5.5Da, 5.8La, 6.5a, 7.4a, 8.3L, 10.2o, 10.3o, 10.4a, 10.4o, 10.4t, 10.6a, 10.6o, 10.6t, 11.1In, 11.1Io, 11.1It, 11.1Kp, 11.2Ct, 12.1a, 12.2D, 12.2E, 12.4B, 12.4E, 13.2, 13.5B, 13.5C, 13.5F, 13.5N, 13.5Q, 13.5R, 14.2t, 14.5p, 14.6o, 14.6p
Mallotus, *Mallotus* 5.3Ap, 5.3Bp, 5.4p, 5.5Dp, 5.6p, 5.7Ep, 5.9, 9.3Dp, 9.5Bp, 13.1p, 13.4Ap, 13.6Bp
Mallow, *Malva* 6.5p
Maltese mushroom (parasitic plant), *Cynomorium* 13.4At, 13.4Ht, 13.8Jt
Mammea, *Mammea* 8.1p, 10.3o
Mammea, *Ochrocarpus* 8.1p
Mammyapple, *Mammea* 8.1p, 10.3o
Manchineel, *Hippomane* 3.1Aa, 6.4a, 8.2t, 14.1Ap
Manchu tuber gourd, *Thladiantha* 10.1t
Mandrake, *Mandragora* 3.1Ba, 5.2Ba
Mango, *Mangifera* 10.2p, 10.3o, 13.4Ip, 13.8Jp, 14.2p, 14.6p
Manihot, *Manihot* 3.3Ao, 9.1A, 10.2o, 13.6Bo
Manila tamarind, *Pithecolobium* 9.3Aa
Manjack, *Cordia* 10.6t, 11.1Jp
Mannia, *Pierroedendron* 9.2t
Manzanita, *Arctostaphylos* 6.4t, 8.1t, 9.3Ct, 9.3Dt, 9.3Ft, 9.3Gt, 9.5Bt, 9.7t, 13.4At, 13.4Ht, 13.4Ip, 13.8Jt, 14.1At
Maple, *Acer* 4.1Bp, 4.1Cp, 5.3Ap, 5.3Bp, 5.4p, 5.5Da, 5.5Dp, 5.6p, 5.7Ep, 5.9, 7.3Ap, 7.3Bp, 9.5Ap, 10.1o, 13.1p, 13.4Ap, 13.6Bp, 13.8D, 13.8ZOp, 14.1Ap
Maple, *Platanus* 7.4p, 8.1p
Mappia, *Mappia* 9.3Fa, 12.1a
Maprounea, *Maprounea* 9.3Ct, 9.5Bt
Marchantia, *Marchantia* 11.2Gp, 14.1Ap, 14.2p
Marigold, *Tagetes* 4.1Cp, 8.1o, 8.1p, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 10.4o, 10.4p, 10.4t, 12.1p, 13.6Ap, 14.1Ap
Marijuana, *Cannabis* 5.7Ep, 5.8C, 6.3p, 11.1Ap, 13.6Bp
Marjoram, *Origanum* 4.5A, 4.5C, 5.1Ap, 5.2At, 6.1F, 6.4t, 7.2B, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 10.2p, 10.4p, 10.4t, 10.5t, 10.6p, 11.2Fp, 13.4Hp, 13.4Ip, 13.8Qp, 14.1Ap, 14.2p, 14.5p, 14.6p
Marl berry, *Ardisia* 7.4t, 14.1Ap
Marsh elder, *Iva* 9.7t, 10.6t, 12.1t, 14.5p
Marsh fleabane, *Tessaria* 10.1p
Marshmallow, *Althaea* 5.2Bo
Mashatu tree, *Xanthocercis* 13.1a, 14.6o
Masterwort, *Astrantia* 7.2B, 9.5Ap, 11.2Gp, 13.4Hp, 14.1Ap, 14.2p, 14.5p
Matchwood, *Schefflera* 4.4Ao, 5.2At, 5.2Bo, 5.4t, 5.5Do, 5.5Dt, 7.3Ao, 14.1Ao
Maté, *Ilex* 4.3Aa, 4.3Ba, 4.3Ca, 4.4D, 4.4E, 5.1Aa, 7.4a, 10.2a, 14.2p
Matico, *Piper* 3.2Bp, 3.4Ba, 4.2p, 5.1Ap, 5.2Aa, 5.7Gp, 6.1F, 6.3a, 6.3p, 6.5p, 10.4o, 10.4p, 10.4t, 10.6p, 12.1p, 13.8Qp, 14.1Ap, 14.6a
Matteuccia, *Matteuccia* 14.5p, 14.6p
Mayapple, *Podophyllum* 4.1Cp, 4.5A, 5.1Ap, 7.1p, 7.3Ap, 7.4p, 8.1p, 8.3Cp, 8.4p, 9.2p, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.6Ep, 11.1E, 11.1Gp, 11.1Hp, 14.6p
Mayten, *Maytenus* 5.3Co, 6.2p, 6.3o, 7.3At, 9.2t, 9.3At, 9.6Eo, 11.2E, 12.1t, 13.7Ht, 14.1At
Meadow rue, *Thalictrum* 3.1Ba, 3.3Da, 4.4Aa, 5.1Ap, 5.2Ba, 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 6.1B, 6.4a, 7.4p, 9.3Aa, 9.5Ba, 12.1a, 13.7Ha
Meadowsweet, *Spiraea* 5.8R, 7.3Bt
Medick, *Medicago* 7.4p, 8.1o, 8.1p, 8.2p, 8.3Cp, 10.3o, 11.1Gp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2It, 12.2A, 13.3, 13.4Hp, 13.5G, 14.1Ap, 14.2t, 14.6t
Melancieira, *Alexa* 13.1a
Melastoma, *Melastoma* 7.3Ap, 7.3Bp
Melastome, *Melastoma* 7.3Ap, 7.3Bp
Melia, *Melia* 4.4At, 5.8R, 7.3Ba
Melicope, *Melicope* 5.5Da
Melicope, *Pelea* 10.1p, 10.4p
Melodinus, *Melodinus* 4.2a
Melon, *Cucumis* 5.8La, 6.5a, 10.2t, 10.4o, 10.5o, 10.6o, 11.1Bo, 11.1Gt, 11.2Bo, 12.2D, 13.5P, 14.1Ao, 14.6o
Mescal, *Lophophora* 5.3Ap, 5.3Bp, 5.3Cp, 5.4p, 5.5Dp, 6.3p, 6.5p, 11.2Jp
Mesquite, *Prosopis* 5.5Da, 5.8La, 6.5a, 10.1o, 13.5K, 14.2p
Methysticodendron, *Methysticodendron* 5.2Ba
Mexican jumping bean, *Sebastiania* 14.1Ap
Mexican mint, *Plectranthus* 3.2Bt, 10.2t, 10.4o
Mezoneuron, *Mezoneuron* 14.2p
Michelia, *Michelia* 5.5Dt, 5.7C, 6.2t, 7.3At, 8.1t, 10.4o, 10.4t, 10.5o, 14.1At
Microcitrus, *Microcitrus* 10.2p
Midsorus fern, *Blechnum* 7.4t
Milk thistle, *Silybum* 7.3Bp, 8.1p, 13.7Hp, 14.1Ap, 14.2p, 14.5p, 14.6p

