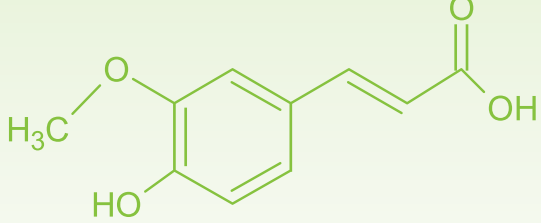
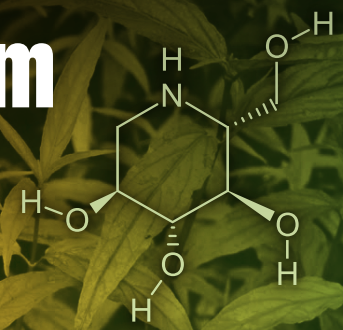


Anti-Diabetes Mellitus Plants

Active Principles, Mechanisms of Action and Sustainable Utilization

Appian Subramoniam



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Contents

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Preface

The worldwide prevalence of diabetes mellitus (one of the oldest diseases known to humans) in the adult population is more than 8%. This is a huge burden to society in terms of quality of life, cost of treatment, and loss in productivity of patients. In traditional medicine all over the world, plant-based crude drugs are used to treat diabetes mellitus from time immemorial. Even today, the majority of the world's population use plant products to control diabetes mellitus. Now, it is time to create new knowledge from traditional knowledge with the help of modern science and technology. There is a necessity to develop plant-based therapies for diabetes mellitus with superior efficacy and safety in light of modern science.

Although there are numerous polyherbal formulations to treat diabetes in traditional medicine, none of them were developed rationally. The reasons for the presence of specific ingredients in the given ratio in a polyherbal formulation and phytochemical interactions in the formulation, if any, are not explained satisfactorily. It should be remembered that most of these formulations existed well before the advancement of modern medical sciences. Polyherbal formulations, if developed scientifically considering the mechanisms of actions and efficacy as projected in Chapter 4, could prove to be the best treatment for diabetes mellitus. Further, it is heartening to note that many vegetables, spices, and fruits are endowed with anti-diabetes mellitus properties. Development of rational polyherbal formulations with these plant products could be very safe and effective.

Other gap areas identified in this book to be filled by future research include the following: Active molecules are not identified fully in a majority of known anti-diabetes mellitus plants including more than 30 very important anti-diabetes mellitus plants. Mechanisms of action also remain to be elucidated in more than 50 established anti-diabetes mellitus plants. Most of the *in vivo* experimental studies have been carried out in alloxan- and streptozotocin-induced type 1 (to a large extent) diabetic animals only. These models provide only limited information regarding mechanisms of action as well as the efficacy in different types of type 2 diabetes mellitus of test drugs (plant products).

In the case of important anti-diabetes mellitus plants, cultivation conditions and elite genotypes were not standardized keeping in view with anti-diabetes mellitus properties. Anti-diabetes mellitus properties of the plants have to be adequately considered while developing the agrotechniques. Although developing intercrops and utilizing unproductive lands are attractive alternatives for growing medicinal plants, the quality of the medicinal plants in terms of their required pharmacological properties should be considered. Micropropagation could aid in achieving uniform quality of the bulk amount of planting materials as per requirement. In many cases, this is essential in large-scale production of uniform quality plant-based medicines.

Type 2 diabetes mellitus is a heterogeneous disease, and tremendous advancement in our knowledge on diabetes mellitus and its complications could enable us to get substantial information regarding specific defect(s) in the metabolic syndrome in individual cases. Therefore, applying full knowledge of the mechanisms of action of anti-diabetes mellitus phytochemicals, tailor-made combination therapy, or single phytochemical entity therapy can even be developed in the future to provide individualized treatment.

There are more than 300 phytochemicals with varying levels and mechanisms of anti-diabetes mellitus activities. A number of such compounds are commonly occurring in many plants including certain edible plant parts. For example, compounds with promising anti-diabetes mellitus properties, such as chlorogenic acid, oleanolic acid, quercetin, and β-sitosterol, are present in a variety of plant species including many fruits, vegetables, and spices. These molecules have pharmacological properties other than anti-diabetes mellitus activities. Plants containing a reasonably high level of one or more of such compounds are considered only as anti-diabetes mellitus plants.

Literature on different animal models of diabetes mellitus show that a sedentary lifestyle coupled with plenty of nutrition and/or fatty diet could lead to type 2 diabetes mellitus. This aspect could have an important bearing in the prevention of type 2 diabetes mellitus in humans.

Another fact from the literature is that many of the anti-diabetes mellitus plants have more than one active molecule and most of the promising active molecules possess more than one pharmacological property and more than one target molecule in the body. Many anti-diabetes compounds show anti-inflammatory and anticarcinogenesis properties as well; this may be partly due to their common antioxidant effect. Besides, the metabolic network may be responsible, to some extent, for the several apparent pharmacological properties of some of the anti-diabetes mellitus compounds. Antioxidant, anti-diabetes mellitus, anticancer, anticardiovascular diseases, and anti-inflammatory activities are interlinked by cross talks between the complex signaling pathways. This is one of the limitations in clearly understanding specific mechanisms of actions of certain anti-diabetes mellitus compounds in the case of *in vivo* studies.

A decade of studies on anti-diabetes mellitus properties of plants has been updated in a recent book (*Plants with Anti-Diabetes Mellitus Properties* [CRC Press, 2016]) by this author. This book is a follow-up to that one. This book begins with a detailed introduction on diabetes mellitus including current treatments for this disease in conventional medicine (Chapter 1). Chapter 2 describes 303 anti-diabetes mellitus phytochemicals; the compounds are arranged alphabetically for easy reference and chemical structures of 70 compounds are provided. In Chapter 3, mechanisms of action of about 400 plants, which include 10 major mechanisms, are presented; multiple mechanisms of action of 10 selected anti-diabetes mellitus plants and berberine are illustrated. Chapter 4, among other things, highlights the likely therapeutic superiority of scientifically developed combinations of anti-diabetes mellitus phytochemicals and polyherbal formulations. An overview of available methods to study anti-diabetes mellitus activities of plant products is provided in Chapter 5. These include *in vitro* assays, *in vivo* animal models including nonmammalian animal models, and clinical trials. Seventeen RET (rare, endangered, and threatened) anti-diabetes mellitus plant species are described in Chapter 6. Further, studies on *in vitro* propagation through tissue culture of 112 anti-diabetes mellitus plants are given.

Lower plant species such as fungi and algae as well as bacteria are not covered in this book.

This book provides new insights with adequate and updated background knowledge on anti-diabetes mellitus phytochemicals, their mechanisms of action, and their combination therapy to promote research and development toward the creation of plant-based superior therapies for diabetes mellitus. An added attraction in this book is the light shed on sustainable and proper utilization of anti-diabetes mellitus plant species. Such a book covering all the relevant areas of study, required for the development of plant-based superior anti-diabetes mellitus therapy, is not available at present. The author sincerely hopes that this book will, certainly, be very useful to researchers, students, doctors, diabetic patients, plant biotechnologists, and others concerned with plant-based treatment of diabetes mellitus.

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Appian Subramoniam, PhD, is the former director of the Tropical Botanic Garden and Research Institute in Kerala, India, and the author of the recent book *Plants with Anti-Diabetes Mellitus Properties* (CRC Press, 2016). He earned his master's degree in zoology in 1974 from Annamalai University, Tamil Nadu, India, and his doctoral degree in biochemistry in 1979 from the Maharaja Sayajirao University of Baroda, India. Dr. Subramoniam carried out his postdoctoral research in biochemical pharmacology at Howard University, Washington, DC, and at Temple University, Philadelphia, Pennsylvania. He has worked in a few reputed institutes in India (Central Food Technology Research Institute, Mysore; Industrial Toxicology Research Centre, Lucknow; and Bose Institute, Calcutta) and carried out original, very high-quality multidisciplinary research work in the broad areas of biomedical sciences and plant sciences. He is a recognized PhD guide for a few universities in India in the fields of biochemistry, biotechnology, pharmacology, chemistry, and zoology. He has guided ten PhD scholars. Dr. Subramoniam is the author of more than 170 scientific publications, which include original research publications in reputed international journals, book chapters, and review papers in journals. He has nine patents to his credit. He served as a reviewer of scientific journals in the fields of ethnopharmacology, phytopharmacology, biochemistry, and toxicology. He joined Tropical Botanic Garden and Research Institute (TBGRI) as a scientist in ethnopharmacology and ethnomedicine in 1994. He was the appointed director of TBGRI in 2009. At TBGRI, he established advanced phytopharmacological research. During his tenure there, TBGRI earned national and international recognition in medicinal plant research for discovering many important leads from plants for the development of valuable medicines. For example, his research group discovered a potent aphrodisiac principle, 2,7.7-trimethyl bicyclo [2.2.1] heptane, from an orchid, *Vanda tessellata*, and his group discovered the promising anti-inflammatory property of chlorophyll-a and its degradation products. Dr. Subramoniam has received several national awards for his excellent scientific contributions, such as the Hari Om Ashram Award for research in Indian medicinal plants, Swaminathan Research Endowment Award for outstanding contribution in the scientific evaluation of medicinal plants for their therapeutic use (awarded by the Indian Association of Biomedical Scientists), Jaipur Prize from the Indian Pharmacological Society, and Dr. B. Mukherjee Prize (2006) from Indian Pharmacological Society. He served as president of Southern Regional Indian Pharmacological Society, 2009; vice president of Indian Association of Biomedical Scientists, 2007–2010, and vice president of Kerala Academy of Sciences (2011–2013). He is currently a consultant in medicinal plant research.

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Introduction

1.1 Diabetes Mellitus and Its Complications

1.1.1 Diabetes Mellitus

Diabetes mellitus (DM) is one of the oldest diseases known to humans. DM is characterized by hyperglycemia resulting mainly from defects in insulin production/secretion and/or insulin action. In DM, varying degrees of failure of normal regulation of metabolism of carbohydrate, lipids, and protein occur. Glucagon, a peptide hormone produced by α-cells of pancreas, and gut-derived hormones such as incretin and other agents, also have important roles in glucose homeostasis, including hepatic glucose production and insulin resistance (Mingrone and Gastagneto-Gissey 2014). Chronic hyperglycemia in DM leads to secondary pathophysiological changes, including long-term life-threatening complications in major organs.

1.1.1.1 Diagnosis of DM

The most reliable and convenient test for identifying DM in asymptomatic individuals is the determination of fasting plasma glucose (FPG) levels. FPG ≥ 7.0 mmol (126 mg/dL) warrants the diagnosis of DM. A random plasma concentration ≥11.1 mmol/L (200 mg/dL) accompanied by polyurea, polydipsia, and weight loss is sufficient for the diagnosis of DM. The impairment of glucose metabolism starts when the fasting glucose concentrations exceed about 7.78 mmol/L (140 mg/dL). Oral glucose tolerance testing is also a valid means for diagnosis of DM; however, it is not recommended as a part of routine care (Powers 2008). Glycohemoglobulin (HbA1c or A1C) values reflect average glycemic control over the previous period of about 3 months. Normal range of HbA1c values is from 4.0% to 6.4%. HbA1c levels of 6.5% or higher indicate diabetes.

1.1.1.2 Prevalence

According to the International Diabetes Federation (IDF), the worldwide prevalence of adults with DM is about 8.3%, accounting for approximately 382 million people (IDF 2012). In 2010, in the People's Republic of China, the prevalence of DM in people aged 20 years or older was 9.7%, accounting for 92.4 million adults with DM (Yang et al. 2010c). Among DM patients, about 90% are affected with type 2 DM. Type 2 DM has become a major health problem in both developed and developing countries. There are considerable geographical variations in the prevalence and severity of both type 1 and type 2 DM. According to IDF (IDF 2011) the Western Pacific region has the most people with DM (132 million). Most of these people have type 2 DM. In the United States, minority ethnic groups such as African Americans and Native Americans have higher incidence of type 2 DM than the non-Hispanic white population. The greatest increase in prevalence is predicted to occur in Africa and the Middle East. Scandinavia has the highest incidence of type 1 DM. Japan and China have relatively low incidences of type 1 DM. The prevalence of type 2 DM is the highest in certain Pacific islanders and relatively low in Russia (Powers 2008). In Basrah, Iraq, one in five adults is affected by DM (Mansour et al. 2014).

1.1.1.3 Effect on Economy and Well-Being

The cost of health care involved in DM is increasing day by day; DM is a huge economic burden for the patients and countries. In 2012, an estimated 22.3 million people in the United States were diagnosed with diabetes; the estimated total economic cost of diagnosed diabetes in 2012 was US$245 billion, a 41% increase from the estimated total economic cost in 2007. This estimate highlights the substantial burden that diabetes imposes on society (American Diabetes Association 2013). DM is a chronic disease; severe DM needs lifelong treatment in almost all cases. DM has tremendous adverse impacts on the economy and happiness of the society and country in terms of quality of life, emotional and social well-being, cost of the treatment, and loss in productivity of patients.

1.1.1.4 Different Types of DM

There are two major types of DM, which are designated type 1 and type 2. Type 1 DM is the result of near total insulin deficiency or absence of insulin. Among the DM patients about 10% suffer from type 1 DM. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production from liver. Type 2 DM accounts for more than 90% of cases of DM all over the world. Malnutrition-related diabetes is prevalent in Africa and certain Asian countries. There are other causes of hyperglycemia, which include chronic pancreatitis or chronic drug therapy with saquinavir (protease inhibitor), glucocorticoids, thiazids diuretics, diazoxide, and growth hormone. Gestational DM (glucose intolerance during pregnancy) is another type of DM. It may be related to the metabolic changes of late pregnancy and the increased insulin requirement. It occurs in about 4% of pregnancies in the United States. Most women revert to normal glucose tolerance postpartum but have a substantial risk of developing type 2 DM later in life. Maturity onset diabetes of the young is a subtype of DM characterized by early onset of hyperglycemia and impairment in insulin secretion. It is inherited (autosomal dominant inheritance). An extremely rare case of DM is pancreatic β-cell destruction by viral infections (Powers 2008). Mutations in the insulin receptor (IR) may cause severe insulin resistance.

1.1.1.4.1 Type 1 DM and Its Causes

The major causes of type 1 DM are shown in a flowchart (Figure 1.1). Type 1 DM most commonly develops before the age of 30, but it can develop at any age. It is commonly caused by complete destruction of β-cells in genetically susceptible individuals by chronic autoimmune disease believed to be triggered by an infection or environmental factor (Kukreja and Maclaren 1999; Pietropaolo 2001). The presence of islet cell antibodies in nondiabetic individuals predicts a risk of developing type 1 DM.

Genetic risk of type 1 DM is conferred by polymorphism in many genes that regulate innate and adaptive immunity. The major susceptibility gene for type 1 DM is located in human leukocyte antigen (HLA) class II gene located in chromosome 6 (Kelly et al. 2001). There are additional modifying factors of genetic risk in determining the development of type 1 DM. Nongenetic factors such as viral infection and vitamin D deficiency may increase risk (Lammi et al. 2005).

Environmental factors and their interaction with the immune system also give rise to the occurrence of type 1 DM. Certain toxic chemicals may also cause type 1 DM. Although in most of the individuals, type 1 DM is caused by autoimmune destruction of β-cells (type 1A), some individuals develop type 1 DM by unknown nonimmunological mechanisms (type 1 B) (Dejkhamron et al. 2007).

1.1.1.4.2 Type 2 DM and Its Causes

Major causes for the development of type 2 DM are shown in Figure 1.2. Type 2 DM typically develops with increasing age (particularly after the age of 40 years). However, it occurs in obese adolescents as well. Obesity is present in over 80% of type 2 diabetic patients (Powers 2008).

Genetic components are associated with insulin resistance. The contribution of the genes to an individual's risk of type 2 DM is influenced by factors such as sedentary lifestyle, increased nutritional intake, and obesity. The dramatic increase in type 2 DM in the present century is due to the changing environmental factors as well as sedentary lifestyle, dietary habits including pro-oxidant food, and mental stress.

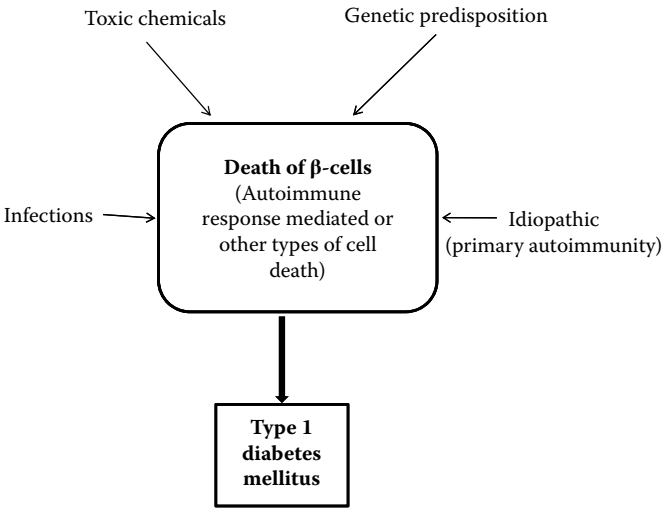

FIGURE 1.1 Major causes of type 1 diabetes mellitus.

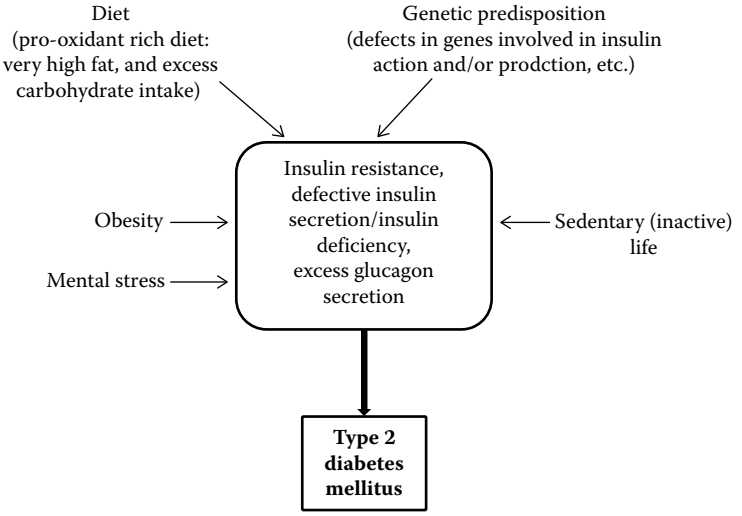

FIGURE 1.2 Major causes of type 2 diabetes mellitus.

The contribution of maternal environment and *in utero* factors to the risk of type 2 DM in subsequent generations via epigenetic modifications is now being recognized as potentially important in explaining the very high rate of type 2 DM currently seen in many populations in the developing world.

Insulin resistance has a central role in the development of type 2 DM. Induction of the resistance is partly by the sustained activation of various serine/threonine protein kinases that phosphorylate insulin receptor substrate (IRS) proteins and other components of the insulin-signaling pathway. This intense signaling leads to activation of negative feedback mechanisms. Normally, these feedback mechanisms are there to terminate excess insulin action. Phosphorylation of IRS proteins inhibits their function and interferes with insulin signaling in a number of ways, leading to the development of an insulin-resistant state (Cooper et al. 2012). In general, post-IR defects in insulin signaling lead to insulin resistance. In rare cases, due to gene defects IR gets mutated at the site of adenosine triphosphate (ATP) binding or

replaces tyrosine residues at the major sites of phosphorylation. This leads to failure of insulin signaling and cell response to insulin (Ellis et al. 1986).

Insulin resistance could develop in humans within an hour of acute increase in plasma nonesterified fatty acids. The increased rates of nonesterified fatty acid delivery and decreased intracellular fatty acid metabolism result in an increase in the levels of diacyl glycerols (DGs), fatty acyl coenzyme A, and ceramides. These metabolites in turn activate serine/threonine phosphorylation of IRS-1 and IRS-2 and reduce the ability of phosphatidyl inositol kinase-3 in proper downstream regulation of insulin signaling (Khan et al. 2006).

An increase in visceral adipose tissue deposition leads to obesity and an increase in the production of proinflammatory adipokines. Such individuals are at a high risk of type 2 DM and cardiovascular diseases. Expansion of adipose tissue is associated with the accumulation of macrophages that expresses several proinflammatory genes, including tumor necrotic factor (TNF) and interleukin-1 (IL-1), which locally impair insulin signaling. Oxidative stress, endoplasmic reticulum stress, and inflammation could promote both insulin resistance and β-cell dysfunction (Kahn et al. 2014).

Clock genes expressed in the brain are important in the establishment of circadian rhythmicity. Changes in diurnal patterns and quality of sleep can have important effects on metabolic processes. Hypothalamic inflammation might also contribute to central leptin (produced by adipose tissue that acts at the level of hypothalamus to suppress appetite) resistance and weight gain (Kahn et al. 2014). Leptin in normal physiological conditions causes accumulation of fat and reduces appetite through hypothalamic effect, but in obese subjects leptin resistance is developed, which leads to excessive flux of free fatty acids. This in turn leads to insulin resistance and β-cell dysfunction.

In addition to the secretion of incretin hormones, the gastrointestinal tract has crucial roles in type 2 DM. The gut may have an important role in insulin resistance in obese type 2 DM (Mingrone and Castagneto-Gissey 2014). Jejunal proteins secreted by type 2 obese diabetic mice or insulin-resistant obese humans impair insulin signaling. These proteins induce insulin resistance in normal mice and inhibit insulin signaling *in vitro* in rat skeletal muscle cells. Metabolic surgery has been shown to be effective in inducing remission of type 2 DM prior to any significant weight reduction. In metabolic surgery, the secretion of these proteins may be drastically impaired or abolished (Mingrone and Castagneto-Gissey 2014). Furthermore, in duodenal–jejunal bypass surgery, jejunal nutrient sensing is required to rapidly lower glucose concentration (Breen et al. 2012). In the proximal jejunum, stimulation of a nutrient sensor by glucose and/or lipid reduces hepatic glucose production. Recent studies suggest that microbes present in the gut also have a role in the development of insulin resistance.

The liver is a major source of glucose production through glycogenolysis and gluconeogenesis. Excess accumulation of lipids in liver develops and causes insulin resistance and type 2 DM. Studies in mice and humans have elucidated an important role for hepatic diacylglycerol activation of atypical protein kinase C (PKC_a) in triggering hepatic insulin resistance (Perry et al. 2014). Lipid accumulation is probably associated with the secretion of proinflammatory cytokines from Kupffer cells (resident macrophages) and the recruited macrophages that impair insulin signaling. Markers of systemic inflammation, including C-reactive proteins and its upstream regulator IL-6, are associated with insulin sensitivity and β-cell function. Decrease in inflammation improves β-cell function in patients with type 2 DM (Kahn et al. 2014).

1.1.1.4.2.1 Pathogenesis of Type 2 DM During the early stage of type 2 DM, insulin resistance is compensated by increased production of insulin; thus, normal glucose levels are preserved (DeFronzo 2004). Studies suggest that insulin resistance precedes defect in insulin secretion. Eventually, the defect in insulin secretion progresses to a level where insulin secretion is grossly inadequate. The delicate balance between β-cell replication and apoptosis is interrupted in DM. Further, the replacement with new β-cells appears to be limited in humans after 30 years of age (Kahn et al. 2014).

At the onset of the pathogenesis of type 2 DM, the peripheral insulin-responsive tissues such as muscle and adipose exhibit a decreased rate of disposal of excess glucose and fatty acid from the circulatory system. At the same time, due to reduced insulin sensitivity of the liver, hepatic glucose production increases. In type 2 DM, pronounced insulin resistance is observed in muscle, liver, and adipocytes.

Increased hepatic glucose output predominantly accounts for increased FPG levels, whereas decreased peripheral glucose utilization results in postprandial hyperglycemia and impaired glucose tolerance.

The ectonucleotide pyrophosphatase, phosphodiesterase-1 (ENPP-1), known to hydrolyze 5′-phosphodiester bond in nucleotides, is very important in insulin signaling. When ENPP-1 interacts with IR, a decrease in insulin-dependent tyrosine phosphorylation of its α-subunit occurs. This leads to the failure of the autophosphorylation of β-subunit and switching off of insulin signaling (Abate and Chandalia 2007; Ohan et al. 2007). Inappropriate degradation of insulin receptor substrate 1 and 2 (IRS-1 and IRS-2) in the insulin-signaling pathway partly through the upregulation of suppressors of cytokine signaling was reported in many cases (Balasubramanyam et al. 2005).

In obese subjects, retinol-binding protein-4 interacts with phosphatidyl inositol 3-kinase (PI3K) and reduces its activity. This also leads to insulin resistance in muscles and enhances the expression of phosphoenol pyruvate carboxylase in liver. The changes in the production of adipokines are also reported in nonobese Asian Indians having a direct link with obesity-independent insulin resistance. Obesity also reduces the phosphorylation of proteins involved in intracellular insulin signaling via IRS-1 and PI3K. This results in the reduction of glucose transporter-4 (GLUT4)-mediated influx of glucose (Ishiki and Klip 2005). The decreased insulin signaling in the skeletal muscles contributes to lipid accumulation and impairment in glycogen formation in the muscle cells. The excessive accumulation of triglycerides in the skeletal muscle cells of obese subjects is observed due to the greater mobilization of free fatty acids from insulin-resistant adipocytes. Increased free fatty acid flux from adipocytes leads to increased synthesis of very low density lipoprotein (VLDL) and triglycerides. This may lead to fatty liver diseases. Lipid accumulation and impaired fatty acid accumulation may generate lipid peroxides. In addition to the contribution of fatty acid and triglycerides in the pathogenesis of type 2 DM, leptin, resistin, adiponectin, and TNF-α produced by adipocytes have roles in the pathogenesis. TNF-α, overexpressed in obese subjects, leads to impaired insulin signaling (Rosen and Spiegelman 2006). Syndromes associated with insulin resistance may include in certain cases acanthosis nigricans (increased thickness of the prickle cell layer of the skin and hyperpigmentation) and ovarian hyperandrogenism and polycystic ovary.

1.1.2 Complications of DM

In both type 1 and type 2 DM, uncontrolled hyperglycemia and, to some extent, hyperlipidemia lead to the development of both acute and long-term complications. The development of complications is simplified and presented in a flowchart (Figure 1.3). Diabetes ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are the acute complications of DM. DKA is very common in type 1 DM patients, but it also occurs in certain type 2 DM cases. Major symptoms include nausea, thirst/polyurea, abdominal pain and shortness of breath; in children, cerebral edema is frequently associated with this. Ketoacidosis results from a marked increase in fatty acid release from adipocytes with a shift toward ketone body synthesis in the liver. Normally, these fatty acids are converted to triglycerides or VLDL in the liver. But high levels of glucagon alter hepatic metabolism to favor ketone body formation. Both insulin deficiency (absolute or relative deficiency) and glucagon excess are generally required for DKA to develop. Excess catecholamines, cortisol, and/or growth hormone also contribute to the development of DKA. HHS is primarily seen in individuals with type 2 DM with a history of polyurea, weight loss, and diminished oral intake. Clinical features include profound dehydration, hyperosmolality, hyperglycemia, tachycardia, and altered mental status. Hyperglycemia associated with DM and inadequate fluid intake induces an osmotic diuresis that leads to intravascular volume depletion (Powers 2008).

Chronic complications of DM can be divided into vascular and nonvascular complications. Microvascular complications lead to retinopathy, neuropathy, and nephropathy, whereas coronal arterial disease, peripheral arterial disease, and cerebrovascular disease are due to macrovascular complications. The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Coronary heart diseases and morbidity are two to four times greater in patients with DM. Dyslipidemia and hypertension also play important roles in macrovascular complications. Nonvascular complications include gastroparesis, diarrhea, uropathy, sexual dysfunction, infections, periodontal diseases, dermatological complications, and glaucoma. Foot ulcers and infections can lead to gangrene, which may require

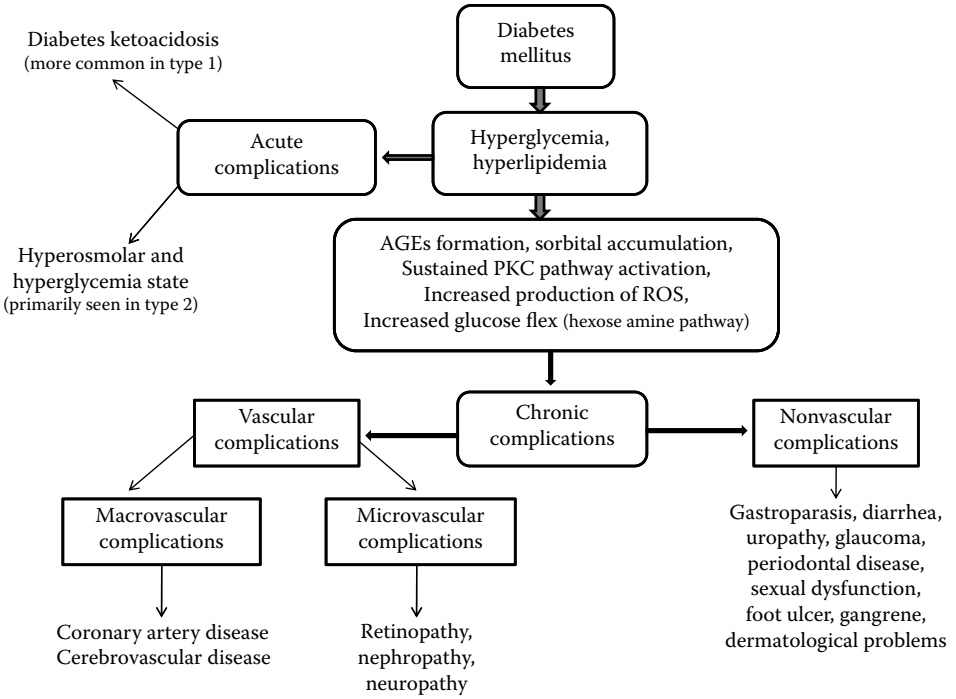

FIGURE 1.3 Complications of diabetes mellitus. AGEs, advanced glycation end products; PKC, protein kinase C; ROS, reactive oxygen species.

amputation. Hyperglycemia facilitates the growth of pathogenic fungi and bacteria. Furthermore, abnormal cell-mediated immunity and phagocyte function and diminished vascularization lead to a greater frequency and severity of infections in DM.