- Milkpea, *Galactia* 14.2t
 Milktree, *Sapium* 8.2t, 14.1Ap
 Milkvetch, *Astragalus* 7.2Co, 7.4p, 9.7o, 10.3o, 13.1a, 14.2o, 14.3Bo, 14.5p
 Milkvetch, *Didymocarpus* 10.4t
 Milkvine, *Vincetoxicum* 9.2a
 Milkweed, *Asclepias* 3.1Aa, 3.1Ba, 4.1Ct, 6.1G, 6.2a, 10.2a, 10.5o, 10.6o
 Milkwood, *Tabernaemontana* 3.2Aa, 3.3Aa, 3.4Aa, 4.2a, 5.1Aa, 5.6a
 Milkwort, *Polygala* 5.7B, 5.8V, 13.7Et, 14.6t
 Millettia, *Millettia* 7.4p
 Miltwaste, *Ceterach* 8.1p, 10.2p, 11.2Fp, 14.5p
 Mimosa, *Mimosa* 5.3Bp, 5.3Cp, 5.5Da, 9.3Ao, 12.1o, 14.3Bo
 Mimusops, *Mimusops* 10.1o
 Miniature beefsteak plant, *Mosla* 10.4o, 10.4t, 10.6o, 10.6t
 Mint, *Mentha* 4.5A, 4.5C, 5.1Ap, 5.6t, 7.2B, 7.3Ap, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 8.3Cp, 9.5Ap, 10.4t, 10.6o, 10.6t, 11.1Hp, 11.2Gp, 13.4Hp, 13.8ZF, 14.1Ap, 14.2p, 14.5p
 Miracle berry, *Richadella* 13.5K
 Miracle fruit, *Gymnema* 5.8J, 10.1o, 10.1t, 10.2t, 13.7Et, 14.6t
 Miracle fruit, *Thaumatococcus* 10.1o, 12.4E
 Miraculous berry, *Synsepalum* 10.1o Synsepalum, *Synsepalum* 10.1o
 Mistletoe, *Phoradendron* 9.1B, 12.2B, 12.4F
 Mistletoe, *Viscum* 4.4Ao, 5.3Bp, 6.3p, 6.5p, 9.1B, 9.6Bn, 9.7o, 10.1o, 12.2B, 12.2C, 12.4F, 13.4At, 13.4Ht, 13.5E, 13.8Jt
 Mitique, *Podanthus* 14.2t
 Mitracarpus, *Mitracarpus* 10.5t, 10.6o
 Mkidori, *Harrisonia* 9.6Et, 10.2t
 Molly, *Kochia* 14.6t
 Mombin, *Spondias* 5.3Ap
 Momordica, *Momordica* 5.8F, 5.8K, 9.1A, 9.5Ao, 12.2B, 12.4C, 13.5N, 13.5P, 14.6o
 Mondia, *Mondia* 6.1F
 Monechma, *Monechma* 5.8Q
 Moneywort, *Alisicarpus* 14.2t
 Monimia, *Monimia* 8.1a
 Monkeypuzzle tree, *Araucaria* 7.3Ap, 7.4p, 9.5Bp, 11.1Ip, 14.5p
 Monkshood, *Aconitum* 3.1Aa, 3.1Ap, 3.1Ba, 4.2a, 4.3Aa, 4.3Ca, 5.3Ca, 5.4a, 6.4a, 7.3Aa, 10.3o, 13.7Ht
 Monochasma, *Monochasma* 10.2p, 14.1Ap, 14.5p, 14.5t
 Montanoa, *Montanoa* 5.8Q
 Moon carrot, *Libanotis* 7.4p
 Moon carrot, *Seseli* 7.4p, 7.4t, 9.3Ap, 10.4t, 10.5t, 12.1p
 Moonseed, *Menispermum* 3.1Ba, 3.2Bt, 3.3Dt, 4.4Aa, 5.7Ga, 7.1a
 Moreton Bay chestnut, *Castanospermum* 13.1a, 14.6a
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 Morning glory, *Pharbitis* 12.2C, 13.1p, 14.2a
 Mosla, *Mosla* 10.4o, 10.4t, 10.6o, 10.6t
 Mount Atlas daisy, *Anacyclus* 14.1Ao
 Mountain ash, *Sorbus* 8.1p, 8.3Cp, 10.1o
 Mountain laurel, *Kalmia* 4.2t, 5.8J, 8.1p, 8.3Cp, 10.2p, 11.1Hp, 11.1Ip, 11.2Gp, 13.6Ap, 13.7Ep, 13.7I
 Mouse plant, *Arisarum* 9.7a
 Movingui, *Distemonanthus* 14.5p
 Mucuna, *Mucuna* 3.1Aa, 3.3Ea, 5.5Da, 5.8La, 6.5a, 10.5a, 13.8F, 14.1Ap, 14.6a
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 Mung bean, *Vigna* 3.2Bp, 7.3Ap, 7.3Cp, 9.5Ao, 9.5Bo, 10.1o, 10.7o, 11.1Bp, 11.1Gp, 11.1Ip, 11.1Jp, 11.1Kp, 12.2A, 12.4A, 13.4Ap, 13.5G, 13.5N, 14.2t, 14.5p, 14.6o
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 Mustard, *Brassica* 3.3Aa, 3.3Bp, 3.3C, 5.5Bo, 5.6a, 6.1C, 7.1o, 7.4p, 10.2a, 10.4o, 10.4p, 10.5o, 10.6o, 10.6t, 10.7, 11.1Gp, 11.1Gt, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Bo, 11.2E, 11.2Go, 12.2E, 12.4B, 12.4C, 13.5I, 13.5J, 13.5K, 13.5M, 13.5O, 13.7F, 13.8ZM, 14.1Ao, 14.2t, 14.4A, 14.6p
 Mustard, *Sinapis* 5.5Bo, 5.8V, 7.1o, 10.4p, 12.4A, 12.4C, 13.5I, 13.5M
 Myoporium, *Myoporium* 14.2p
 Myroxylon, *Myroxylon* 8.1p, 10.2p, 10.4t
 Myrrh, *Commiphora* 6.1F, 6.5p, 7.3Bt, 10.4p, 10.4t, 14.6t
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 Myrtus, *Myrtus* 10.4t, 10.6t
 Naked lady, *Brunsvigia* 9.2a
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 Narcissus, *Narcissus* 3.1Aa, 3.1Aa, 6.4a, 9.2a, 9.7a, 10.1o, 10.4p, 12.2B, 13.8O
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 Nardoo, *Marsilia drummondii* 13.8ZK
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- Necklace pod, *Sophora* 3.1Aa, 3.1Ba, 3.2Bp, 4.4Ap, 4.5A, 4.5C, 5.1Ap, 5.6a, 5.9, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Gp, 9.7p, 10.5a, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2A, 13.4Ap, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 14.1Ap, 14.5p, 14.6a
- Nectarine, *Prunus* 3.2Ap, 3.2Bp, 4.2p, 4.5A, 4.5C, 5.1Ap, 5.5Dp, 5.7C, 5.8O, 7.3Ap, 7.3Cp, 8.1p, 8.3Cp, 9.3Do, 9.3Gp, 9.7p, 10.1o, 10.2o, 10.3o, 10.4o, 10.4t, 10.5o, 10.5t, 10.6o, 10.6t, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2E, 12.4E, 13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C, 13.8D, 14.1Ap, 14.2p, 14.2t, 14.5o, 14.5p
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- Needleleaf, *Tillandsia* 14.6o
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- Nettlespurger, *Jatropha* 4.4At, 5.5Bt, 12.1t
- Neverdie, *Kalanchoe* 7.4a
- New Jersey tea, *Ceanothus* 13.8Zop
- New South Wales Christmas bush, *Ceratopetalum* 8.1t
- Ng bamu, *Teclea* 5.1Aa
- Ngaio tree, *Myoporum* 14.2p
- Nicker, *Caesalpinia* 6.1E
- Nigella, *Nigella* 10.4a, 14.1Ap
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- Nipplewort, *Lapsana* 14.2p
- Nolina, *Nolina* 7.4t
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- Onosma, *Onosma* 5.7C, 9.3Fp, 9.3Gp
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- Oregano, *Origanum* 4.5A, 4.5C, 5.1Ap, 5.2At, 6.1F, 6.4t, 7.2B, 7.3Bp, 7.3Cp, 7.4p, 8.1p, 10.2p, 10.4p, 10.4t, 10.5t, 10.6p, 11.2Fp, 13.4Hp, 13.4Ip, 13.8Qp, 14.1Ap, 14.2p, 14.5p, 14.6p
- Orient vine, *Sinomenium* 5.1Aa, 7.3Ba, 8.3J, 8.3Q
- Oriental arborvitae, *Biota* 5.1Ap, 5.7Gt
- Orixa, *Orixa* 3.1Ba, 5.5Da
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- Ormosia, *Ormosia* 3.1Aa
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 Otholobium, *Otholobium* 14.6t
 Ouratea, *Ouratea* 14.5p
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 Paeonia, *Paeollia* 8.1p, 13.1p, 13.6Bp, 13.8Zop
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 Pancratium, *Pancratium* 3.1Aa, 6.4a, 9.2a, 14.1Ap
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 Paterson's curse, *Echium* 5.7C, 9.3Fp, 9.3Gp, 13.8ZF, 14.5p
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 Pawpaw, *Asimina* 5.3Aa, 5.3Ca, 5.5Da, 8.1p, 13.6Bo
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 Pea, *Lathyrus* 3.3Ao, 3.3Bo, 5.3Ba, 5.8Lo, 6.3o, 8.3A, 8.3M, 12.2A, 13.8Z, 14.1Ap
 Pea, *Pisum* 3.1Ao, 3.2Bo, 3.3Bo, 5.2Ao, 5.3Bp, 5.3Cp, 5.5A, 7.4a, 7.4p, 8.1p, 8.3Cp, 9.1A, 10.3o, 11.1Gp, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 12.2A, 12.2E, 12.4A, 12.4E, 13.5G, 14.1Ao, 14.2t, 14.6p
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 Pearl millet, *Pennisetum* 7.1o, 11.2Fp, 13.5B
 Pearly everlasting, *Anaphalis* 4.4B, 8.1t, 11.1Jt, 13.6Dt, 13.8Qt
 Pegalum, *Pegalum* 3.2Aa, 3.3Aa, 4.1Ca, 4.2a, 4.4Aa, 5.3Aa, 5.3Ba, 5.5Da, 5.8La, 5.9, 6.2a, 6.4a, 6.5a, 9.3Gt, 12.1a, 13.1a
 Pelargonium, *Pelargonium* 6.5p, 10.3o, 10.4t, 14.1Ap, 14.5p
 Pencil flower, *Stylosanthes* 14.2t
 Pennyroyal, *Hedeoma* 10.4t
 Penstemon, *Penstemon* 4.4Ap, 8.1p
 Peony, *Paeollia* 8.1p, 13.1p, 13.6Bp, 13.8Zop
 Peony, *Paeonia* 4.1Bp, 4.1Cp, 4.3Ap, 4.4Ap, 5.1Ap, 5.3Bp, 5.4p, 5.6p, 11.1C, 11.1D, 11.1F, 11.1Ip, 11.2Gp, 13.1p, 13.1t, 13.6Bp, 13.8ZOp, 14.6o
 Pepper, *Capsicum* 3.4Bp, 4.2p, 4.3Cp, 4.4Aa, 5.3Ap, 5.7C, 5.8V, 6.4a, 6.1F, 7.4p, 10.4o, 11.2Ct, 12.2D, 12.2E, 12.4B, 12.4D, 12.4E, 12.4F, 13.5O, 14.1At, 14.2o, 14.2t, 14.5p
 Pepper, *Piper* 3.2Bp, 3.4Ba, 4.2p, 5.1Ap, 5.2Aa, 5.7Gp, 6.1F, 6.3a, 6.3p, 6.5p, 10.4o, 10.4p, 10.4t, 10.6p, 12.1p, 13.8Qp, 14.1Ap, 14.6a
 Peppertree, *Schinus* 4.1Bp, 13.1p, 13.6Bp, 13.8ZOp, 14.1Ap
 Pepperweed, *Lepidium* 10.4p
 Pepperwort, *Lepidium* 10.4p
 Pera, *Pera* 8.1p, 9.3Ap, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp
 Pergularia, *Pergularia* 9.2a, 9.4Aa, 9.4Ba
 Periandra, *Periandra* 10.1t
 Perilla, *Perilla* 9.3Do, 10.1n, 14.1Ap, 14.5o, 14.5p, 14.5t
 Periploca, *Periploca* 5.7C
 Periwinkle, *Catharanthus* 4.2a, 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 5.6a, 5.8D, 6.3a, 9.3Ga, 10.2t, 12.1a, 13.7Ha
 Periwinkle, *Vinca* 6.3a, 9.6Ea, 13.4Ap, 13.7Ha, 14.5p
 Peronia, *Ormosia* 3.1Aa
 Perriera, *Perriera* 13.8W
 Persian shield, *Strobilanthes* 7.3Aa, 11.2Aa, 14.1Aa
 Persimmon, *Diospyros* 4.3At, 6.5p, 7.3Ap, 8.1p, 8.1t, 9.3Ap, 9.3Fp, 9.3Gp, 11.1Hp, 12.1p, 13.8Jp, 13.8Kp, 14.5p
 Perupok, *Lophopetalum* 13.8Mt
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 Petrocoptis, *Petrocoptis* 9.1A