Diabetes nephropathy develops in 30%–40% of patients with both type 1 and type 2 DM within 20–25 years after the onset of DM (Powers 2008). Diabetic nephropathy is the leading cause of DM-related morbidity and mortality (Lopes 2009; Wada and Makino 2009). DM is the leading cause of blindness in the United States. Individuals with DM are 25 times more likely to become blind than normal individuals. Blindness is primarily due to diabetic retinopathy and macular edema. Diabetic neuropathy occurs in about 50% of individuals with chronic type 1 or type 2 DM. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative retinopathy is marked by retinal vascular microaneurysms. In proliferative retinopathy, neovascularization appears in response to retinal hypoxia (Powers 2008). Neuropathy involving the autonomic nervous system may lead to genitourinary dysfunction.

The mechanisms wherein hyperglycemia leads to the aforementioned serious complications are not fully understood. However, the suggested mechanisms include (1) formation of advanced glycosylation end products (AGEs), (2) increased levels of sorbitol formation, (3) sustained activation of the PKC pathway, and (4) increased glucose flux through the hexosamine pathway. Intracellular hyperglycemia causes the formation of AGEs by nonenzymatic glycosylation of proteins. AGEs have been shown to cross-link proteins and accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, and induce endothelial dysfunction. During hyperglycemia, a part of the glucose is converted to sorbitol by the enzyme aldolase reductase; increased sorbitol concentration leads to increase in cellular osmolality, alterations in redox potential, and increase in reactive oxygen species (ROS) generation. These may facilitate retinopathy, nephropathy, and neuropathy. Hyperglycemia increases the formation of DG, which activates PKC. This enzyme, among other actions, alters transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells. Hyperglycemia increases glucose flux through the hexose amine pathway, which generates fructose-6-phosphate, a substrate for O-linked glycosylation and proteoglycan production. This pathway may

alter functions of proteins by glycosylation of proteins such as endothelial nitric oxide synthase. The production of growth factors such as transforming growth factor-β, vascular endothelial growth factor-β, platelet-derived growth factor, and epidermal growth factor is increased by most of these proposed pathways. Excess of these growth factors may play an important role in complications of DM. Increased production of ROS in the mitochondria under hyperglycemic conditions and peroxidation of lipids may influence the aforementioned pathways. Intensive glycemic control in DM can prevent the complications more effectively (Powers 2008).

1.2 Glucose Homeostasis

A feedback loop operates to ensure the integration of glucose homeostasis and maintenance of glucose concentration in a specific range. This feedback loop relies on cross talk between β-cells and insulin-sensitive tissues. These tissues feed the information back to β-cells. The mediator of this process has not been identified. The brain and humoral system may be involved in this process. Furthermore, the brain is involved in the regulation of appetite and satiety as well as in modulating the function of pancreatic α-cells and β-cells. The hypothalamus and sympathetic and parasympathetic systems are involved in this. The hypothalamus is an integrator of insulin secretion and the vagus nerve is important in insulin secretion. Structural changes occur in the hypothalamus consistent with the occurrence of gliosis in obesity.

If insulin resistance is present, β-cells increase insulin output to maintain normal glucose tolerance. When β-cells fail to respond adequately due to impaired β-cell function, glucose levels increase beyond the normal range. The magnitude of reduction in β-cell function establishes the degree of increase in plasma glucose. Besides, an age-associated reduction in the responsiveness of β-cells to carbohydrate partly underlines the fall in glucose tolerance with aging. Human pancreas seems to be incapable of renewing β-cell loss resulting from apoptosis after 30 years of age. In addition to insulin and glucagon, certain other hormones and cytokines have important roles in controlling glucose homeostasis (Kahn et al. 2014).

1.2.1 Insulin and Glucose Homeostasis

Insulin is synthesized in the β-cells of islets of Langerhan's in the pancreas. Cleavage of an internal 31-residue connecter fragment (C peptide) from the proinsulin generates chain A (21 amino acids) and chain B (30 amino acids) of insulin molecule. A and B chains are connected by two disulfide bonds. The newly synthesized insulin and C-peptide are released in equimolar concentrations. Since the C-peptide is cleared more slowly than insulin, it is a useful marker of insulin secretion.

Normally, glucose is the prime stimulus for insulin secretion. Certain amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also stimulate insulin secretion. Glucose levels above a critical level (3.9 mmol/L) stimulate insulin synthesis. Glucose is transported into the β-cells by glucose transporter-2 (GLUT2). Metabolism of glucose via glycolysis in mitochondria generates ATP. Increase in intracellular ATP levels causes the closure of ATP-sensitive K^+ channels. Closure of this channel results in depolarization of plasma membrane and opening of voltage-gated calcium channels. The increased intracellular calcium ion concentration leads to the exocytosis of insulin containing secretary granules. High levels of intracellular glucose in β-cells also stimulate calcium-independent pathways that enhance secretion of insulin. These pathways involve enhanced glucokinase activity, increased citrate levels, increased DG formation, and enhanced PKC signaling.

Binding of glucagon-like peptide-1 (GLP-1) to its receptor in β-cells promotes insulin release via intermediates such as protein kinase B (Akt) and also increases the number of β-cells via improved cell survival and decreased apoptosis (Cooper et al. 2012).

The major functions of insulin are the stimulation of glucose uptake from the systemic circulation and suppression of hepatic gluconeogenesis. It activates the transport systems as well as the enzymes engaged in the intracellular utilization and storage of glucose, amino acids, and fatty acids. Besides,

insulin inhibits the breakdown of glycogen, fat, and protein. Insulin stimulates glycolysis (catabolism of glucose) and glycogenesis (synthesis of glycogen from glucose) and inhibits both hepatic gluconeogenesis and glycogenolysis (Cummings 2006). Postprandially, the glucose load elicits a rise in insulin, which promotes the storage of carbohydrates and fat and synthesis of protein. Insulin reduces circulating free fatty acid levels and promotes triglyceride synthesis and storage. It reduces intracellular lipolysis of stored triglyceride in adipocytes and increases glucose transport into adipocytes to generate glycerophosphate, which permits the esterification of fatty acids.

Insulin mediates its multiple actions by binding to its receptors and triggering intracellular signaling. There are two types of IR, namely IR-A and IR-B. IR-B preferentially activates metabolic signals, whereas IR-A leads the predominance of growth and proliferation signals. The IRs are found over the surface of cell membranes in all mammalian cells. IR-B is found in hepatocytes, adipocytes, and muscle cells in higher concentrations (about 300,000/cells), whereas it is present in very low concentrations in blood cells, neurons, and so on (about 40/cells) (Khan and White 1998). Tissues that contain low concentrations of IR-B, brain in particular, utilize glucose, to a large extent, in an insulin-independent fashion. Both IR-A and IR-B are present in brain, heart, kidney, pancreas, and many other tissues (Belfiore and Malaguarnera 2011). IR is a large transmembrane glycoprotein with two α-subunits and two β-subunits linked by disulfide bridges to form a heterotetramer. When the insulin binds to α-subunits of the IR, the internal domain of its β-subunit undergoes autophosphorylation in its several tyrosine residues, which enhances the receptor's tyrosine kinase activity toward other substrates in insulin-signaling pathways. The activated IR-kinase phosphorylates IRS proteins IRS 1–6 on their tyrosine residues. Most of the insulin responses are mediated through IRS-1 and IRS-2. Phosphorylation of IRSs leads to the activation of phosphatidylinositol 3-kinase (PI-3K) pathway of signal transduction. Phosphorylation of IRS at multiple tyrosine motifs by IR-kinase serves as the docking site for PI-3K. Another pathway activated by insulin is mitogen-activated protein kinase (MAPK) pathway, which mediates the mitogenic effects. The MAPK and PI-3K pathways are linear in nature but in many places they cross-talk. The activated PI-3K leads to the formation of plasma membrane–bound phosphatydylinositol 3,4,5-trisphosphate (PIP3) from phosphatydylinositol 4,5-bisphosphate (PIP2), which in turn recruits protein kinase B (PKB/Akt), PIP3-dependent protein kinase-1 (PDK-1), and PKCa to the plasma membrane. There are three isoforms of Akt, of which Akt-2 is the relevant isoform, which associates tightly to GLUT4-containing vesicles in the cytosol and stimulates translocation of GLUT4 to the plasma membrane (Cho et al. 2001; Balasubramanyam and Mohan 2004). GLUT4 transports glucose into the cell. Defects in phosphorylation and activation of PKB/Akt lead to insulin resistance. Akt also phosphorylates many substrates like Bcl2 antagonists of cell death, glycogen synthase kinase-3, and forkhead transcription factor FOXO1. The activation of these substrates finally leads to multifarious effects like survival and multiplication of cells, glycogen synthesis, lipogenesis, and controlling of gene expression (Mackenzie and Elliott 2014). Akt inhibits adenosine monophosphate–activated protein kinase (AMPK) (Kovacic et al. 2003). Glucose transport activity in skeletal muscle is also facilitated by AMPK-dependent mechanisms (Mackenzie and Elliott 2014). GLUT4 is primarily present in striated muscles and in adipose tissue; absence of insulin results in deficiency of glucose in these tissues; hyperglycemia causes excess of glucose entry in cells where it penetrates freely without insulin. Noninsulin-dependent glucose carriers are present in liver, pancreas, kidney, intestine, erythrocytes, and so on. Among the noninsulin-dependent glucose transporters, cocarriers glucose/Na^+ ensure the digestive absorption of glucose and reabsorption of glucose in the renal tubules.

Even though GLUT4 is expressed sufficiently in the cell, the insulin resistance is associated with insufficient recruitment of GLUT4 to plasma membrane (McCarthy and Elmendorf 2007). In addition to the major insulin-dependent GLUT4 translocation, a noninsulin-dependent GLUT4 translocation mechanism is also present and it could be due to the combined action of AMP-activated protein kinase and muscle contractions (Jessen and Goodyear 2005). Insulin regulates GLUT4 recruitment in adipocytes through one minor PI3-kinase independent pathway also. In addition to insulin, several other hormones and growth factors can also activate signaling targets downstream of IR. However, only insulin and highly related hormones such as insulin-like growth factor-1 (IGF-1) efficiently stimulate acute glucose transport.

Termination of insulin signaling is effected by different mechanisms. Inositol 3′ and 5′ phosphatases dephosphorylate PIP3 and attenuate PIP3 signaling. Insulin signaling is also terminated by internalization of insulin–IR complex into endosomes and the degradation of insulin by insulin-degrading enzymes.

1.2.2 Glucagon, Incretins, and Other Hormones in Glucose Homeostasis

Glucagon is a peptide hormone secreted by α-cells of the pancreas and, to a small extent, by intestinal tract. Its plasma half-life is a few minutes only. The actions of insulin are opposed by glucagon, which is normally secreted when the blood glucose level tends to be low. Glucagon has hyperglycemic effects by stimulating the breakdown of glycogen into glucose (glycogenolysis) and gluconeogenesis and by inhibiting the synthesis of glycogen (glycogenesis) (Klover and Mooney 2004; Postic et al. 2004). Secretion of glucagon is inhibited by glucose and somatostatin (produced by δ-cells in pancreas) and is stimulated by certain amino acids.

The incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), play great roles in glucose homeostasis by improving β-cell differentiation, mitogenesis, survival, and insulin secretion. It also inhibits the gastric emptying. The GLP-1 potentiates glucose-stimulated insulin release through G-protein-coupled receptor and the activation of protein kinase A (Drucker 2006; Nauck 2014). GLP-1 is the most potent incretin released from L cells in the small intestine; it stimulates insulin secretion only when the blood glucose is above the fasting level (Powers 2008).

In addition to incretins, many gastrointestinal hormones such as gastrointestinal inhibitory peptide, gastrin, secretin, cholecystokinin (CCK), vasoactive intestinal peptide, gastrin releasing peptide, and entroglucagon promote insulin secretion. In glycemic regulation and in appetite regulation, several hormones secreted by the digestive tract, adipose tissue, and hypothalamic neurons are involved. Hormones such as adiponectin, leptin, resistin (from adipocytes), CCK, GLP-1, and ghrelin (from digestive tract) modulate the actions of insulin. Resistin and adiponectin also have rolls in insulin sensitivity in obese subjects. Adiponectin, the sensitizer of the insulin, stimulates fatty acid oxidation through AMPK and peroxisome proliferator–activated receptor-γ (PPAR-γ)-dependent ways (Rosen and Spiegelman 2006). PPAR-γ is an essential transcriptional mediator of adipogenesis, lipid metabolism, insulin sensitivity, and glucose homeostasis, which is increasingly recognized as a key factor in inflammatory cells as well as in cardiovascular diseases (Duan et al. 2008).

Catecholamine stimulates glycogen breakdown and production of glucose through its β-receptor.

Bile acids also have important roles in glucose homeostasis. Bile acids are ligands for the farnesoid X receptor. Activation of this receptor by bile results in the release of fibroblast growth factor (FGF)1. This growth factor has insulin-like actions and insulin-sensitizing properties (Suh et al. 2014). Furthermore, when bile acid binds its receptor in the L-cells, GLP-1 secretion from the cells increases (Kahn et al. 2014).

1.3 Treatment/Management of DM in Current Conventional Medicine

Insulin is the major therapeutic agent used for DM, particularly for type 1 DM. Parenteral therapy includes insulin, GLP-1, and amylin. Oral glucose lowering agents currently in use are biguanides, insulin secretagogues (sulfonylureas, repaglinide, nateglinide, etc.), thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and so on. In addition to therapy, management of DM includes appropriate nutrition, required level of exercise, and removing mental stress.

1.3.1 Insulin and Other Parenteral Therapy

Treatment of DM with insulin follows different regimens in accordance with the type and severity of diabetes, and age, meal pattern, and physiological status of the patient. Insulin is the major therapy used for the treatment of type 1 DM and also in certain cases of type 2 DM. Since in type 1 DM, insulin is absent without insulin resistance, it can be treated with insulin. Nowadays, the insulin used is produced through

recombinant DNA technology using genetically engineered *Saccharomyces cerevisiae* or *Escherichia coli*. The recombinant insulin consists of the amino acid sequence of human insulin or minor variants of that. For example, in one of the short-acting insulin variants, insulin lispro, the 28th and 29th amino acids have been reversed by genetic manipulations. This insulin analog has fewer tendencies for self-aggregation, resulting in more rapid absorption and onset of action and a shorter duration of action. The different classes of insulin used for the treatment of diabetes are rapid-acting insulin, short-acting insulin, intermediate-acting insulin, and long-acting insulin. The rapid-acting insulin starts its action within 5–15 min after administration and lasts for about 3–5 h. Generally, the short-acting insulin is the soluble crystalline zinc insulin. The intermediate-acting insulin starts its action after 2 h of administration and lasts for 18–24 h; it includes lente and neutral protamine hagedorn insulin. Long-acting insulin includes ultralente insulin and insulin glargine with no pronounced peak of activity and the duration of action is more than 24 h. The standard mode of insulin administration is subcutaneous and it can be done with syringes and needles, pen injectors, or insulin pumps. In addition, powered and aerosolized insulin formulations are used for inhalation.

It should be noted that the precise normal insulin secretary pattern of the β-cells in response to blood glucose levels is not reproduced by any of the insulin regimen. Hypoglycemia is the most common complication of insulin therapy. It mostly results from inadequate carbohydrate diet after insulin administration or very high physical exertion or a very high insulin dose. In certain cases, antibodies are produced against insulin, which leads to both neutralization of some quantity of administered insulin and allergic reactions. In certain cases, atrophy of subcutaneous fatty tissue may occur at injection sites secondary to immune reactions. However, use of recombinant human insulin has reduced these complications.

Amylin is a 37-amino acid peptide cosecreted with insulin in normal glucose homeostasis. An analog of amylin (pramlintide) was found to reduce postprandial glycemic cxcursions in type 1 and type 2 DM patients taking insulin. Addition of pramlintide with insulin produces a modest reduction in A1C and seems to dampen meal-related glucose excursions. It slows gastric emptying and suppresses glucagon levels, but not insulin levels. The major side effects of this peptide are occasional nausea and vomiting (Powers 2008).

Analogs of GLP-1 amplify glucose-stimulated insulin release. GLP-1 receptors are found in islets, the gastrointestinal tract, and the brain. Exenatide, an analog of GLP-1, which differs from GLP-1 in amino acid sequence, has more half-life time compared to native GLP-1 by virtue of its resistance to the enzyme that degrades GLP-1 (dipeptidyl peptidase-4 or DPP-4). Exenatide lowers glucose and suppresses appetite without weight gain in type 2 DM. The A1C reduction with exenatide is only moderate. This drug is given as an adjuvant or combination therapy with metformin or sulfonylurea. Nausea is the reported side effects especially at higher doses (Powers 2008).

1.3.2 Oral Hypoglycemic Agents

The major oral hypoglycemic agents (OHA) used in the treatment of type 2 DM are sulfonylureas, biguanides, repaglinide, nateglinide, thiazolidinediones, agents that enhance GLP-1 receptor signaling, α-glucosidase inhibitors, and inhibitors of sodium glucose cotransporter-2 (SGLT2) (Kahn et al. 2014). The diverse major mechanisms of most of the oral hypoglycemic agents used in the treatment of type 2 DM are shown in Figure 1.4. The pathophysiology of type 2 DM is highly heterogeneous and the individual response to drugs can differ greatly.

1.3.2.1 Insulin Secretagogues

Sulfonylurea drugs constitute the majority of the insulin secretagogues used in the treatment of type 2 DM. Normally, pancreatic β-cells sense and secrete appropriate amount of insulin in response to a glucose stimulus. The sulfonylureas increase insulin release from β-cells by interaction with ATP-sensitive potassium channel on the β-cells. The ATP-sensitive potassium channels have two subunits: one subunit contains the cytoplasmic-binding sites for both sulfonylureas and ATP, which is named as the sulfonylurea receptor type 1, the other subunit of the potassium channel, which acts as the pore-forming subunit. Higher rate of mitochondrial activity leads to an increase in the ATP/adenosine diphosphate ratio. Either

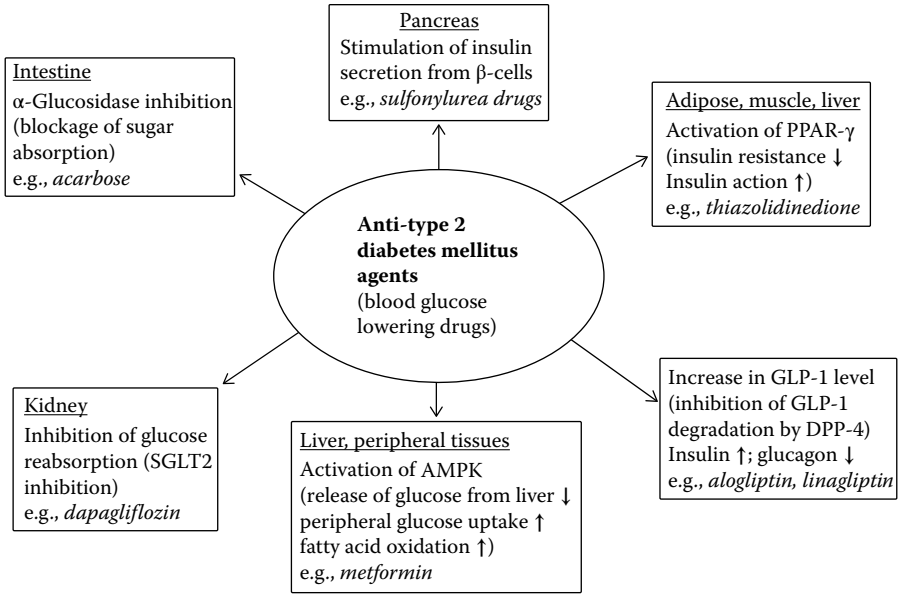

FIGURE 1.4 Diverse mechanisms of action of oral hypoglycemic agents used in conventional medicine in the treatment of diabetes mellitus (type 2). AMPK, adenosine monophosphate–activated protein kinase; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PPAR-γ, peroxisome proliferator–activated receptor-γ; SGLT2, sodium glucose cotransporter-2; upward arrows in the boxes indicate increase and downward arrow indicate decrease.

this ATP or sulfonylurea interacts with the sulfonylurea receptor type 1 resulting in the closure of the ATP-sensitive potassium (K_{ATP}) channel. Closure of this channel depolarizes the plasma membrane and triggers the opening of voltage-sensitive calcium channels, leading to the rapid influx of calcium. Increased intracellular calcium causes an alteration in the cytoskeleton, which stimulates the translocation of insulin-containing secretary granules to the plasma membrane leading to the exocytotic release of insulin.

Sulfonylurea drugs are classified into first and second generations, of which acetohexomide, chlorpropamide, tolbutamide, and tolazamide are the first-generation drugs, which possess a lesser affinity to bind sulfonylurea receptor type 1. Second generation sulfonylureas include glibenclamide (also known as glyburide), glipizide, gliclazide, and glimepiride; these drugs are now used widely. These second-generation sulfonylureas are most effective in individuals with type 2 DM of recent onset (less than 5 years). They generally possess a more rapid onset and shorter half-life (Powers 2008). However, glimeperide (1–4 mg) is administered once a day and has a long duration of action.

Meglitinides are also insulin secretogogues. These include repaglinide and nateglinide, characterized by a very rapid onset and short duration of action. Repaglinide is a structural analog of glyburide, while nateglinide is the derivative of the amino acid D-phenylalanine. Unlike sulfonylureas, meglitinides stimulate first-phase insulin release in a glucose-sensitive manner. Repaglinide is approximately five times more potent in stimulating insulin secretion than glyburide, and in the case of nateglinide, it is threefold more rapid than repaglinide. The mechanism of action of meglitinides is binding with sulfonylurea receptor type 1, stimulating the closing of K_{ATP} channel resulting in an influx of calcium and insulin exocytosis. This class of drugs can control postprandial glucose increase and can be used in patients with sulfonylureas allergy. These drugs have relatively short half-life and are given along with meals (Powers 2008).

1.3.2.2 AMPK Activators with Hypoglycemic and Hypolipidemic Effects

Metformin is the major therapeutically useful biguanide; it is regularly advised for the treatment of type 2 DM in the United States and it is the second most prescribed OHA in Europe. The mechanisms of action of metformin are not fully understood and the receptors of the compounds, if any, are yet to be identified.

Metformin reduces hepatic glucose production, increases peripheral utilization of glucose, reduces fasting plasma glucose levels, and improves lipid profiles. *In vitro* and *in vivo* studies show that instead of stimulating insulin secretion, metformin activates AMPK, which is a major cellular regulator of lipid and glucose metabolism. Metformin increases peripheral glucose uptake and reduces hepatic glucose production in an AMPK-dependent manner (Mackenzie and Elliott 2014). Metformin can reduce acetyl-coenzyme A carboxylase activity, induce fatty acid oxidation, and increase expression of enzymes for lipogenesis (Cleasby et al. 2004; Zhang et al. 2007). Reported side effects of metformin include diarrhea, anorexia, nausea, metallic taste, and lactic acidosis (Powers 2008).

Phenformin is another OHA coming under the group biguanides. Phenformin is not prescribed extensively nowadays due to increased co-occurrence of lactic acidosis with DM and relatively fewer long-term benefits.

1.3.2.3 PPAR-γ Agonists

Thiazolidinediones are the class of insulin-sensitizing compounds with glucose and lipid-lowering activity. They are the selective agonist for the PPAR-γ. PPAR-γ is a transcription factor of the nuclear receptor family. PPAR-γ is highly expressed in adipose tissue, macrophages, and cells of the vasculature, but is expressed at lower levels in many other tissues. PPAR-α is the receptor for the fibrate class of lipid-lowering drugs, and PPAR-δ orchestrates the regulation of high-density lipoprotein metabolism (Balasubramanyam and Mohan 2000). Synthetic ligands of PPAR-α and PPAR-γ such as fibric acid and thiazolidinediones showed a significant improvement in insulin resistance in type 2 DM and prediabetes (Jay and Ren 2007). PPAR-γ receptor-signaling plays essential roles in adipogenesis, glucose, and lipid homeostasis (Auwerx 1999; Lehrke and Lazar 2005).

Pioglitazone and rosiglitazone are the major therapeutically used thiazolidinediones, which decrease insulin resistance and enhance biological activity of both endogenous and injected insulin. The pioglitazone acts on both PPAR-γ and PPAR-α and hence it has a better glucose and triglyceride lowering activity than that of rosiglitazone (Giaginis et al. 2009; Borniquel et al. 2010).

Thiazolidinediones may cause liver toxicity, peripheral edema, and heart failure in certain cases. Increased risk of fractures in women has been reported (Powers 2008). Rosiglitazone was withdrawn from the market in many countries due to concern about a possible increase in the risk of cardiovascular adverse effects, including congestive heart failure. Pioglitazone has been withdrawn in 2011 in France considering the possible high risk of bladder cancer. The risks are not substantiated. The continued use of this drug is a subject of debate (Kahn et al. 2014).

1.3.2.4 α-Glucosidase Inhibitors

The α-glucosidase inhibitors in current use are acarbose, miglitol, and voglibose. These drugs inhibit the enzymatic degradation of complex carbohydrates in the small intestine and thereby reduce the entry of glucose into the blood stream. Acarbose is a nitrogen-containing pseudotetrasaccharide α-glucosidase inhibitor, while miglitol is a synthetic analog of deoxynojirimycin. These compounds improve glycemic control in DM without increasing the risk of weight gain or hypoglycemia. The pancreatic α-amylase and membrane-bound intestinal α-glucosidase enzymes are inhibited by the inhibitors in competitive and reversible manner. Acarbose shows little affinity for isomaltase and no affinity for lactase, while miglitol does inhibit intestinal isomaltase. Side effects of these drugs include diarrhea, flatulence, and abdominal distention. It is contraindicated to individuals with inflammatory bowel disease, gastroparesis, and so on (Powers 2008).

1.3.2.5 Dipeptidyl Peptidase-4 Inhibitors

DPP-4 is the major enzyme responsible for degrading the incretin hormones *in vivo*. The inhibitor of DPP-4 increases the insulin secretion, reduces glucagon secretion, improves glucose tolerance, and reduces glycated hemoglobin levels in type 2 DM patients (McIntosh 2008). Thus, the inhibition of DPP-4 improves type 2 DM (McIntosh et al. 2005; Ahrén 2007; Green 2007). DPP-4 inhibitors in current use are alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin (Kahn et al. 2014).

These orally active DPP-4 inhibitors show antihyperglycemic effect without severe hypoglycemia, reduce glycated hemoglobin, improve islet function, and modify the course of DM. These agents promote insulin secretion without hypoglycemia or weight gain and appear to have preferential effects on postprandial blood glucose.

Dipeptidyl peptidase-4 has a wide range of substrates other than GLP-1, GIP, and peptide YY. Therefore, the inhibitors of DPP-4 influence not only the regulation of energy homeostasis but also other functions unrelated to energy homeostasis like immunity. The long-term effect of these drugs on cardiovascular and immune systems and safety are yet to be studied in detail (Fisman et al. 2008; Richter et al. 2008). GLP-1 mimetics and DPP4 inhibitors possibly increase the risk of pancreatitis and pancreatic cancer. However, the causal association between these drugs and pancreatic cancer, if any, is not established (Kahn et al. 2014).

1.3.2.6 Inhibitors of Sodium–Glucose Cotransporter-2

The kidney not only excretes and reabsorbs glucose, but also produces glucose through gluconeogenesis. Generally, the quantity of glucose that the kidney filters does not exceed the kidney's threshold to reabsorb it and thus little glucose appears in the urine. The finding that SGLT2 reabsorbed glucose from the urine led to the development of inhibitors of this transporter. Dapagliflozin and canagliflozin were recently introduced to the market and others are under clinical trial. SGLT2 inhibitors appear to be generally tolerated and have been used as monotherapy or in combination with other oral anti-DM agents or insulin. The risk of hypoglycemia is low with these inhibitors (Nauck 2014). However, the increase in urinary glucose is associated with a five times higher rate of genital mycotic infections and a 40% increase in infections of the lower urinary tract. Long-term studies are in progress to assess the cardiovascular safety of these drugs (Kahn et al. 2014).

1.3.2.7 Dopamine Receptor Agonist

The dopamine receptor agonist bromocriptine is an approved drug to regulate glucose metabolism. The drug acts centrally and probably restores circadian rhythm. The circadian rhythm influences several organ systems associated with metabolism (Kahn et al. 2014).

1.3.2.8 Bile Acid Binding Resins

Bile acid-binding resin colesevelam is also approved to treat type 2 DM. Bile acids are ligands of the farnesoid X-receptor and activation of this receptor results in release of FGF19. FGF19 has insulin-like actions. Bile acids also activate G-protein-coupled bile acid receptor 1 located on intestinal L-cells leading to GLP-1 secretion (Kahn et al. 2014).

1.3.2.9 Other Therapies

In addition to these (insulin and oral hypoglycemic drugs) therapies, attempts are being made to find a cure for type 1 DM; these include gene therapy, islet transplantation, and stem cell therapy (Tang and Desai 2016). Although these may be promising in the future, there is still a long way to go. Furthermore, considering the likely high cost of these possible treatments, even in the near future, these may not be accessible to patients in the lower economic conditions.

1.4 Herbal Therapies for DM

Long before the birth of conventional therapies for DM, plant-based crude medicinal preparations were used to manage DM. Although these ancient methods of treatment were originally based on trial and error, experience, and empirical knowledge, their long-term existence proves that these medicines have

some level of efficacy, at least, in most of the cases. Scientific studies on these herbal medicines also support this belief (Marles and Farnsworth 1995; Campbell-Tofte et al. 2012; Khan et al. 2012; Raman et al. 2012; Behera and Yadav 2013; Gulshan and Rao 2013; Tripathi and Verma 2014). Even today, medicinal plants play a prominent role in the control of DM, in particular, in the rural areas and tribal pockets of the world.