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- Petrocosmea, *Petrocosmea* 11.2Gp
Pettigree, *Ruscus* 13.4Ht
Petunia, *Petunia* 12.2D, 12.4A, 12.4B, 12.4D
Peucedanum, *Peucedanum* 4.4Ap, 5.7Gp, 5.8W,
7.3Bp, 7.4p, 14.1Ap
Peumus, *Boldea* 8.1a
Peumus, *Peumus* 3.1Aa, 8.1a, 14.2a
Peyote, *Lophophora* 5.3Ap, 5.3Bp, 5.3Cp, 5.4p,
5.5Dp, 6.3p, 6.5p, 11.2Jp
Pfaffia, *Pfaffia* 11.1Gt
Phaseolus, *Rudua* 14.2t
Pheasant's eye, *Adonis* 4.1Ct, 10.3o
Phebalium, *Phebalium* 6.5p, 8.1p, 9.3Ap, 12.1p
Phool, *Woodfordia* 9.3Gp
Phycanthus, *Phycanthus* 5.4a
Phyllocladus, *Phyllocladus* 8.1p
Physena, *Physena* 9.7t
Pichi pichi, *Fabiana* 10.1o
Picralima, *Picralima* 5.6a
Picrorhiza, *Picrorhiza* 5.8R, 8.3M, 10.2p,
13.4Ip
Pieris, *Pieris* 4.2t, 5.8J, 8.1p, 8.3Cp, 10.2p,
11.1Hp, 11.1Ip, 11.2Gp, 13.6Ap, 13.7Ep,
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Pigweed, *Amaranthus* 9.1A, 12.2C, 13.2, 13.5N
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Pimentum, *Pimentum* 6.1F, 10.4p, 13.8Qp,
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11.1Kp, 11.1Kt, 11.2Fp, 11.2It, 12.1p, 12.2D,
12.4B, 13.6Ap, 13.6Cp, 13.7Hp, 13.8W,
13.8Yp, 13.8ZN, 13.8ZOp, 14.1Ap, 14.1At,
14.2p, 14.5p
Pineapple broom, *Argyrocytisus* 4.1Ep
Pineapple bush, *Argyrocytisus* 4.1Ep
Pineapple guava, *Feijoa* 4.3Ap, 5.3Ap, 5.3Bp,
5.4p, 5.6p, 7.3Bp, 13.6Bp, 13.7Ho
Pineapple, *Ananas* 3.1Aa, 3.3Ea, 5.5Da, 10.5a,
13.5B, 13.5G, 13.8F, 14.2t, 14.6a
Piptadenia, *Piptadenia* 5.5Da, 5.8La, 6.5a
Pistache, *Pistacia* 8.1t, 10.3o, 11.1Ip, 13.4Dp
Pistachio, *Pistacia* 8.1t, 10.3o, 11.1Ip, 13.4Dp
Pitcher plant, *Nepenthes* 5.7Ea
Pitcher plant, *Sarracenia* 3.1Aa, 5.7Ea
Pituri, *Duboisia* 3.1Aa, 5.2Ba, 6.2a
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5.3Bp, 5.3Ca, 5.3Cp, 5.4a, 5.4p, 5.5Da, 5.6a,
5.7Ea, 5.8F, 5.8O, 7.4p, 8.2p, 10.3o, 10.4o,
10.4p, 10.4t, 10.5a, 10.6o, 11.2Jp, 12.2D,
12.2E, 12.4E, 13.6Ba, 13.8F, 13.8Qp, 14.1Ap,
14.6a, 14.6p
Plantain, *Plantago* 3.2Ap, 5.2Bo, 5.7C, 5.7I, 7.4p,
8.1p, 8.3Cp, 8.4t, 9.7t, 10.1o, 10.2t, 10.6t,
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14.2t, 14.5p, 14.6o
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4.3Ba, 4.4Aa
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7.4p, 8.1p, 8.3Hp, 9.5Bp, 10.2p, 10.5t,
11.1Gt, 13.4Ip, 14.1Ap, 14.5p, 14.6p
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5.1Ap, 5.5Dp, 5.7C, 5.8O, 7.3Ap, 7.3Cp,
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11.1Ip, 11.1Jp, 11.1Kp, 11.2Fp, 12.2E, 12.4E,
13.4Ht, 13.6Ap, 13.7Ep, 13.7Hp, 13.8C,
13.8D, 14.1Ap, 14.2p, 14.2t, 14.5o, 14.5p
Plume grass, *Saccharum* 10.1o, 10.3o
Plume poppy, *Macleaya* 3.1Ba, 3.2Ba, 4.1Aa,
5.2Ba, 6.1A, 6.1B
Plumeria, *Plumeria* 9.3Ct
Pochote, *Ceiba* 14.1Ap
Podanthus, *Podanthus* 14.2t
Podocarpus, *Podocarpus* 3.2Ap, 5.3Cp, 5.4p, 6.5p,
7.4p, 8.1p, 8.3Hp, 9.5Bp, 10.2p, 10.5t,
11.1Gt, 13.4Ip, 14.1Ap, 14.5p, 14.6p
Podochaenium, *Podochaenium* 7.3At
Pogonopus, *Pogonopus* 9.2a, 9.3Aa, 12.1a
Pogostemon, *Pogostemon* 10.4p, 10.4t
Poison ivy, *Rhus* 3.2Ap, 4.1Bp, 4.1Cp, 6.1F, 7.4p,
8.1p, 9.5Ap, 9.5Bp, 9.7p, 11.2Fp, 13.1p,
13.4Ap, 13.4Fp, 13.6Bp, 13.8ZOp, 14.1Ap,
14.5p
Poison ivy, *Toxicodendron* 14.1Ap
Poison oak, *Toxicodendron* 14.1Ap
Pokeweed, *Phytolacca* 6.1A, 9.1A, 12.2C, 14.1Ao
Polianthes, *Polianthes* 9.2a
Polygala, *Polygala* 5.7B, 5.8V, 13.7Et, 14.6t
Polypody, *Polypodium* 5.7Go, 7.4t, 10.1t, 11.1Gt
Pomegranate, *Punica* 7.3Ap, 7.3Bp, 8.1t, 9.5Bp,
10.2p, 11.1Bo, 11.1It, 13.8Ip, 13.8Jp, 13.8ZJ,
14.2p, 14.5p
Poncirus, *Poncirus* 8.1p, 14.2p, 14.5p
Pond lily, *Nuphar* 4.1Bp, 13.1p, 13.6Bp, 13.8ZOp
Popcorn flower, *Plagiobothrys* 9.3Fp
Poplar, *Populus* 3.2Ap, 4.3Co, 6.5p, 7.3Ap, 7.4p,
8.1p, 9.7p, 9.5Ap, 10.4o, 10.4t, 11.1Hp,
11.1Ip, 11.1Jp, 11.1Kp, 12.2D, 13.5K,
13.7Hp, 13.8Yp, 14.1Ap, 14.2p, 14.5p
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3.3Da, 3.4Aa, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa,
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6.1B, 6.4a, 7.4a, 8.1a, 9.2p, 9.3Aa, 9.3Ca,
9.5Ba, 10.1p, 10.3o, 13.8ZOp, 5.4a, 12.1a,
14.1Aa, 14.1Ap, 14.2p

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- Potato orchid, *Gastrodia* 3.3Bo, 6.1E, 6.6A
- Potato, *Solanum* 3.2Aa, 3.2An, 3.3Ea, 4.3At, 4.4E, 5.3Bp, 5.3Cp, 5.7F, 5.8D, 5.8La, 5.8R, 6.4a, 6.4o, 6.5a, 8.1a, 8.1t, 8.3Co, 10.6o, 10.2a, 10.3o, 10.4o, 10.4t, 10.5a, 10.5t, 10.6o, 10.7, 11.1It, 11.2It, 12.2B, 12.2C, 12.2D, 12.2E, 12.4A, 12.4D, 13.3, 13.5A, 13.5B, 13.5D, 13.5G, 13.5K, 13.5N, 13.5O, 13.6Ao, 13.7Ha, 13.8W, 14.2p, 14.5p, 14.6o
- Powder flask, *Afraegle* 4.4Aa, 12.1a
- Prairie clover, *Dalea* 13.4E
- Prangos, *Prangos* 5.8W, 7.3Bp, 14.1Ap
- Prestonia, *Prestonia* 5.5Da
- Prickly ash, *Xanthoxylum* 6.5p, 8.1p, 9.3Ap, 12.1p, 14.1Ap
- Prickly ash, *Zanthoxylum* 3.1Ba, 3.2Ba, 4.1Aa, 4.4Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 5.7D, 5.8Xa, 6.1A, 6.1B, 6.4a, 7.3Bp, 7.4a, 8.1a, 8.3B, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 14.1Aa, 14.6p
- Prickly pear, *Cactus* 8.1p
- Prickly pear, *Opuntia* 5.7Ea
- Pricklypoppy, *Argemone* 3.1Aa, 3.1Ba, 3.2Ba, 4.1Aa, 5.2Ba, 5.3Aa, 5.3Ba, 5.5Da, 5.6a, 5.8Xa, 6.1A, 6.1B, 6.4a, 8.1a, 8.1p, 9.3Aa, 9.3Ca, 9.5Ba, 12.1a, 14.1Ao
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- Primrose, *Primula* 4.1Cp, 5.1Ap, 7.3Cp, 7.4p, 8.1p, 8.3Cp, 9.3Cp, 9.3Dp, 9.3Gp, 9.5Ap, 9.5Bp, 9.7p, 10.1o, 11.1Hp, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Ap, 11.2Fp, 13.4Ap, 13.4Fp, 13.6Ap, 13.7Hp, 13.8Yp, 13.8ZB, 14.1Ap
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- Pristimeria, *Pristimera* 7.3At, 14.1At
- Privet, *Ligustrum* 4.2a, 6.5p, 10.2t, 13.8Kp, 13.8ZP, 14.1Ap, 14.1At, 14.2p
- Prophet flower, *Arnebia* 9.3Fp
- Protea, *Protea* 10.5p
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- Psophocarpus, *Psophocarpus* 4.3At, 6.1B, 6.1D, 8.1t, 9.3Dt, 9.3Ft, 12.2A, 13.4At, 13.4C, 13.5K, 14.1At
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- Puerto Rico hibiscus, *Montezuma* 4.1At, 7.1t, 8.1t, 9.3Dt, 14.1At, 14.2p
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- Puncture vine, *Tribulus* 3.2Aa, 4.2a, 4.4Aa, 5.3Aa, 5.5Da, 5.8La, 5.9, 6.2a, 6.5a, 11.1At, 12.1a
- Purslane, *Portulaca* 5.3Bp, 5.3Cp, 14.6t
- Pussy ears, *Cyanotis* 11.1Gt
- Putterlickia, *Putterlickia* 9.6Eo
- Pycnarrhena, *Pycnarrhena* 7.1a
- Pyrethrum, *Tanacetum* 3.2Bt, 4.2t, 5.5Dt, 5.7C, 5.8C, 5.8N, 5.8O, 6.2t, 7.3At, 7.3Bp, 7.3Bt, 8.1t, 10.4t, 10.6t, 14.1Ap, 14.1At
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- Qiang ho, *Notopterygium* 14.1Ao, 14.1Ap
- Quackgrass, *Elytrigia* 10.1o
- Quassia, *Picrasma* 10.2t
- Quassia, *Quassia* 10.2p, 10.2t, 13.8W
- Quebracho, *Aspidosperma* 5.1Aa, 5.6a, 9.3Aa, 9.3Ba, 9.3Ga, 12.1a
- Quebracho, *Schinopsis* 7.4p, 8.1p
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- Queen of the night cactus, *Selenicereus* 3.1Ba
- Queen, *Filipendula* 5.3Bp, 5.3Cp, 5.4p, 5.6p, 5.7Ep
- Queensland maple, *Flindersia* 4.4Aa, 5.8W, 7.3Bp, 12.1a, 14.1Ap
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- Radish, *Raphanus* 7.1o, 10.4o, 10.6o, 12.4A, 12.4B, 12.4C, 14.4A
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- Rambutan, *Nephelium* 10.4o, 10.4p, 10.4t, 14.2p
- Ramin, *Gonystylus* 5.8R
- Rangoon creeper, *Quisqualis* 3.3Ba, 3.3C, 5.5Ba
- Rape, *Brassica* 3.3Aa, 3.3Bp, 3.3C, 5.5Bo, 5.6a, 6.1C, 7.1o, 7.4p, 10.2a, 10.4o, 10.4p, 10.5o, 10.6o, 10.6t, 10.7, 11.1Gp, 11.1Gt, 11.1Ip, 11.1Jp, 11.1Kp, 11.2Bo, 11.2E, 11.2Go, 12.2E, 12.4B, 12.4C, 13.5I, 13.5J, 13.5K, 13.5M, 13.5O, 13.7F, 13.8ZM, 14.1Ao, 14.2t, 14.4A, 14.6p
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- Rattleweed, *Crotalaria* 10.5a, 12.2A
- Rauwolfia, *Rauwolfia* 3.4Aa, 4.2a, 4.4Aa, 5.3Aa, 5.3Ba, 5.4a, 5.5Da, 5.8D, 5.8La, 6.3a, 6.4a, 7.4a, 9.3Aa, 9.3Ga, 9.6Ea, 11.1Ha, 12.1a, 13.7Ha
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- Red cedar, *Thuja* 3.2Bt, 5.8C, 8.1p, 10.4p, 10.4t, 13.4Gt, 14.1At
- Red gum, *Eucalyptus* 3.3Ep, 4.3Ap, 4.4At, 5.3Ap, 5.3Bp, 5.4p, 5.6p, 5.8H, 6.4t, 6.1F, 6.4t, 6.5p, 7.3Ap, 7.3Bp, 7.4p, 8.1p, 9.3Dp, 9.5Bp, 9.7p, 10.4t, 10.5t, 10.6t, 11.1Bp, 11.1Ip, 11.1Jp, 13.4Ip, 13.6Ap, 13.6Bp, 13.6Cp, 13.8Jp, 13.8ZE, 13.8ZN, 13.8ZOp, 14.1Ap, 14.2p, 14.5p
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Abbreviations