In traditional medicine, the use of medicinal plants as decoctions, extracts, or homogenates (alone or combination with other herbs) is more common. This type of treatment is actually a combination therapy in view of a large number of bioactive phytochemicals present in such crude preparations. These traditional medicines may have multiple benefits by targeting key molecules of several metabolic pathways involved in DM. A few scientific studies in light of modern science also support this. However, these benefits may not be true in all cases. At least in limited cases, the ancient polyherbal formulations may have compounds with adverse effects along with beneficial molecules, because these combinations were not developed rationally based on experimental evidence. However, the future of anti-DM drugs may shift from single chemical entity treatment to combination therapy and polyherbal phytomedicines.

Plants are known to be excellent sources of anti-DM medicines (Marles and Farnsworth 1995). A perusal of literature shows that there are more than 1700 recorded plants used around the world to treat or control DM by different cultural groups in traditional medicine. Varying levels of pharmacological evaluation and/or bioassays were carried out on more than 1000 of these traditional anti-DM plants (Subramoniam 2016). In most of the cases, the studies on these plants are not complete to determine their likely therapeutic value. These studies showed very marginal or no activity to substantial therapeutically promising antihyperglycemic/hypoglycemic/anti-DM activities. Based on the studies carried out, about 120 plants are very promising for further studies for the development of medicine for DM (Subramoniam 2016). In some cases, the same active molecules are distributed in nature in many plants. The known mechanisms of actions and active molecules of the anti-DM plants are diverse (Saravanamuttu and Sudarsanam 2012; Chang et al. 2013; Singh et al. 2013; Arif et al. 2014; Gaikwad et al. 2014; Wang et al. 2014; Nazaruk and Borzym-Kluczyk 2015).

It is true that most of the traditional anti-DM plants do not have any practical utility in controlling/managing satisfactorily type 1 and type 2 DM. Furthermore, some of these plant drugs may have adverse side effects. Scientific studies in light of present knowledge are required to select the potential plants. Since a majority of world population is using the anti-DM plants to control or treat DM, there is a need to do more thorough systematic studies on these plants, not only to determine their safety and efficacy but also to develop new and improved drugs in light of modern science.

Even from ancient time onward, in traditional medicine, doctors advise the DM patients on what to eat and what not to eat to control diabetes. Many edible plant materials are known to have anti-DM properties (Subramoniam 2016). These plants are consumed in various forms in local health traditions to manage diabetes. Food materials containing antioxidants, anti-inflammatory agents, and/or antihyperlipidemic property (nutraceuticals) could protect or delay the expression of type 2 DM and work as antirisk factors. Regular intake of appropriate amount of specific immune modulatary nutraceuticals may prevent or delay the development of type 1 DM.

It is believed that certain herbal drugs or herbal combinations may have the potential to cure certain types of type 2 DM by rejuvenating β-cells and removing insulin resistance; research is needed in this direction.

Despite the advancement in modern medical sciences, DM is globally increasing in incidence and severity. Currently available anti-DM drugs cannot fully control glucose level. Besides, these drugs can cause side effects and/or insufficient response. Therefore, it is necessary to look for new medicines and interventions that can be used to manage this complex and highly heterogeneous metabolic disorder. This is one of the main reasons for the persistent and renewed interest in the complement and alternative system of therapy for DM. In this system, medicinal plants are the main source of medicines. Herbal medicines not only can complement current conventional therapy but also can provide hope that scientific studies on these traditional anti-DM medicines can lead to a cure for type 2 DM.

1.5 Conclusion

This book is a follow-up to the recently published book titled *Plants with Anti-Diabetes Mellitus Properties* (Subramoniam 2016). In that book, more than 1000 anti-DM plants are described. In the recent past, the quantity of publications on medicinal plants and diabetes has been multiplying along with the appearance of many new journals in the general area of medicinal plant and related areas. There is a need to provide all relevant information in one place for easy reference, among other things, for the development of very safe and effective anti-DM medicines and food supplements (nutraceuticals) for diabetic patients. Various phytochemicals with varying levels of anti-DM properties are reported from different plant sources; mechanism of action studies on many of the phytochemicals and crude phytomedicines/extracts have been done. However, these studies are insufficient to a large extent. Knowledge on anti-DM phytochemicals is required among other things to select out appropriate molecules for the development of therapies (monotherapy and combination therapy) and lead molecules for drug development. Besides, knowledge on anti-DM phytochemicals is needed in the development of suitable agrotechniques for anti-DM plants. Phytochemical studies should progress in concert with mechanism of action studies for rational drug development which includes multichemical therapies. In this context, a book with full or almost full information on the subject could serve as a ready source of information to facilitate further research aimed at the development of new and safe medicines for DM. All efforts will go in vain, if a ready source of plant materials is not available for medicinal purposes. Therefore, agrotechniques developments and biotechnological interventions are required in the case of deserving important anti-DM plants to get uniform good quality plant materials. This aspect and important methods required for herbal anti-DM drug development are also described in this book.

To facilitate systematic research for the development of anti-DM medicines important *in vitro* and *in vivo* methods for identifying anti-DM plants and for detailed studies on them are provided.

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2

Anti-Diabetes Mellitus Phytochemicals

2.1 Background/Introduction

There are more than 1050 anti-diabetes mellitus (anti-DM) plants subjected to varying levels of scientific studies (Subramoniam 2016). Out of these plants, active anti-DM compounds (compounds with blood glucose-lowering properties and/or other beneficial effects against DM and its complications) were isolated from more than 300 plants. Even in most of these cases, all the active anti-DM compounds present were not identified. Identification of active principles and understanding their structure and activity relationships are very important in the context of developing therapeutic agents and studying their actions and interactions with other molecules in the living system.

The major phytochemical groups with anti-DM activities are polyphenols, terpenoids, and steroids including their glycosides (saponins), alkaloids, and nonstarch polysaccharides. Many antioxidant polyphenols (flavonoids, anthocyanins, xanthones, stilbenes, quinines, tannins, etc.) are beneficial to diabetic patients; they reduce lipid peroxidation, glycation of proteins, and oxidative stress. Examples of these compounds are α-lipoic acid, curcumin, genistein, apigenin, mangostin, and bellidifolin. However, all polyphenols are not beneficial; there are prooxidant and toxic polyphenols too (McCune et al. 2005). This is true in the case of all classes of phytochemicals. Triterpenes are widely distributed in plants and many of the pentacyclic triterpenes exhibit several biological properties including anti-diabetes properties (Nazaruk and Borzym-Kuluczyk 2015). Many triterpines show anti-diabetic properties mainly by influencing the activities of target enzymes. Plant nonstarch polysaccharide extracts that form viscous solution in water have specific effects in reducing postprandial blood glucose (Judd and Ellis 2005). Examples of these include soluble nonstarch carbohydrate from guar gum (*Cyamopsis tetragonoloba*), which is reported to have beneficial effects in diabetes including reduction in postprandial blood glucose levels and increase in insulin sensitivity. It is believed that galactomannon component of guar gum reduces the rate of digestion and absorption of carbohydrate in the gastrointestinal tract. A number of human studies have shown that guar gum decreases the postprandial rise in plasma gastric inhibitory polypeptide and glucagon-like peptide-1 (GLP-1). Flour from seeds of *Detarium senegalense* also exhibited similar properties (Judd and Ellis 2005).

Anti-DM molecules including glucose-lowering compounds can be classified based on plant source, chemical class, and mechanism of actions. Plants with known anti-DM compounds are arranged alphabetically as per botanical name (scientific name) and presented in Table 2.1 along with the identified anti-DM phytochemicals. However, plants with extremely low level or traces of active principles are not included in this table. Such plants are numerous. For example, a data search has shown that there are 1620 plant species reported to contain varying levels of oleanolic acid (Fai and Tao 2009). Most of the important anti-DM phytochemicals are described alphabetically in Section 2.2 of this chapter. Compounds with very small level of *in vitro* α-glucosidase or carbohydrate breakdown inhibition activities without any possible therapeutic value are not included in this chapter. Similarly compounds with negligible *in vitro* protein tyrosine phosphatase 1B (PTP1B) inhibitory activity are not included. Structure of most of the very important anti-DM compounds (based on anti-DM activity and occurrence in different plants) are given in Figures 2.1 through 2.70.

TABLE 2.1

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
1.	*Abelmoschus moschatus* Medik., Malvaceae	Myricetin from aerial parts	Liu et al. 2005
2.	*Abroma augusta* L. f, Sterculiaceae	β-Sitosterol and α-amyrin	Gupta et al. 2011
3.	*Acacia leucophloea* (Roxb.) Willd., Fabaceae	Myricetin, β-sitosterol, and β-amyrin	Ahmed et al. 2014
4.	*Acanthopanax koreanum* Nakai, Araliaceae	Diterpene (possessing an isovaleryloxy group at C-17 of kaurane-type)	Jiang et al. 2012
5.	*Acanthopanax senticosus* Rupr. & Maxim, Araliaceae	Syringin	Niu et al. 2008
6.	*Acer saccharum* Marshall, Sapindaceae	Acertannin (2,6-di-O-galloyl-1,5-anhydro-D-glucitol)	Honma et al. 2010
7.	*Achyrocline satureioides* (Lam) DC, Asteraceae	Achyrofuran (a prenylated dibenzofuran)	Carney et al. 2002
8.	*Aconitum carmichaelii* Debeaux, Ranunculaceae	Glycans (aconitans A, B, C, and D)	Konno et al. 1985c
9.	*Acorus calamus* L., Acoraceae	1β,5α-guaiane-4β,10α-diol-6-one (a sesquiterpenoid)	Zhou et al. 2012
10.	*Aegiceras corniculatum* (L.) Blanco, Myrsinaceae	Falcarindiol	Jiang et al. 2012
11.	*Aegle marmelos* (L.) Correa Correa, Rutaceae	Aegeline 2 (an alkaloid-amide), Scopoletin (7-hydroxy-6-methoxy coumarin)	Narender et al. 2007; Panda and Kar 2006
12.	*Aesculus hippocastanum* L., Hippocastanaceae	Escins (triterpine oligoglycosides)	Yoshikawa et al. 1994, 1996b
13.	*Agave tequilana* Gto., Asparagaceae	Fructons	Urias-Silvas et al. 2007
14.	*Alisma orientale* (Sam.) Juzepcz., Alismataceae	Alisol F and Alisol B (triterpenes)	Li and Qu 2012
15.	*Allium cepa* L., Lilliaceae	S-Methyl cysteine sulfoxide, diphenyl amine, and oleanolic acid	Karawya et al. 1984; Kumari and Augusti 2002; WHO 1999
16.	*Allium sativum* L., Alliaceae	Allicin (diallyl thiosulfinate), S-allyl cysteine, and kaempferol	Chang et al. 2011; WHO 1999
17.	*Alnus incana* sub sp. *rugosa* (Du Roi) R.T. Clausen, Betulaceae	Oregonin (a diarylheptanoid glycoside)	Eid and Haddad 2014
18.	*Aloe vera* (L.) Burm. f., Aloaceae	Lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol, 24-methylene cycloartanol, β-sitosterol (phytosterols), quercitin, rutin, and polysaccharides	Sahu et al. 2013
19.	*Alstonia macraphylla* Wall & G. Don, Apocynaceae	Picraline type alkaloids (alstiphyllanines E and F) and their derivatives	Arai et al. 2010
20.	*Althaea officinalis* L., Malvaceae	Scopoletin (7-hydroxy-6-methoxy coumarin), and polysaccharide (althaeamucilage-O)	Al-Snafi 2013
21.	*Amorpha fruticosa* L., Fabaceae	Amorfrutins	Wang et al. 2014
22.	*Anacardium occidentale* L., Anacardiaceae	Stigmast-4-en-3-one, anacardic acid (polyphenol)	Tedong et al. 2010
23.	*Andrographis paniculata* (Burm. f.) Nees, Acanthaceae	Andrographolide	Nugroho et al. 2012

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
24.	*Anemarrhena asphodeloides* Bunge, Lilliaceae	Pseudoproto-timosaponin AIII (glycoside), timosaponin AIII and mangiferin and its glucoside	Nakashima et al. 1993
25.	*Anoectochilus roxburghii* (Wall.) Lindl.	Kisenoside	Zhang et al. 2007
26.	*Anthocleista schweinfurthii* Gilg., Gentianaceae	Bauerenone, bauerenol, and schweinfurthiin (steroid)	Mbouangouere et al. 2007
27.	*Aralia chinensis* L., Araliaceae	Oleanoic acid	Simmonds and Howes 2005
28.	*Aralia elata* (Miq.) Seem, Araliaceae	Elatosides E, G, H, and I (saponins); araliosides	Yoshikawa et al. 1995; Xi et al. 2009
29.	*Areca catechu* L., Arecaceae	Arecoline, an alkaloid	Amudhan et al. 2012
30.	*Artemisia dracunculus* L., Asteraceae	6-Demethoxycapillarisin and 2,4-dihydroxy-4-methoxy dihydrochalcone (polyphenolic compounds)	Govorko et al. 2007
31.	*Artemisia herba-alba* Asso, Asteraceae	β-Sitosterol, cycloartenol (9,19-cyclolanost-24-en-3-ol), 24-methylenecycloartanol, apigenin, and chlorogenic acid	Awad et al. 2012; Mohamed et al. 2010
32.	*Artemisia minor* Jacq. ex Besser, Compositae	1,4-Benzodioxane lignin and caffeic acid (occurs in many plants)	Jiang et al. 2012
33.	*Aspalathus linearis* (Burm.f.) R. Dahlgren, Fabaceae	Aspalathin and nothofagin (2 dihydrochalcones)	Kawano et al. 2009; Ku et al. 2015
34.	*Asparagus racemosus* Willd., Liliaceae	Kaempferol, quercetin, and rutin	Sharma and Sharma 2013
35.	*Astianthus viminalis* (H.B.K.) Baill., Bignoniaceae	Oleanolic acid, ursolic acid, and a new tetracyclic triterpenoid	Perez-Gutierrez et al. 2009
36.	*Astilbe grandis* Stapf ex E.H. Wilson	Triterpenes: 3α,24-dihydroxyolean-12-en-27-oic acid, and so on	Jiang et al. 2012
37.	*Astragalus membranaceus* Moench, Fabaceae	Formononetin, isoflavone	Wang et al. 2014
38.	*Atractylodes japonica* Koidz., Asteraceae	Three glycans (attractans A, B, and C)	Konno et al. 1985d
39.	*Atractylodes macrocephala* Koidz, Asteraceae	A complex polysaccharide (AMP-B)	Shan and Tian 2003
40.	*Azadirachta indica* A. Juss. Meliaceae	β-Sitosterol and quercetin	Hashmat et al. 2012
41.	*Azorella compacta* Phil, Ambelliferae	Mulenic acid and azorellanol, azorellanol (diterpenoids)	Fuentes et al. 2005
42.	*Bacopa monnieri* (L.) Wettst., Scrophulariaceae	Bacosine, a triterpene from whole plant	Ghosh et al. 2011
43.	*Balanites roxburghii* Plunch, Balanitaceae	β-Sitosterol	Saboo et al. 2014
44.	*Bambusa arundinacea* (Retz.) Willd, Poaceae	α-Amyrin and its derivatives and β-sitosterol glucoside	Aakruti et al. 2013
45.	*Bauhinia forficata* Link, Fabaceae	Flavonoid glycosides: Kaempferitrin (kaempferol-3,7-O-(α)-L-dirhamnoside); quercetin 3-O-α-(2”-galloyl) rhamnoside and kaempferol 3-O-α-(2” galloyl) rhamnoside	Cazarolli et al. 2006

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
46.	*Bauhinia multiner*via (Kunth) DC, Caesalpeniaceae	Flavonoid glycosides: Quercetin 3-O-α-(2”-galloyl) rhamnoside and kaempferol 3-O-α-(2” galloyl) rhamnoside	Estrada et al. 2005
47.	*Bauhinia variegata* L., Caesalpeniaceae	Roseoside and β-sitosterol	Frankish et al. 2010; Sahu and Gupta 2012
48.	*Berberis aristata* DC., Berberidaceae	Berberine and β-sitosterol	Arif et al. 2014
49.	*Berberis brevissima* Jafri, Berberidaceae	Berberine and 8-oxo-berberine	Ali et al. 2013
50.	*Berberis parkeriana* C.K.Schneid., Berberidaceae	Berberine and 8-oxo-berberine	Ali et al. 2013
51.	*Berberis vulgaris* L., Berberidaceae	Berberine (high concentration in root), 8-oxo-berberine, lupeol, and oleanolic acid	El-Wahab et al. 2013; Mokhber-Dezfuli et al. 2014
52.	*Bergenia ciliata* (Haw.) Sternb., Saxifragaceae	(−)-3-O-galloylepicatechin and (−)-3-O-galloylcatechin	Bhandari et al. 2008
53.	*Bergenia himalaica* Boriss. or *Bergenia pacumbis* (Buch.-Ham. ex D.Don) C.Y.Wu & J.T.Pan., Saxifragaceae	Bergenicin and bergelin	Siddiqui et al. 2014
54.	*Beta vulgaris* L., Amaranthaceae	Betavulgaroside (glucuronide saponin)	Yoshikawa et al. 1996a
55.	*Bidens pilosa* L., Asteraceae	Polyynes: 3-β-D-glucopyranosyl-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne; 2-β-D-glucopyranosyloxy-1-hydroxy- 5(*E*)-tridecene-7,9,11-triyne; 2-β-D-glucopyranosyloxy-1-hydroxyl trideca-5,7,9,11-tetrayne (cytopiloyne); 3-β-D-glucopyranosyl-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne; 2-β-D-glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne; cytopiloyne	Yang 2014
56.	*Bixa orellana* L., Bixaceae	Bixin and norbixin (anti-DM activity is dependent on species); isoscutellarein	Terashima et al. 1991; Wang et al. 2014
57.	*Blighia sapida* Koenig, Sapindaceae	Hypoglycin A and hypoglycin B (unusual amino acids)	Atolani et al. 2009; Olubunmi et al. 2009;
58.	*Boerhaav*ia *diffusa* L., Nyctaginaceae	Ursolic acid and myricetin were reported	Riaz et al. 2014
59.	*Bombax ceiba* L., Bombacaceae	Shamimin (flavonoid glycoside)	Saleem et al. 1999
60.	*Boswellia serrata* Roxb. ex Colebr., Burseraceae	Boswellic acid	Rao et al. 2013
61.	*Bougainvillea spectabilis* Willd., Nyctaginaceae	D-Pinitol, β-sitosterol, quercetin and quercetin-3-O-α-L-rhamnopyranoside from stem bark	Jawla et al. 2013; Narayanan et al. 1987
62.	*Broussonetia papyrifera* L., Moraceae	Flavonoids: 8-(1,1-dimethylallyl)-5′-(3-methylbut-2-enyl)-3′,4′,5,7-tetrahydroxyflanvonol, 3′-(3-methylbut-2-enyl)-3′,4′,7-trihydroxyflavane, quercetin, uralenol, and broussochalcone A (isolated from root)	Jiang et al. 2012

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
63.	*Brucea javanica* (L.) Merr, Simaroubaceae	Quassinoids: Bruceine D and E	Noorshahida et al. 2009
64.	*Bruguiera gymnorrhiza* (L.) Lam., Rhizophoraceae	Gymnorrhizol (unusual 15-membered macyrocylic polydisulfide)	Jiang et al. 2012
65.	*Bumelia sartorum* Mart., Sapotaceae	Bassic acid, an unsaturated triterpene acid	Naik et al. 1991
66.	*Caesalpinia bonbuc* (L.) Roxb., Caesalpiniaceae/Febaceae	Pintol and sitosterol	Singh and Radhav 2012
67.	*Caesalpinia digyna* Rottler, Leguminosae	Bergenin	Kumar et al. 2012b
68.	*Caesalpinia sappan* L., Caesalpiniaceae	Brazilin (7,11b-dihydrobenz[b]indeno-[1,2-d] pyran-3,6a,9,10 (6H)-tetrol, β-sitosterol, and quercitin	Ajikumaran and Subramoniam 2005; Kim et al. 1995
69.	*Cajanus cajan* (L.) Millsp., Fabaceae	Genistein, β- and α-amyrin, β-sitoterol, and lupeol	Pal et al. 2011
70.	*Callistemon lanceolatous* DC., Myrtaceae	5,7-Dihydroxy-6,8-dimethyl-4′ -methoxy flavone and 8-(2-hydroxypropan-2-yl)-5-hydroxy-7-methoxy-6-methyl-4′-methoxy flavones	Nazreen et al. 2012
71.	*Callistemon rigidus* R. Br., Myrtaceae	Piceatannol and scirpusin B (inhibition of α-glucosidase)	Kobayashi et al. 2006
72.	*Camellia sinensis* (Linn.) Kuntze, Theaceae	Epigallocatechin gallate and catechin	Anderson and Polansky 2002; Kumar et al. 2012a
73.	*Campsis grandifolia* (Thunb.) K.Schum, Bignoniaceae	Pentacyclic triterpenoid such as ursolic acid	Jung et al. 2007
74.	*Cannabis sativa* L., Cannabaceae	Tetrahydrocanabivarin and Delta-9-tetrahydrocannabinol (nonpsychoactive cannabinoids)	Weiss et al. 2006; Wargent et al. 2013; Wang et al. 2014
75.	*Capsicum annum* L., Solanaceae	Capsaicin	Magied et al. 2014
76.	*Carissa edulis* Vahl, Apocynaceae	Chlorogenic acid	Al-Youssef and Hassan 2014
77.	*Casearia esculenta* Roxb., Flacourtiaceae	3-Hydroxymethyl xylitol, β-sitosterol and leucopelargonidin	Chandramohan et al. 2008; The Wealth of India 1992
78.	*Cassia alata* L., Caesalpiniaceae	Kaempferol and kaempferol 3-O-gentiobioside	Varghese et al. 2013
79.	*Cassia auriculata* L., Cesalpinaceae	Kaempferol, kaempferol 3-O-rutinoside, luteolin, quercetin, β-sitosterol, and β-sitosterol-β-D-glucoside	Majumder and Paridhavi 2010
80.	*Cassia fistula* L., Cesalpinaceae	Kaempferol from flower, (–)-epicatechin from leaf, lupeol and β-sitosterol from bark	Rajagopal et al. 2013
81.	*Castanospermum austral* A. Cunn. ex Mudie, Fabaceae	Castanospermine from seed	Ghisalberti 2005
82.	*Catharanthus roseus* (L.) G. Don f., Apocyanaceae	Methyl (18β)-3,4-didehydroibogamine-18-carboxylate	Chattopadhyay 1999
83.	*Cecropia obtusifolia* Bertol., Cereopiaceae	Isoorientin and chlorogenic acid (3-caffeoylquinic acid) were identified as the major constituents in the active extracts of leaf (these are known anti-DM compounds)	Andrade-Cetto and Wiedenfeld 2001

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
84.	*Cecropia pachystachya* Trecul, Cecropiaceae	Chlorogenic acid, β-sitosterol, α-amirin, ursolic, and oleanolic acids were reported	Hikawczuk et al. 1998
85.	*Cecropia peltata* L., Cecropiaceae	Chlorogenic acid and isoorientin from leaf	Nicasio et al. 2005
86.	*Celastrus vulcanicola* J.D. Smith, Celastraceae	Friedelane-type triterpenes from root bark and astragaloside IV	Nazaruk and Borzym-Kluczyk 2014
87.	*Centaurea alexandrina* Delile, Compositae	Kaempferol 3-O-rutinosise, rutin, kaempferol, and quercetin	Kubacey et al. 2012
88.	*Centaurea seridis* L., Compositae	β-sitosterol-3-β-D-glucoside and β-sitosterol	Ivorra et al. 1998
89.	*Centella asiatica* (L.) Urban, Apiaceae	Centellsapogenol A and asiatic acid (triterpenoids)	Matsuda et al. 2001; Ramachandrana et al. 2014
90.	*Chamaemelum nobile* (L.) All., Compositae	3-Hydroxy-3-methylglutaric acid containing flavonoid glucoside chamaemeloside	Konig et al. 1998
91.	*Chelidonium majus* L., Papaveraceae	Berberine, an alkaloid	Xia et al. 2011
92.	*Chromolaena odorata* (L.) R.M. King &H. Rob., Asteraceae	(9*S*,13*R*)-12-Oxo-phytodienoic acid and odoratin	Wang et al. 2014
93.	*Cichorium glandulosum* Boiss. & A. Huet, Compositae	Lactucin from root	Jiang et al. 2012
94.	*Cichorium intybus* L., Asteraceae	Esculetin	Hozayen et al. 2011
95.	*Cimicifuga dahurica* (Turcz. ex Fisch. & C. A. Mey.) Maxim, Ranunculaceae	Isoferulic acid	Liu et al. 1999
96.	*Cinnamomum cassia* (Nees & T. Nees) J. Presl. and *Cinnamomum verum* J.S. Presl.	Cinnamtannin B1, methylhydroxychalcone, and polyphenol type A molecules	Bandara et al. 2012; Jarvill-Taylor et al. 2001
97.	*Citrullus lanatus* (Thunb.) Matsumara & Makai, Cucurbitaceae	Quercetin, gallic acid, and catechin are reported in leaves	Aruna et al. 2014
98.	*Citrus lemon* (L.) Burm.f., Rutaceae	Hesperidin and naringin (flavonoids)	Jung et al. 2006
99.	*Clausena lansium* (Lour.) Skeels, Rutaceae	Clausenacoumarine, imperatorin, and chalepin	Adebajo et al. 2008; Shen et al. 1989;
100.	*Coffea arabica* L., Rubiaceae	Chlorogenic acid (major component of coffee), trigonelline and secoisolariciresinol	Bisht and Sisodia 2010; Ong et al. 2012
101.	*Coffea canephora* Pierre ex A. Froehner, Rubiaceae	Chlorogenic acid	Zottich et al. 2011
102.	*Coix lacryma-jobi* var. ma-yuen (Rom. Caill.) Stapf ex Hook. f., Poaceae	Glycans and hydroxy unsaturated fatty acids	Takahashi et al. 1986; Wang et al. 2014
103.	*Combretum lanceolatum Pohl ex Eichler*, Combretaceae	Quercetin from flower	Dechandt et al. 2013
104.	*Commiphora mukul* (Hook. ex Stocks) Engl., Burseraceae	Commipheric acid	Wang et al. 2014
105.	*Conyza dioscorides* (L.) Desf. DC Asteraceae	β-Sitosterol, β-sitosterol glucoside, α-amyrin, lupeol acetate, gallic acid, syringic acid, rutin, quercitin, and kaempferol	Zalabani et al. 2012

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
106.	*Coptis chinensis* Franch, Ranunculaceae	Berberine and protoberberine-type alkaloids	Ma et al. 2010
107.	*Coptis deltoides* C.Y. Cheng et Hsiao, Ranunculaceae	Berberine	Chen and Xie 1986
108.	*Coriandrum sativum* L., Apiaceae	Chlorogenic acid, β-sitosterol, quercetin, and rutin (reported from seeds)	Paarakh 2009
109.	*Cornus alternifolia* L.f., Cornaceae	Kaempferol-3-O-b-glucopyranoside	Wang et al. 2014
110.	*Cornus officinalis* Sieb., Cornaceae	Triterpinoids: ursolic acid and loganin	Ma et al. 2014; Qi et al. 2008
111.	*Costus pictus* D. Don., Costaceae	A novel protein (functionally similar to insulin)	Joshi et al. 2013
112.	*Costus speciosus* (Koenig) Sm., Costaceae	Eremanthin and costunolide	Eliza et al. 2009a, 2009b
113.	*Croton cajucara* Benth., Euphorbiaceae	*Trans*-dehydrocrotonin, a nor-clerodane diterpene	Farias et al. 1997
114.	*Cucurbita ficifolia* Bouche, Cucurbitaceae	D-Chiro-inositol from fruit	Miranda-Perez et al. 2013; Xia and Wang 2006b
115.	*Cucurbita moschata* Duchesne ex Poiret, Cucurbitaceae	Protein-bound polysaccharide from fruit	Song et al. 2012a
116.	*Cuminum cyminum* L., Apiaceae	Cuminaldehyde	Lee 2005
117.	*Curcuma longa* L., Zingeberaceae	Curcumin, demethoxycurcumin, sesquiterpenoids, bisdemethoxycurcumin, and arturmerone	Arun and Nalini 2002; Kuroda et al. 2005; Nishiyama et al. 2005
118.	*Cuscuta reflexa* Roxb., Cuscutaceae	6,7-Dimethoxy-2H-1-benzopyran-2-one, kaempferol, and quercitin	Anis et al. 2002
119.	*Cyamopsis tetragonoloba* (L.) Taub., Fabaceae	Quercetin, gallic acid, genistein, ellagic acid, kaemferol, and chlorogenic acid (reported to contain)	Sharma et al. 2011
120.	*Cyclocarya paliurus* (Batal.) Ijinskaja, Cyclocaryaceae	A naphthoquinone derivative, cyclonoside A; quercetin-3-O-β-D-glucuronide (phenolic compound)	Jiang et al. 2012
121.	*Cymbopogon citratus* (DC.) Stapf, Poaceae	Geraniol and myrcene (components of essential oil); myrcenol, linalool, α-elemol, β-eudesmol, pimelyl dihydrazide, and citral	Wang et al. 2014
122.	*Cymbopogon proximus* Stapf, Graminiae	Quercetin, kaempferol, and apiginin (reported to contain)	Shah et al. 2011
123.	*Cyperus rotundus* L., Cyperaceae	β-Sitosterol and ferulic acid (reported from this plant)	Ajikumaran and Subramoniam 2005
124.	*Daucus carota* L., Apiaceae	Falcarinol (polyacetylene)	Bhattacharya et al. 2014
125.	*Dendrobium moniliforme* (L.) Sw., Orchidaceae	A phenanthraquinone-type metabolite	Jiang et al. 2012
126.	*Dendrobium nobile* Lindl, Orchidaceae	Syringic acid	Wei et al. 2012
127.	*Dillenia indica* L., Dilleniaceae	β-Sitosterol, stigmasterol, stigmasteryl palmitate, betulinic acid, n-heptacosan-7-one, n-nonatriacontan-18-one, and quercetin	Kumar et al. 2013