Quantitative terms

(-), inhibits
⊕, activates
↓, decreases or inhibits
↑, increases or stimulates
[A], concentration of A
°C, degrees Centigrade
Da, Dalton (carbon 12 mass = 12.0 Da)
E, energy
E, redox potential
*E*_o, standard redox potential
EC₅₀, concentration giving 50% effect
G, free energy
*G*_{act}, activation energy
H, enthalpy
IC₅₀, concentration giving 50% inhibition
I.U., international unit (μmol/min)
k, rate constant for a reaction
K, Kelvin
*K*_d, dissociation constant
*K*_{equ}, equilibrium constant
*K*_i, enzyme-inhibitor dissociation constant
*K*_m, Michaelis–Menten constant
M, molar (mol/L)
MW, molecular weight
P, pressure
p.d., potential difference
p*K*, $-\log_{10} K_d$ (*K*_d = dissociation constant of protonated entity HA)
*P*_{Cl⁻}, permeability of membrane for Cl⁻
*P*_{K⁺}, permeability of membrane for K⁺
*P*_{Na⁺}, permeability of membrane for Na⁺
R, gas constant
S, entropy
T, temperature

V, volume
F, Faraday constant
(*x*), IC₅₀ (μM)
[*x*], *K*_d (μM) or *K*_i (μM)
(>*x*), substantial but less than 50% inhibition was obtained at a concentration of *x* μM; (~*x*), about 50% inhibition observed at *x* μM (at *x*), effect observed at *x* μM
z, charge on ion
ψ_m, transmembrane potential
Δ, change (e.g. Δ*G* = free energy change)

Other abbreviations

A, adenine
A, alanine
2,5-A, 2',5'-oligoadenylate
αA, α-amylase
aa, amino acids
AA, arachidonic acid
AA-TR, amino acid transporter
AB, allylbenzene
ABC-TR, ATP binding cassette transporter
AC, adenylyl cyclase, adenylate cyclase
ACAT, acylCoA: cholesterol *O*-acyltransferase
ACC, acetylCoA carboxylase
ACE, angiotensin converting enzyme
ACE, angiotensin I converting enzyme
ACh, acetylcholine
AChE, acetylcholinesterase
ACTH, adrenocorticotrophic hormone
ACTH-R, corticotropin (ACTH) receptor
AD, Alzheimer's disease

- AD, alloxan-induced diabetic
 ADH, alcohol dehydrogenase
 ADH, antidiuretic hormone, vasopressin
 ADHD, attention deficit and hyperactivity disorder
 ADP, adenosine 5'-diphosphate
 5'-ADP, adenosine 5'-diphosphate
 ADP-R, ADP receptor
 AD-R, adenosine receptor
 AGE, advanced glycation endproduct
 AHR, aldehyde reductase
 AI, anti-inflammatory
 α AI, α -amylase inhibitor
 Akt, insulin-activated protein kinase, PKB
 Ala, alanine
 β -Alanine-TR, β -alanine transporter
 ALDH, aldehyde dehydrogenase
 ALDO-R, aldosterone receptor
 Alk Pase, alkaline phosphatase
 ALL-DB, alloxan-induced diabetic
 AMCV, artichoke mottled crinkle virus
 AMP, adenosine 5'-monophosphate
 5'-AMP, adenosine 5'-monophosphate
 AMPA-R, AMPA-receptor
 AMPK, AMP-dependent protein kinase
 AMPKK, AMP-dependent protein kinase kinase
 AMV, avian myeloblastosis virus
 AND-R, androgen receptor
 ANF, atrial natriuretic factor
 ANP, atrial natriuretic peptide
 AO, antioxidant
 AO/FRS, antioxidant/free radical scavenger
 AP, aminopeptidases
 AP-1, activator protein 1
 APC, antigen presenting cell
 APL, allosteric potentiating ligand
 AR, aldose reductase
 α 1A-R, α 1-adrenergic receptor
 α 2A-R, α 2-adrenergic receptor
 Ara, arabinose, arabinoside, arabinosyl
 Arg, arginine
 ARH-R, aryl hydrocarbon receptor
 AROM, cytochrome P450-linked aromatase
 Asn, asparagine
 ASNS, asparagine synthetase
 Asp, aspartate, aspartic acid
 ASPPR, aspartate protease
 ATP, adenosine 5'-triphosphate
 5'-ATP, adenosine 5'-triphosphate
 ATP-K⁺ CH, ATP-sensitive K⁺ channel
 ATP-R, ATP receptor
 autophos'n, autophosphorylation
 BBB, blood brain barrier
 BBI, Bowman-Birk serine protease inhibitor
 BB-R, bombesin receptor
 BChE, butyryl cholinesterase
 BDNF, brain-derived neurotrophic factor
 BDNF-RTK, brain-derived neurotrophic factor receptor tyrosine kinase
 α BgTX, α -bungarotoxin
 BKAS, β -ketoacyl-ACP synthase
 BK-R, bradykinin receptor
 BZ-R, benzodiazepine receptor
 C, cysteine
 C, cytosine
 CA, carbonic anhydrase
 Ca²⁺ CH, Ca²⁺ channel
 Ca²⁺₄-CaM, Ca²⁺₄-calmodulin complex
 Ca²⁺-K⁺ CH, Ca²⁺-dependent K⁺ channel
 CAB Pase, cyclic AMP-binding phosphatase
 CABNase, cyclic nucleotide-binding nucleotidase
 cADPR, cyclic adenosine-5'-diphosphate ribose
 CaM, calmodulin
 CAM, Crassulacean acid metabolism
 CaM-Ca²⁺-Mg²⁺-ATPase, Ca²⁺-CaM-activated Ca²⁺-Mg²⁺-ATPase
 CaM-Ca²⁺-ATPase, Ca²⁺-calmodulin-dependent Ca²⁺-ATPase
 CaM-FC, Ca²⁺-dependent calmodulin fluorescence change
 cAMP-PDE, cyclic AMP phosphodiesterase
 cAMP, 3',5'-cyclic adenosine monophosphate
 CaM-PDE, Ca²⁺-calmodulin-activated cyclic nucleotide phosphodiesterase
 CaM-cAMP PDE, Ca²⁺-calmodulin-dependent cAMP phosphodiesterase
 CaM-PK I-IV, Ca²⁺-calmodulin-activated protein kinases I-IV
 CaM-PK, Ca²⁺-calmodulin-activated protein kinase

840 *Abbreviations*

- CaMPKs I–IV, calmodulin-dependent protein kinases I–IV
CART, cocaine- and amphetamine-regulated transcript
CART-R, cocaine- and amphetamine-regulated transcript receptor
CAT, catecholamine
CAT-REL, vesicular catecholamine release
CB-R, cannabinoid receptor
CB1-R, CB2-R, cannabinoid receptors
CBD, chitin-binding domain
CBG, cortisol-binding globulin
CBZ-R, central benzodiazepine receptor
CCK-R, cholecystokinin receptor
CDC, chrysanthemum dicarboxylic acid
CDK, cell division kinase, cyclin-dependent protein kinase
CDK1–CDK7, cyclin-dependent protein kinases 1–7
CDK2, cell division kinase 2
cDNA, complementary DNA
CDP, cytidine 5'-diphosphate
CDPK, Ca²⁺-dependent protein kinase, calmodulin domain protein kinase
CFTR, cystic fibrosis transmembrane conductance regulator
cGMP, 3',5'-cyclic guanosine monophosphate
cGMP PDE, cyclic GMP phosphodiesterase
CGRP, calcitonin-gene-related peptide
ChAT, choline acetyltransferase
CHK, chemokine
CHK-R, chemokine receptor
CHS, chitin synthetase
CHY, chymotrypsin
CK, creatine kinase
CK1, casein kinase 1
CK2, casein kinase 2
CK-R, chemokine receptor
ClC, voltage-regulated chloride channel
CMC, chrysanthemum monocarboxylic acid
CMP, cytidine 5'-monophosphate
cNOS, constitutive nitric acid synthase
CNS, central nervous system
COLL-R, collagen receptor
COMT, catechol-*O*-methyltransferase
Corticotropin, adrenocorticotropic hormone
CORT-R, cortisol receptor
COUP-TF, chicken ovalbumin upstream promoter transcription factor
COX, cyclooxygenase
COX-1, cyclooxygenase 1
COX-2, cyclooxygenase 2, inducible cyclooxygenase
CPA, carboxypeptidase
CRE, cAMP response element
CREB protein, cAMP response element (CRE) binding protein
CRF, corticotropin releasing factor
CRF-R, corticotropin releasing factor receptor
CRH, corticotropin-releasing hormone
CRH-R, corticotropin releasing hormone receptor
CT-1, ciliotrophin-1
CTNF, ciliary neurotrophic factor
CTP, cytidine 5'-triphosphate
Cyclic AMP, adenosine 3',5'-cyclic monophosphate
3',5'-cyclic AMP, adenosine 3',5'-cyclic monophosphate
Cyclic GMP, guanosine 3',5'-cyclic monophosphate
3',5'-cyclic GMP, guanosine 3',5'-cyclic monophosphate
CYP, cytochrome P450 oxygenase
Cys, cysteine
CYSPR, cysteine protease
D, aspartate, aspartic acid
D, dopamine
dADP, 2'-deoxyadenosine 5'-diphosphate
DAG, diacylglycerol
DALS, deacetylpecoside synthase
dAMP, 2'-deoxyadenosine 5'-monophosphate
Dansyl-CaM, dansyl-calmodulin
Dansyl-CaM-FC, Ca²⁺-dependent dansyl-calmodulin fluorescence change
dATP, 2'-deoxyadenosine 5'-triphosphate
DB, diabetic
DBH, dopamine- β -hydroxylase
dCDP, 2'-deoxycytidine 5'-diphosphate
dCMP, 2'-deoxycytidine 5'-monophosphate
dCTP, 2'-deoxycytidine 5'-triphosphate
dGDP, 2'-deoxyguanosine 5'-diphosphate