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TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
128.	*Dioscorea bulbifera* L., Dioscoriaceae	Diosgenin (a phytosterol)	Ghosh et al. 2014a.
129.	*Dioscorea japonica* Thunb., Dioscoriaceae	Glycans (dioscorans A, B, C, D, E, and F) from rhizome	Hikino et al. 1986
130.	*Dioscorea nipponica* Makino, Dioscoriaceae	Diosgenin (a phytosterol)	Kang et al. 2011
131.	*Dodecadenia grandiflora* Nees, Lauraceae	Phenylpropanoyl esters of catechol glycosides, lignane bis(catecol glycoside) esters, and phenolic glycosides	Kumar et al. 2009, 2010
132.	*Echinacea purpurea* (L.) Moench, Asteraceae	Isomeric dodeca-2E,4E,8Z,10E/Z-tetraenoic acid 2-methylbutylamides, and alkamides	Kotowska et al. 2014; Wang et al. 2014
133.	*Eclipta alba* (L.) Hassk., Asteraceae	Eclalbasaponin VI (echinocystic acid glycoside)	Kumar et al. 2012
134.	*Elaeis guineensis* Jacq., Arecaceae	Tocotrienols	Wang et al. 2014
135.	*Elephantopus scaber* L., Asteraceae	28-Nor-22(R) with a 2,6,23-trienolide (a new steroid), anddeoxyelephantopin	Daisy et al. 2009; Wang et al. 2014
136.	*Eleutherococcus senticosus* (Rupr. & Maxim) Maxim., Araliaceae	Eleutheroside E; Syringin	Ahn et al. 2013; Liu et al. 2008
137.	*Enicostemma littorale* Blume, Gentianacea	Swertiamarine (glycoside) and compound SGL-1 (uncharacterized isolate)	Gupta et al. 2010; Vishwakarma et al. 2010
138.	*Ephedra distachya* L., Ephedraceae	Ephedrines Ephedrans A, B, C, D, and E (glycans)	Xiu et al. 2001; Konno et al. 1985a
139.	*Epimedium brevicornum* Maxim, Berberidaceae	Icarin and baohuoside I (a flavonol from the leaves)	Bao and Chen 2011; Phan et al. 2013
140.	*Epimedium elatum* C. Morren &Decne., Berberidaceae	Acylated flavonol glycosides	Wang et al. 2014
141.	*Eremophila alternifolia* R. Br., and *Eremophila longifolia* (R.Br.) F. Muell., Myoporaceae	Phenylethanoid verbascoside (acteoside) and deacetyl-asperulosidic acid methyl ester	Ghisalberti 2005
142.	*Erigeron annuus* (L.) Pers, Compositae	2,3-Dioxygenated flavanone, erigeroflavanone	Yoo et al. 2008
143.	*Erigeron breviscapus* (Vaniot) Hand., Asteraceae	Breviscapine (a flavonoid)	Wang et al. 2009
144.	*Eriobotrya japonica* Lindl., Rosaceae	Sesquiterpene glycosides, polyhydroxylated triterpenoids, cinchonain Ib, epicatachin, ursolic acid, oleanolic acid, and chlorogenic acid	Nazaruk and Borzym-Kluczyk 2014; Qadan et al. 2009
145.	*Ervatamia microphylla* (Pit.) Kerr (Botanical name: *Tabernaemontana bufalina* Lour.), Apocynaceae	Canophylline, an alkaloid from leaf	Chang et al. 2013
146.	*Erythrina abyssinica* DC, Fabaceae	Prenylated flavanones and terocarpan derivatives	Jiang et al. 2012
147.	*Erythrina addisoniae* Hutch. & Dalziel, Fabaceae	Prenylated isoflavonoids	Jiang et al. 2012
148.	*Erythrina lysistemon* Hutch., Fabaceae	Pterocarpan derivatives	Jiang et al. 2012
149.	*Erythrina mildbraedii* Harms, Fabaceae	Isoprenylated flavonoids	Jiang et al. 2012

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TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
150.	*Euclea undulata* Thunb, Ebenaceae	Epicatechin, betulin (triterpene), α-amyrin-3O-β-(5-hydroxy) ferulic acid and lupeol	Deutschlander et al. 2011
151.	*Eucommia ulmoides* Oliv., Eucommiaceae	Flavonal glycosides: quercetin 3-O-α-L-arabinopyranosyl-(1->2)-β-D-glucopyranoside, astragalin, and quercetin	Kim et al. 2004
152.	*Euonymus alatus* (Thunb.) Siebold, Celastraceae	Kaempferol and quercetin	Wang et al. 2014
153.	*Euphorbia hirta* L., Euphorbiaceae	Quercetin	Ghisalberti 2005
154.	*Eysenhardtia platycarpa* Pennell. & Saff., Fabaceae	3-O-Acetyloleanolic acid from methanol extract	Narvaez-Mastache et al. 2006
155.	*Fagophyrum tataricum* Geartn, Polygonaceae	D-Chiroinositol	El-Abhar and Schaalan 2014
156.	*Ficus bengalensis* L., Moraceae	Bengalenoside, glycoside of pelargonidin, leucopelargonin, glycosides of leucopelargonidin, leucocyanidin derivative, leucodelphinidin glycoside, α-amyrin, β-amyrin, α-amyrin acetate, and β-amyrin acetate	Augusti et al. 1994; Geetha et al. 1994; Karan et al. 2013; Kumar and Augusti 1994; Santos et al. 2012; Singh et al. 2009
157.	*Ficus carica* L., Moraceae	Flavonol esters [3,5-dihydroxy-7,4′-dimethoxy-flavonol-3-octadec-9”-en-oxy-5-hexadecanoate, and 3,5,3′-trihydroxy-7,4, dimethoxy flavonol-3-octadec-9”-en-oxy-5-hexadecanoate], β-amyrin acetate, β-sitosterol, ferulic acid, and quercitin	Bhat et al. 2013; El-Shobaki et al. 2010
158.	*Ficus racemosa* L., Moraceae	Reported anti-DM compounds: β-sitosterol glucoside, lupeol, and α-amyrin acetate	The Wealth of India 1992
159.	*Fraxinus rhynchophylla* Hance, Oleaceae	Fraxisecoside (coumarin-secoiridoid hybrid glycoside)	Xiao et al. 2008
160.	*Galega officinalis* L., Leguminosae	Galegine and other guanidine derivatives	Patade and Marita 2014
161.	*Garcinia kola* Heckel, Guttiferae	Kolaviron, a bioflavonoid complex	Akinmoladun et al. 2014
162.	*Gentiana olivieri* Griseb., Gentianaceae	Isoorientin, C-glycosylflavone	Sezik et al. 2005
163.	*Girardinia heterophylla* Decne, Urticaceae	β-Sitosterol and γ-sitosterol	Tripathi et al. 2013
164.	*Globularia alypum* L., Globulariaceae	Globularin, an iridoid glucoside	Merghache et al. 2013
165.	*Glycine max* (L.) Merr., Fabaceae	Genistein and 6-hydroxydaidzein	Wang et al. 2014
166.	*Glycyrrhiza glabra* L., Fabaceae	Glycyrin, glycyrrhizin, 50-formylglabridin, echinatin, kanzonol X, kanzonol W, shinpterocarpin, licoflavanone A, glabrol, shinflavanone, gancaonin L, and glabrone	Kuroda et al. 2004; Takii et al. 2000; Wang et al. 2014
167.	*Glycyrrhiza foetida* Desf., Fabaceae	Amorfrutins	Wang et al. 2014
168.	*Glycyrrhiza inflata* Batalin, Fabaceae	Chalcones and their derivatives and licochalcone E	Jiang et al. 2012; Park et al. 2012

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TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
169.	*Glycyrrhiza uralensis* Fisch., Fabaceae	Glycyrrhizin, glycyrrhetinic acid; semilicoisoflavone B, glycyrrhisoflavone, glisoflavone, licoflavone A, 2-arylbenzofuran glycybenzofuran, and licocoumarone	Jiang et al. 2012; Lee et al. 2010; Ko et al. 2007
170.	*Goodenia ovata* Sm., Goodeniaceae	Ursolic acid in the leaf	Ghisalberti 2005
171.	*Gymnema sylvestre* R. Br Asclepiadaceae	Dihydroxy gymnemic triacetate (saponine from leaves); gymnemic acid IV, a triterpene glycoside and other gymnemic acids	Daisy et al. 2009; Tiwari et al. 2014
172.	*Gynostemma pentaphyllum* (Thunb.) Makino, Cucurbitaceae	Gypenosides; dammarane derivatives	Jiang et al. 2012; Yeo et al. 2008
173.	*Hedyotis biflora* (L.) Lamk., Rubiaceae	Ursolic acid	Nimal Christhudas et al. 2013
174.	*Hemidesmus indicus* (L.) R. Br., Periplocacea	β-Amyrin palmitate, α-, β-amyrin, 2-hydroxy 4-methoxy benzoic acid; β-sitosterol and lupeol	Austin 2008; Ajikumaran et al. 2014; Gayathri and Kannabiran 2009
175.	*Hibiscus vitifolius* L., Malvaceae	Gossypin, a pentahydroxy flavone glucoside	Venkatesan and Pillai 2012
176.	*Hintonia latiflora* (Sesse & Moc.) Bullock., Rubiaceae	Coutareagenin (neoflavonoid) and 5-O-[β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyl]-7-methoxy-3′,4′-dihydroxy-4-phenylcoumarin; 25-O-acetyl-3-O-β-D-glucopyranosyl-23,24-dihydrocucurbitacin F; ursolic acid and chlorogenic acid	Cristians et al. 2009; Guerrero-Analco et al. 2005, 2007
177.	*Humulus lupulus* L., Cannabaceae	Isohumulones, bitter acids	Miura et al. 2005
178.	*Hunteria umbellata* K.Schum. Hallier f., Apocynaceae	Erinidine	Adejuwon et al. 2013
179.	*Hydnocarpus wightiana* Blume, Achariaceae	Hydnocarpin, luteolin, and isohydnocarpin from seed hull	Reddy et al. 2005
180.	*Hydrangea macrophylla* (Thunb.) Ser., Hydrangeaceae	Hydrangeic acid	Zhang et al. 2009
181.	*Hydrastis canadensis* L., Ranunculaceae	Berberine	Brown and Roman 2008
182.	*Hymenaea courbaril* L., Leguminosae	Sitosterol and astilbin	Alarcon-Aguilar and Roman-Ramos 2005
183.	*Hypolepis punctata* (Thunb.) Mett., Dennstaedtiaceae	Pterosin A	Hsu et al. 2013
184.	*Ilex paraguariensis* A. St-Hill	Chlorogenic acid (polyphenol)	Pereiraa et al. 2012
185.	*Ipomoea batatas* L., Convolvulaceae	High molecular weight glycol-protein from cortex of tuber; an arabinogalactan-protein and polyphenols such as caffeoylquinic	Kusano et al. 2001; Nagamine et al. 2014; Oki et al. 2011
186.	*Ipomoea digitata* L., Convolvulaceae	Flavonoids and β-sitosterol	Pandey et al. 2013
187.	*Juglans regia* L., Juglandaceae	Reported to contain ellagic acid, gallic acid, and caffeoylquinic acids	Shah et al. 2014

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TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
188.	*Kalopanax pictus* (Thunb.) Nakai., Araliaceae	Kalopanaxsaponin A, hederagenin 3-O-α-L-arabinopyranoside and hederagenin (metabolites of kalopanaxsaponin B)	Park et al. 1998
189.	*Kochia scoparia* (L.) Schrad., Chenopodiaceae	Momordin Ic and its 2′-O-β-D-glucopyranoside (saponins)	Yoshikawa et al. 1997
190.	*Lactuca indica* L., Compositae	Lactucain C (sesquiterpene lactone); furofuran lignin, lactucaside; reported compounds include quercitin, quercitin 3-O-glucoside, rutin, luteolin, and chlorogenic acid	Hou et al. 2003
191.	*Lagerstroemia speciosa* L., Lathraceae	Ellagitannin, lagerstroemin; gallotannins, penta-O-galloyl-glucopyranose; oleanolic acid and corosolic acid	Stoha et al. 2012; Klein et al. 2007; Yamada et al. 2008
192.	*Larix laricina* (Du Roi) K. Koch, Pinaceae	A new triterpenoid and the diterpene labdane derivative 13-epitorulosol	Eid and Haddad 2014; Shang et al. 2012
193.	*Larrea tridentata* (DC) Coville, Zygophyllaceae	Masoprocal (nordy hydroguaiaretic acid)	Luo et al. 1998
194.	*Lathyrus sativus* L., Fabacea	Inositol phosphoglycan	Paneda et al. 2001
195.	*Lawsonia intermis* L., Lythraceae	Lawsone and gallic acid	Sultana et al. 2009
196.	*Leandra lacunosa* Cogn., Melastomataceae	Ursolic acid, kaempferol, luteolin, and quercetin	Cunha et al. 2008
197.	*Leonotis leonurus* (L.) R. Br., Lamiaceae	Marrubiin	Mnonopi et al. 2012
198.	*Lepidium sativum* L., Brassicaceae	Quercetin and kaemferol glycosides were reported from this plant	Sharma and Agrawal 2011
199.	*Ligularia fischeri* (Ledeb.) Trucz., Compositae	Eremophilane sesquiterpene	Jiang et al. 2012
200.	*Ligusticum chuanxiong* Hort, Apiaceae	Tetramethylpyrazine	Yang et al. 2011
201.	*Ligustrum lucidum* Ait., Oleaceae	Oleanolic acid	Gao et al. 2009
202.	*Limnocitrus littoralis* (Miq.) Swingle, Rutaceae	Meranzin from leaves	Wang et al. 2014
203.	*Linum usitatissimum* L., Linaceae,	Secoisolariciresinol diglucoside (phytoestrogen)	Kaithwas and Majumdar 2012
204.	*Lippia nodiflora* L., Verbenaceae	γ-Sitosterol	Balamurugan et al. 2011
205.	*Liriope spicata* var. prolifera (Thunb.) Lour.	Fructans	Chen et al. 2009
206.	*Lithocarpus polystachyus* Rehd., Fagaceae	Trilobatin (sweet compound)	Dong et al. 2012
207.	*Lithospermum erythrorhizon* Sieb. et Zucc., Boraginaceae	Shikonin, a naphthoquinone; glycans, lithospermans A, B, and C	Konno et al. 1985b; Oberg et al. 2011
208.	*Lobelia chinensis* Lour., Campanulaceae	Pyrrolidine alkaloids radicamines A and B	Shibano et al. 2001
209.	*Lonicerae japonica* Thunb., Caprifoliaceae	3,5-Dicaffeoylquinic acid, rutin; chlorogenic acid and luteolin are reported	Peng et al. 2005
210.	*Lupinus mutabilis* Sweet, Fabaceae	Seed glycoproptein conglutin-γ; lupanine, spartine (quinolizidine alkaloids from the seed); multiflorine and derivatives of spartine and lupanine	Garcia Lopez et al. 2004; Gurrola-Diaz et al. 2008; Lovati et al. 2012; Terruzzi et al. 2011