dGMP, 2'-deoxyguanosine 5'-monophosphate
dGTP, 2'-deoxyguanosine 5'-triphosphate
DHF, 7,8-dihydrofolate
DHFR, dihydrofolate reductase
DHPhe, dihydrophenyl
DIFP, diisopropylfluorophosphate
DM, diabetes mellitus
DNA GAAL, DNA glycosylase/apurinic/aprimidinic lyase
DNA, deoxyribonucleic acid
DNAH, DNA helicase
DNAL, DNA ligase
DNAp, DNA-dependent DNA polymerase
DNAS, DNA synthesis
DPPH, 1,1-diphenyl-2-picrylhydrazyl radical
D-R, dopamine receptor
D1-R, D2-R, dopamine receptors
D-REL, vesicular dopamine release
dsDNA, double stranded DNA
dTDP, 2'-deoxythymidine 5'-diphosphate
dTMP, 2'-deoxythymidine 5'-monophosphate
D-TR, dopamine transporter
dTTP, 2'-deoxythymidine 5'-triphosphate

E, glutamate, glutamic acid
EAE, experimental autoimmune encephalomyelitis
EC, Enzyme Commission
ECDY-R, ecdysone receptor
ECE, endothelin-converting enzyme
ECMOX, cytochrome P450-dependent ecdysone 20-monooxygenase
eEF-2, eukaryote elongation factor 2
EF, elongation factor
EGF, epidermal growth factor
EGF-RTK, epidermal growth factor receptor tyrosine kinase
eIF2, eukaryote initiation factor 2
eIF2 α K, eukaryote initiation factor 2 α kinase
ELA, elastase
END, endothelin
END-R, endothelin receptor
eNOS, endothelial nitric oxide synthase
EPO, erythropoietin
ER, endoplasmic reticulum
ERE, estrogen response element

ERK, external signal-regulated protein kinase (MAPK)
EST-R, estrogen receptor
ETC, electron transport chain

F, phenylalanine
F26BP, fructose-2,6-bisphosphate
FA, fatty acid
FAD, fatty acid desaturase
FADH₂/FAD, reduced/oxidized flavin adenine dinucleotide
F₁-ATPase, ATP synthetase F₁ complex
FGF, fibroblast growth factor
FGF-RTK, fibroblast growth factor receptor tyrosine kinase
Fmet, formylmethionine
FMNH₂/FMN, reduced/oxidized flavin mononucleotide
FPTase, farnesyl-protein transferase
FR, free radical
FRS, free radical scavenger
Fru, fructose, fructoside, fructosyl
FSH, follicle stimulating hormone
Fuc, fucose, fucoside, fucosyl

G protein, heterotrimeric guanyl nucleotide-binding protein
G, glycine
G, guanine
G-6-P-TR, glucose-6-phosphate transporter
GABA, γ -aminobutyric acid
GABAA-R, GABA(A) receptor
GABAA-R, ionotropic GABA(A) receptor
GABAB-R, metabotropic GABA(B) receptor
iGABA-R, ionotropic GABA receptor
GABAT, GABA transaminase
GABA-TR, GABA transporter
Gal, galactose, galactoside, galactosyl
GALLDH, 1-galactono- γ -lactone dehydrogenase
GalN, galactosamine, galactosaminoside, galactosaminosyl
GalNac, *N*-acetyl galactosamine, *N*-acetylgalactosaminoside, *N*-acetylgalactosaminosyl
GAP, GTPase activating protein
Gastrin-R, gastrin receptor
GC, guanylyl cyclase, guanylate cyclase

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- G-CSF, granulocyte colony stimulating factor
GDP, guanosine 5'-diphosphate
GEF, guanyl nucleotide exchange factor
GH, growth hormone
GHB, γ -hydroxybutyrate
GHB-R, γ -hydroxybutyrate receptor
GH-RIF, growth hormone-release inhibiting factor, somatostatin
GI, gastro-intestinal
GIP, gastric inhibitory peptide, glucose-dependent insulinotropic polypeptide
Glc, β -D-glucose
Glc, glucose, glucoside, glucosyl, β -D-glucopyranosyl, β -D-glucopyranoside
GlcA, glucuronic acid, glucuronide, glucuronyl
GlcN, glucosamine, glucosaminoside, glucosaminosyl
GlcNAc, *N*-acetylglucosamine, *N*-acetylglucosaminoside, *N*-acetylglucosaminosyl
Glc-R(GIP), glucose receptor for GIP secretion
Glc-TR, glucose transporter
Gln, glutamine
GLP-1, glucagon like peptide-1
Glu, glutamate, glutamic acid
GluDC, glutamate decarboxylase
Glu-R, glutamate ionotropic receptor
Gly, glycine
Gly-R, glycine receptor
GMP, guanosine 5'-monophosphate
GDNF, glial cell line-derived neurotrophic factor
GDNF-RTK, glial cell line-derived neurotrophic factor receptor tyrosine kinase
GN-R, glucagon receptor
GPCR, G protein-coupled receptor
GPI, guinea pig ileum relaxation by opioid
GRH, gonadotropin-releasing hormone
GS, glycogen synthase
GSK3, glycogen synthase kinase 3
GST, glutathione-S-transferase
GTP, guanosine 5'-triphosphate
- H, histidine
H, hormone
HAD, histone deacetylase
HAT, histone acetyl transferase
- Hb, haemoglobin
His, histidine
HISK, histidine-specific protein kinase
HIS-R, histamine receptor
HIV-1, human immunodeficiency virus 1
HIV-1 IN, HIV-1 integrase
HIV-1 PR, HIV-1 protease
HIV-1 RT, HIV-1 reverse transcriptase
HMG protein, high mobility group protein
HMGCoAR, hydroxymethylglutarylCoA reductase
HPGDH, 15-hydroxyprostaglandin dehydrogenase
HPLC, high performance liquid chromatography
11 β HSDH, 11- β -hydroxysteroid dehydrogenase
17 β HSOR, 17- β -hydroxysteroid oxidoreductase
5HT, serotonin
5HT1A-R, metabotropic 5-hydroxytryptamine (serotonin) receptor
5-HT1-R, metabotropic 5-hydroxytryptamine (serotonin) receptor
5HT2-R, metabotropic 5-hydroxytryptamine (serotonin) receptor
5HT3-R, ionotropic 5-hydroxytryptamine receptor
5HT-R, 5-hydroxytryptamine (serotonin) receptor
5HT-REL, serotonin (5HT) release
5HT-REL, vesicular serotonin release
HYAL, hyaluronidase
HypoGlc, hypoglycaemic
- I, isoleucine
I κ B, inhibitor of NF- κ B
I κ B, inhibitor of nuclear factor κ B
I1-R, I2-R, imidazoline Rs
IDD, iodide deficiency disorder
IDDM, insulin-dependent diabetes mellitus
IFN- γ , interferon- γ
IFN γ -R, interferon- γ receptor
IFNs, interferons
IGF-RTK, insulin-like growth factor receptor tyrosine kinase
IGF-1, insulin-like growth factor-1

- IGF-1-RTK, insulin-like growth factor-1 receptor tyrosine kinase
 IGF-2, insulin-like growth factor-2
 IGF-2-RTK, insulin-like growth factor-2 receptor tyrosine kinase
 iGlu-R, inhibitory glutamate receptor
 IKK, inhibitor κ B kinase
 IL, interleukin
 IL-1 β , interleukin-1 β
 IL-1 β -R, interleukin-1 β receptor
 IL-1, interleukin-1
 IL-8, interleukin-8
 IL-8-R, interleukin-8-receptor
 Ile, isoleucine
 Im, imidazole
 iNOS, inducible nitric oxide synthase
 Inr, initiation region
 INS-RTK, insulin receptor tyrosine kinase
 IP, intraperitoneal
 IP₃, inositol-1,4,5-triphosphate
 IP₃-R, inositol-1,4,5-triphosphate receptor
 IQ, isoquinoline
 I-R, imidazoline R
 IRS1 and IRS2, insulin receptor substrates
 ITD, iodothyronine deiodinase
- JAK, Janus kinase
 JH, juvenile hormone
- K, lysine
 KAL, kallikrein
 KATI and KATII, kynurenine amino-transferases I and II
 KPI, Kunitz protease inhibitor
 K-R, kainate receptor
 KTI, Kunitz trypsin inhibitor
- L, leucine
 LARI, lens aldose reductase inhibitor
 L-Ca²⁺CH, L-type voltage-gated Ca²⁺ channel
 LDL, low density lipoprotein
 Leu, leucine
 LH, luteinizing hormone
 LH-R, luteinizing hormone receptor
 LHRH, luteinizing hormone release hormone
 LIF, leukaemia inhibitory factor
- LOX, lipoxygenase
 5-LOX, 5-lipoxygenase
 12-LOX, 12-lipoxygenase
 15-LOX, 15-lipoxygenase
 LPS, lipopolysaccharide
 LT, leukotriene
 LTB₄, leukotriene B₄
 LTP, lipid transfer protein, non-specific lipid transfer protein
 L-type Ca²⁺ CH, L-type Ca²⁺ channel
 Lys, lysine
- M, methionine
 mACh-R, muscarinic acetylcholine receptor
 Man, mannose, mannoside, mannosyl
 MAO, monoamine oxidase
 MAO-A and MAO-B, monoamine oxidases
 MAPK, mitogen activated protein kinase (ERK)
 MAPKK, MAPK kinase, mitogen activated protein kinase kinase
 MAPKKK, MAPK kinase kinase, mitogen activated protein kinase kinase kinase
 MARCKS, myristoylated alanine-rich C kinase substrate
 MA-TR, monoamine transporter
 MCP-1, monocyte chemoattractant protein 1
 MC-R, α -melanocyte-stimulating hormone (α -MSH) receptor
 MD, methylenedioxy
 MDR-TR, multidrug-resistance transporter
 Met, methionine
 mGlu(1-8)-Rs, metabotropic glutamate receptors
 mGlu-R, metabotropic glutamate receptor
 MHC, major histocompatibility complex
 MHCP, methylhydroxychalcone polymer
 MLC, myosin light chain
 MLCK, Ca²⁺-calmodulin-dependent myosin light chain kinase
 MLV, murine leukaemia virus
 MMP, matrix metalloprotease
 MPR, metalloprotease
 mRNA, messenger RNA
 MSG, monosodium glutamate (glutamate)
 α -MSH, melanocyte-stimulating hormone

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- MT, microtubule
MT-R, melatonin receptor
MVD, mouse vas deferens relaxation by opioid
- N, asparagine
Na⁺/Glc TR, Na⁺/glucose symport transporter
Na⁺/Ca²⁺ TR, Na⁺/Ca²⁺ antiporter transporter
Na⁺/H⁺ TR, Na⁺/H⁺ TR antiporter transporter
Na⁺/K⁺/Cl⁻ TR, Na⁺-K⁺-2Cl⁻ co-transporter
NAADP, nicotinic acid adenine dinucleotide 2'-phosphate
NAADP-R, nicotinic acid adenine dinucleotide 2'-phosphate receptor
nACh-R, nicotinic acetylcholine receptor
NADH DH, NADH dehydrogenase
NADH/NAD⁺, reduced/oxidized nicotinamide adenine dinucleotide
NADH-UQ OR, NADH-ubiquinone oxidoreductase
NADPH/NADP⁺, reduced/oxidized nicotinamide adenine dinucleotide phosphate
Nase, nucleotidase
NBD, nucleotide-binding domain of ABC-TR
NDP, nucleoside 5'-diphosphate
NE, norepinephrine
NEP, neutral endopeptidase
NE-REL, vesicular norepinephrine release
NeuNac, *N*-acetylneuraminic acid (sialic), *N*-acetylneuraminoside (sialoside), *N*-acetylneuraminosyl acid (sialosyl)
NEUT, neurotensin
NEUT-R, neurotensin receptor
NFκB, nuclear factor κB
NFAT, nuclear factor of activated T cells
NGF, nerve growth factor
NGF-RTK, nerve growth factor receptor tyrosine kinase
NIDDM, non-insulin-dependent diabetes mellitus
n-m, nicotinic-muscarinic
- NM, neuromuscular
NMDA, *N*-methyl-D-aspartate
NMDA-Glu-R, *N*-methyl-D-aspartate-binding glutamate receptor
NMP, nucleoside 5'-monophosphate
nNOS, neuronal nitric oxide synthase
NO, nitric oxide,
non-NMDA-Glu-R, non-NMDA-binding glutamate receptor
NOS, nitric oxide synthase
NPY, neuropeptide Y
NQOR, NADPH:quinone oxidoreductase (DT-diaphorase)
NT, neurotransmitter
NTP, nucleoside 5'-triphosphate
N-type Ca²⁺ CH, N-type Ca²⁺ channel
- ODC, ornithine decarboxylase
OD-R, odorant receptor
O-R, opiate receptor
OSM, oncostatin M
OTCase, ornithine transcarbamoylase
Ox. phos., oxidative phosphorylation
OX-R, oxytocin receptor
- P, proline
p56^{lck} TK, lck tyrosine kinase
PA, platelet aggregation
PADPRH, poly(ADP-ribose)glycohydrolase
PAF, platelet activating factor, 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphorylcholine
PAF-R, platelet-activating factor receptor
PAG, polynucleotide aminoglycosidases
PAG, polynucleotide:adenosine glycosidase
PAI, platelet aggregation inhibitor
PAI-1, plasminogen activator inhibitor-1
PAR, protease-activated receptor
PB, phenylprop-1-ene
PBZ-R, peripheral benzodiazepine receptor
P-Ca²⁺ CH, P-type voltage-gated Ca²⁺ channel
PDB-R, phorbol dibutyrate receptor (PKC)
PDGF, platelet-derived growth factor
PDGF-RTK, platelet-derived growth factor receptor tyrosine kinase
PDPK, phosphatidylinositol lipid-dependent PK

- PE, phorbol ester
 PEP, phosphoenolpyruvate
 PEP, prolyl endopeptidase
 PEPCK, PEP carboxykinase
 PEPCK, phosphoenolpyruvate carboxylase
 PfCDPK, *Plasmodium falciparum* Ca²⁺-dependent protein kinase
 PG, polygalacturonase
 PG, prostaglandin
 PGH₂S, prostaglandin H₂ synthase
 PGI₁, polygalacturonase inhibiting protein
 PGK, 3-phosphoglycerate kinase
 PGP-TR, P-glycoprotein transporter
 PG-R, prostaglandin receptor
 PGS, prostaglandin synthetase
 PH domain, pleckstrin homology domain
 Phe, phenyl
 Phe, phenylalanine
 phos'n, phosphorylation
 PhosbK, phosphorylase b kinase
 PI, protease inhibitor
 PI3K, phosphatidylinositol-3-kinase
 PI₃,4P₂, phosphatidylinositol-3,4-bisphosphate
 PI₄,5P₂, phosphatidylinositol-4,5-bisphosphate
 PI₃,4,5P₃, phosphatidylinositol-3,4,5-trisphosphate
 PK, protein kinase
 PKA, cAMP-dependent protein kinase
 PKA, cyclic AMP-dependent protein kinase
 PKB, insulin-activated protein kinase, Akt
 PKC, Ca²⁺- and phospholipid-dependent protein kinase, protein kinase C
 PKG, cGMP-dependent protein kinase
 PLA₂, phospholipase A₂
 PLC, phospholipase C
 PLCγ, phospholipase Cγ
 PLD, phospholipase D
 PM NADH OX, plasma membrane NADH oxidase
 PM, plasma membrane
 POMC, preopiomelanocortin
 PP, phosphoprotein phosphatase
 PP2B, calcineurin, Ca²⁺-dependent phosphoprotein phosphatase
 PP2C, Mg²⁺-dependent phosphoprotein phosphatase
 PPA-R, peroxisome proliferator-activated receptor
 PPC, proprotein convertase
 PRL, prolactin
 Pro, proline
 PROG-R, progesterone receptor
 ProH, prolyl hydroxylase
 PROP, 6-propylthiouracil
 PRP, pathogenesis related protein
 PS, protein synthesis
 PSI, photosystem I
 PSI, protein synthesis inhibitor (inhibition)
 PSII, photosystem II
 PSTase, phenolsulphotransferase
 PT, peptidyltransferase
 PTH, parathyroid hormone
 PTH-R, parathyroid hormone/parathyroid hormone-related protein receptor
 PTPases, P-Tyr phosphatases
 PUVA therapy, psoralen with ultraviolet A light therapy
 PYK, pyruvate kinase
- Q, glutamine
 Q, quinone
- R, arginine
 R, receptor
 R, R group of amino acid
 5αR, testosterone 5α-reductase
 σ-R, sigma receptor (metabotropic or ionotropic)
 R/S domain, highly conserved ricin/α-sarcin-interacting domain of 28S rRNA
 RA-R, retinoic acid receptor
 RER, rough endoplasmic reticulum
 Rha, rhamnose, rhamnoside, thamnosoyle, α-1-rhamnopyranosyl, α-1-rhamnopyranoside
 RI, ribosome inactivation
 Rib, ribose, riboside, ribosyl
 RIP, ribosome-inactivating protein
 RLV, Raucher leukaemia virus
 RNA, ribonucleic acid

846 *Abbreviations*

- RNAP, DNA-dependent RNA polymerase
RNAS, RNA synthesis
ROS, reactive oxygen species
rRIP, recombinant RIP
RRL, rabbit reticulocyte lysate (for *in vitro* PSI measurement)
rRNA, ribosomal RNA
RT, reverse transcriptase
RTK, receptor tyrosine kinase
RY-R, ryanodine receptor,
- S, serine
S. Am., South American
70S PS, 70S ribosome (prokaryote) protein synthesis
80S PS, 80S ribosome (eukaryote) protein synthesis
SAR, systemic acquired resistance
S1P, sphingosine-1-phosphate
S1P-R, sphingosine-1-phosphate receptor
SBG, steroid binding globulin
SEC-R, secretin receptor
SEP, squalene epoxidase
Ser, serine
SERPR, serine protease
SialylT, sialyltransferase
SLOX, soya bean 15-lipoxygenase, soya bean lipoxygenase
SNF1K, SNF1 protein kinase kinase
80S PT, 80S ribosome (eukaryote) peptidyl transferase
snRNA, small nuclear RNA
snRNPs, small nuclear ribonucleoproteins
SP, substance P
SPH-R, sphingosine receptor
SP-R, substance P receptor
Src, a soluble tyrosine kinase
SRIF, somatotropin release inhibiting factor, somatostatin
SRIF-R, somatostatin (somatotropin release inhibiting factor) receptor
SRP, signal recognition particle
S-S, disulphide
SSADH, succinic semialdehyde dehydrogenase
SSAR, succinic semialdehyde reductase
ssDNA, single stranded DNA
SSV, simian sarcoma virus
- STAT, signal transducers and activators of transcription
Steroid X R, steroid X receptor
STX, saxitoxin
STZ-DB, streptozotocin-induced diabetic
SUB, subtilisin
Succinate DH, succinate dehydrogenase
SU-R, sulphonylurea receptor (ATP-K⁺ CH)
- T, thymine
T, threonine
T3, triiodothyronine
T4, tetraiodothyronine
TBPS, *tertiary*-butylbicyclophosphorothioate
TCA, tricarboxylic acid
TF, transcription factor
TGF- β , transforming growth factor β
TGF- β -Rs, transforming growth factor β receptors
TGL, triglyceride lipase
THPhe, tetrahydrophenyl
Thr, threonine
THY-R, thyroid hormone receptor
TIMP, tissue inhibitor of metalloprotease
TK, tyrosine kinase
TLC, thin layer chromatography
TLRs, Toll-like receptors
TMAOX, trimethylamine oxidase
TMV, tobacco mosaic virus
TNF, tumour necrosis factor
TNF- α , tumour necrosis factor- α
TNF- α -RTK, tumour necrosis factor- α receptor tyrosine kinase
TOPI, DNA topoisomerase I
TOPII, DNA topoisomerase II
t-PA, tissue plasminogen activator
TPA, 12-Tetradecanoylphorbol 13-acetate
TPO, thyroid peroxidase
TPP, thiamine pyrophosphate
TR, transporter
TRADD, TNF receptor-associated death domain
TRE, tetradecanoyl phorbol acetate (TPA) response element
TRH, thyrotropin release hormone, thyrotropin releasing hormone

tRNA, transfer RNA
 Trp, tryptophan
 TRY, transthyretin
 TRY, trypsin
 TS, thymidylate synthetase
 TSH, thyroid stimulating hormone
 TTX, tetrodotoxin
 TUB, tubulin
 TX, thromboxane
 TXA₂, thromboxane A₂
 TXA₂-R, thromboxane A₂ receptor
 TXB₂, thromboxane B₂
 Tyr, tyrosine
 TYRase, tyrosinase
 TyrH, tyrosine hydroxylase

U, uracil
 UDP, uridine 5'-diphosphate
 UDPG, uridine 5'-diphosphate α-D-glucopyranosyl ester
 UDP-Glc, uridine 5'-diphosphate α-D-glucopyranosyl ester
 UDP-glucose, uridine 5'-diphosphate α-D-glucopyranosyl ester
 UMP, uridine 5'-monophosphate
 UTP, uridine 5'-triphosphate

V, valine
 VACHTR, vesicle transporter of acetylcholine
 Val, valine
 VAN-R, vanilloid receptor
 VAS-R, vasopressin (ADH, antidiuretic hormone) receptor
 V-Ca²⁺ CH, voltage-gated Ca²⁺ channel
 VEGF, vascular endothelial growth factor
 VEGF-RTK, vascular endothelial growth factor-receptor tyrosine kinase

VGATR, vesicle transporter of GABA and glycine
 VITD-R, vitamin D receptor
 V-K⁺ CH, voltage-gated K⁺ channel
 VMAT1 & VMAT2, vesicular monoamine transporters
 VMA-TR, vesicular monoamine transporter
 V-Na⁺ CH, voltage-gated Na⁺ channel

W, tryptophan
 w.r.t., with respect to

Xa, XIa, XIIa, blood clotting factors (proteases)
 XO, xanthine oxidase
 X-R, X receptor
 Xyl, xylose, xyloside, xylosyl

Y, tyrosine

Note on glycosylation abbreviations

Many natural products are glycosylated and the following example illustrates the abbreviations variously used here.

Dioscin = (25*R*)-Spirost-5-ene-3β-ol 3-*O*-α-L-rhamnopyranosyl-(1 → 2)-*O*-[α-L-rhamnopyranosyl-(1 → 4)]-β-D-glucopyranoside) = (25*R*)-Spirost-5-en-3β-ol 3-*O*-rhamnosyl-[rhamnosyl]-glucoside) = (25*R*)- Spirost-5-en-3β-ol 3-*O*-Rha-[Rha]-Glc, noting that the [rhamnosyl] in square brackets is a sugar side chain linked to the rhamnosyl-glucosyl residue via the rhamnosyl residue.

How do plant compounds affect our bodies? Plants defend themselves from other organisms through the production of bioactive metabolites. Introduced to the body, these compounds bind to particular biochemical targets, most notably to proteins involved in signalling by hormones and neurotransmitters. This, essentially, is the basis for the effects of herbal medicine. While herbal medicinal preparations may act by complex synergistic interactions, molecular explanations of herbal medicine efficacy and side effects will ultimately require definition of the biochemical targets of individual plant bioactive constituents.

This volume is a comprehensive and user-friendly reference guide to the biochemical targets of plant defensive compounds. It presents a mine of succinctly summarized information relating bioactive compound structures, plant sources, biochemical targets and physiological effects which can be readily accessed via the plant genus index, plant common name index and chemical compound index. With introductory chapters providing reviews of the structural diversity of plant defensive compounds and biochemistry, *Biochemical Targets of Plant Bioactive Compounds* is an invaluable reference for biomedical professionals in the fields of complementary medicine, natural product chemistry, toxicology and pharmacology.

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