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TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
211.	*Lycium barbarum* L., Solanaceae	Polysaccharides (glycol-conjugates) containing several monosaccharides and 17 amino acids, taurine, β-sitosterol, quercetin, and kaempferol	Luo et al. 2004; Potterat 2010; Song et al. 2012b
212.	*Macaranga adenantha* Gagnep., Euphorbiaceae	Triterpene metabolite: Oleanolic acid; 3β,28-dihydroxy-12-en-olean; maslinic acid and 3β-O-acetyl aleuritolic acid	Jiang et al. 2012
213.	*Magnolia officinalis* Rehder & E.H. Wilson, Magnoliaceae	4-O-Methylhonokiol; magnolol; honokiol	Kotani et al. 2012; Wang et al. 2014; Zhang et al. 2014
214.	*Mangifera indica* L., Anacardiaceae	Mangiferin, 3-β-taraxerol; 1,2,3,4,6 penta-O-galloyl-β-D-glucose; 6-O-galloyl-5-hydroxy mangiferin, 5-hydroxy mangiferin and methyl gallate from kernel; gallic acid, syringic acid, mangiferin, ellagic acid, gentisyl-protocatechuic acid and quercetin were reported from mango peel	Ajila et al. 2010; Firdous 2014; Mirza et al. 2013; Mohan et al. 2013
215.	*Melampyrum pratense* L., Orobanchaceae	Lunularin and fatty acids	Wang et al. 2014
216.	*Melothria mederaspatana* (L.) Cogn. Cucurbitaceae	Quercetin, phloroglucinol	Srilatha and Ananda 2014
217.	*Memecylon umbellatum* Burm.f., Melastomaceae	β-amyrin, sitosterol, sitosterol glucoside, oleanolic acid, ursolic (occurrence reported)	Ajikumaran and Subramoniam 2005
218.	*Momordica charantia* L., Cucurbitaceae	Polypeptide-p (plant insulin), charantin (a mixture of sitosteryl glucoside and stigmasteryl glucoside); momordicines, momordicosides (cucurbitan-type triterpenoids), cucurbitane-type triterpene glycosides; conjugated linolenic acid; momordicine 1 and momordicine 2; cucurbitacins such as 5β,19-epoxycucurbit-23-en-7-on-3β,25-diol; glycol alkaloid vicine (a pyrimidene nucleoside), β-sitosterol and β-amyrin; clerosterol and oleanolic acid glycosides	Chan et al. 2015; Firdous 2014; Joseph and Jini 2013; Khanna et al. 1981; Sheng et al. 2004; WHO 2009
219.	*Momordica cymbalaria* Hook., Fenzl ex Naud, Chcurbitaceae	Oleanane-type triterpenoid saponin (roots)	Koneri et al. 2014a
220.	*Morinda citrifolia*, Rubiaceae	β-Sitosterol, ursolic acid, and iridoide glycosides (leaves)	Ghisalberti 2005
221.	*Morus alba* L., Moraceae	Moracin M, steppogenin-4-O-β-glucoside, and mullberroside (phenolic compounds); chalcomoracin, moracin C, moracin D and moracin M The plant is reported to contain quercetin, β-sitosterol, rutin, and oleanolic acid (known anti-diabetic compounds)	Firdous 2014; Devi et al. 2013; Zhang et al. 2009
222.	*Morus bombycis* Koidzumi, Moraceae	2,5-Dihydroxy-4,3-di(β-D-glucopyranosyloxy)-trans-stilbene; chalcone-derived kuwanons; and sanggenons C and G	Heo et al. 2007; Jiang et al. 2012

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TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
223.	*Morus insignis* Bureau, Moraceae	β-Sitosterol, β-sitosterol-3-O-β-glucopyranoside, ursolic acid, moracin M, kaempferol-3- O-β-glucopyranoside and quercetin-3-O-β-glucopyranoside were reported in the ethyl acetate extract of leaf (known anti-DM compounds)	Basnet et al. 1993
224.	*Morus nigra* L., Moraceae	Deoxynojirimycin, an alkaloid	Kumar and Chauhan 2008
225.	*Murraya koenigii* (Linn.) Spreng., Rutaceae	Mahanimbine (carbazole alkaloid)	Dineshkumar et al. 2010
226.	*Musa sapientum* L., Musaceae	Known anti-DM compounds β-sitosterol, stigmasterol, sitosterol-3-O-myoinosityl(1-6)-β-D-glucose, ferulic acid and gallic acid were reported from this plant	Ajikumaran and Subramoniam 2005
227.	*Myrcia multiflora* DC., Myrtaceae	Quercitrin, and myricitrin (flavonoids); myrciacitrin I and myrciaphenone B (glycosides); gallic acid and β-amyrin	Matsuda et al. 2002; Varma et al. 1975; Yoshikawa et al. 1998
228.	*Myrciaria dubia* Mc Vaaugh, Myrtaceae	Ellagic acid and its two derivatives, 4-O-methylellagic acid and 4-(α rhamnopyranosyl) ellagic acid	Ueda et al. 2004
229.	*Myristica fragrans* Houtt, Myristicaceae	Lignans: *meso*-dihydroguaiaretic acid and otobaphenol	Jiang et al. 2012
230.	*Nelumbo nucifera* Gaertn., Nymphaeceae	Catechin and quercetin (leaf and rhizome)	Huang et al. 2011
231.	*Nephelium lappaceum* L., Sapindaceae	Geraniin	Palanisamy et al. 2011
232.	*Nigella sativa* L., Ranunculaceae	Thymoquinone	Ghorbani et al. 2013
233.	*Notopterygium incisum* C.T. Ting ex H.T. Chang, Apiaceae	Polyacetylenes	Wang et al. 2014
234.	*Nymphaea stellata* OW, Nymphaeceae	Nymphayol (25,26-dinorcholest-5-en-3b-ol)	Rajagopal et al. 2008a, 2008b
235.	*Ocimum gratissimum* L., Lamiaceae	Ursolic acid and chicoric acid	Casanova et al. 2014; Rao et al. 2013
236.	*Ocimum sanctum* L., Labiatea	16-Hydroxy-4,4,10,13-tetramethyl-17-(4-methyl-pentyl)-hexadecahydro-cyclopenta [a]phenanthren-3-one (a tetracyclic triterpenoid); and ursolic acid	Patil et al. 2011a
237.	*Olneya tesota* A. Gray, Fabaceae	lectin	Guzman-Partide et al. 2007
238.	*Ophiopogon japonicus* (L.f) Ker Gawl., Liliaceae	A polysaccharide (isolated in pure form)	Chen et al. 2011
239.	*Opuntia dillenii* Haw., Cactaceae	A polysaccharide (isolated)	Zhao et al. 2011
240.	*Opuntia ficus-indica* (L.) Mill., Cactaceae	Fruit peel contains kaempherol and quercetin; flower contains gallic acid, kaempherol and quercetin; cladode contains rutin, ferulic acid, gallic acid, and polysaccharides	Alarcon-Aguilar et al. 2003; El-Mostafa et al. 2014
241.	*Origanum majorana* L., Lamiaceae	6-Hydroxyapigenin (scutellarein)	Kawabata et al. 2003
242.	*Origanum vulgare* L., Lamiaceae	Biochanin A	Mueller et al. 2008

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TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
243.	*Paeonia lactiflora* Pall, Paeoniaceae	Paeoniflorin and 1,2,3,4,6-penta-O-galloyl-D-glucopyranose	Jianfang et al. 2009; Jiang et al. 2012
244.	*Paeonia suffruticosa* Andrews, Paeoniaceae	Palbinone (a triterpines)	Ha et al. 2009
245.	*Panax ginseng* L., Araliaceae	Triterpene saponins: ginsenoside Re, ginsenoside Rh2, 20(S)-gingenoside Rg3, ginsenoside Rb1, ginsenoside Rg1; malonyl ginsenosides, panacene (a peptidoglycan) and a peptide	Gao et al. 2013; Hwang et al. 2007; Lee et al. 2006; Liu et al. 2013a; Park et al. 2008a, 2008b; Shang et al. 2008
246.	*Panax quinquefolius* L., Araliaceae	Quinquefolans A, B, and C (glycans); ginsenoside	WHO 2009
247.	*Pandanus amaryllifolius* Roxb., Pandanaceae	4-Hydroxybenzoic acid	Pengvicha et al. 1998a, 1998b
248.	*Papaver somniferum* L., Papaveraceae	Papaverine	Bustanji et al. 2009
249.	*Parmentiera edulis* C. Am., Bignoniaceae	Gyaianolide (lactucin-8-O-methylacrylate)	Perez et al. 2000
250.	*Peganum harmala* L., Zygophyllaceae	Harmine (major alkaloid)	Moloudizargari et al. 2013
251.	*Perilla frutescens* (L.) Britton, Lamiaceae	Chlorogenic acid, rosmarinic acid and methyl rosmarinic acid	Higashino et al. 2011
252.	*Phaseolus mungo* L., Fabaceae	Specific polysaccharides; reported compounds include β-sitosterol, rutin, kaempferol and quercetin	Ajikumaran and Subramoniam 2005; Menon and Kurup 1976
253.	*Phellodendron amurense* Ruprecht, Rutaceae	Berberine	Kim et al. 2008
254.	*Phoradendron reichenbachianum* (Seem.) Oliv., Viscaceae	Morolic, moronic acids; oleanolic acid and ursolic acid	Nazaruk and Borzym-Kluczyk 2014
255.	*Phyllanthus amarus* Schum & Thonn, Phyllanthaceae	Anti-DM compounds present in this plant include rutin, quercetin, quercetin glucoside and geraniin	Adeneye et al. 2006; Verma et al. 2014
256.	*Phyllanthus emblica* Linn., Euphorbiaceae	Hydrolyzable tannins; gallic acid, ellagic acid and quercetin (reported)	Khan 2009; Suryanarayana et al. 2004
257.	*Phyllanthus fraternus* G L Webster, Phyllanthaceae	Rutin and quercetin	Garg et al. 2010
258.	*Pinellia ternata* (Thunb.) Ten. ex Breitenb., Araceae	Fatty acids of rhizome	Wang et al. 2014
259.	*Piper retrofractum* Vahl., Piperaceae	Piperidine alkaloids (piperine, pipermonaline and dehydropipermonaline)	Kim et al. 2011
260.	*Pistacia lentiscus* L. (var. Chia), Anacardiaceae	Oleanonic acid	Wang et al. 2014
261.	*Polygala senega* L. var. latifolia Torry et Gray, Polygalaceae	Triterpenoid glycosides: senegins II and desmethoxysenegin; E and Z-senegasaponins, and E and Z-senegins II, III, and IV	Kako et al. 1995; Yoshikawa et al. 1996c
262.	*Pomaderris kumeraho* A.Cunn. ex Fenzl, Rhamnaceae	Anti-DM compounds reported from leaf: quercetin, kaempferol, and ellagic acid	Ghisalberti 2005
263.	*Pongamia pinnata* (L.) Pierre, Polygalaceae	Cycloart-23-ene-3β, 25-diol; pongamol and karanjin (flavonoids)	Badole and Bodhankar 2009a; Tamrakar et al. 2008

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
264.	*Populus balsamifera* L., Salicaceae	Salicortin, an ester of salicyl alcohol glucoside	Eid and Haddad 2014
265.	*Potentilla chinensis* Ser., Rosaceae	Trans-tiliroside; β-sitosterol, ursolic acid and oleanic acid have been reported	Qiao et al. 2011; Tomczyk and Latte 2009
266.	*Potentilla discolor* Bunge, Rosaceae	Tormentic acid, asiatic acid, and potengriffioside A	Song et al. 2012c; Yang et al. 2010b
267.	*Poterium ancisroides* D, Rosaceae	Tormentic acid	Ivorra et al. 1989
268.	*Premna latifolia* Thwartes, Verbenaceae	β-Sitosterol and its glucoside (reported)	Ghosh et al. 2014b
269.	*Protium heptophyllum* (Aubl.) L. Marchand	α, β-Amyrin, oleanolic acid, maslinic acid, asiatic acid, ursolic acid and astragaloside IV	Nazaruk and Borzym-Kluczyk 2014; Santos et al. 2012
270.	*Prunella vulgaris* L., Labiatae	Caffeic acid ethylene ester	Li et al. 2012
271.	*Prunus amygdalus* Batsch., Rosaceae	Reported known anti-DM compounds include quercitin, kaempferol and β-sitosterol	Ajikumaran and Subramoniam 2005
272.	*Prunus davidiana* Fr., Rosaceae	Prunin (naringenin 7-O-β-D-glucoside)	Choi et al. 1991
273.	*Psacalium decompositum* A. Gray, Compositae,	Fructan-type oligosaccharides; eremophilanolides: 3-hydroxycacalolide and epi-3-hydroxycacalolide; and eremophilanolide sesquiterpenes	Jimenez-Estrada et al. 2011; Inman et al. 1998, 1999
274.	*Psacalium peltatum* (H.B.K.) Cass, Compositae	Fructan (a carbohydrate) fraction from root	Alarcon-Aguilar et al. 2010
275.	*Pseudolarix amabilis* (J. Nelson) Rehder	Pseudolaric acid B	Wang et al. 2014
276.	*Psidium guajava* L., Myrtaceae	Psidials B and C (sesquiterpenoid-based meroterpenoids) from leaves; β-sitosterol, oleanolic acid and ursolic acid (known anti-DM compounds) present in leaves	Jiang et al. 2012; Kamath et al. 2008
277.	*Psoralea corylifolia* L., Fabaceae	Psoralen and isopsoralen; psoralidin and bakuchiol [seed]	Jiang et al. 2012; Seo et al. 2014
278.	*Pterocarpus marsupium* Roxb., Fabaceae	Marsupin and pterostilbene, phenolic constituents; (–) epicatechin (flavonoid)	Ahmed et al. 1991; Manickam et al. 1997
279.	*Pterocarpus santalinus* Linn. f., Fabaceae	β-Sitosterol and β-amyrin (presence was reported)	Ajikumaran and Subramoniam 2005
280.	*Pueraria lobata* (Willd.) Ohwi, Leguminosae	Puerarin, kakonein	Wu et al. 2013
281.	*Pueraria thomsonii* Benth., Leguminosae	Daidzein and tectorigenin (flavonoid)	Lee et al. 2000; Shen et al. 2006a
282.	*Punica granatum* L., Lythraceae	Valonic acid dilactone from methanol extract of fruit rinds; ursolic acid, gallic acid, ellagic acid, kaempferol, rutin and epigallocatechin 3-gallate are present in the fruit	Jain et al. 2012; Middha et al. 2013; WHO 2009
283.	*Rheum palmatum* Linn., Polygonaceae	Emodin	Xue et al. 2010
284.	*Rhoroedendron brachycarpum* G. Don., Ericacea	Rhododendric acid A and corosolic acid	Choi et al. 2012

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
285.	*Rhynchelytrum repens* (Willd.) C.E. Hubb., Poaceae	B-glucan	DePaula et al. 2005
286.	*Ricinus communis* L., Euphorbiaceae	Phytochemicals with anti-DM properties isolated include rutin, β-sitosterol, β-amyrin and quercetin	Ajikumaran and Subramoniam 2005
287.	*Robinia pseudoacacia* var. umbraculifer DC., Fabaceae	Amorphastilbol	Wang et al. 2014
288.	*Rosmarinus officinalis* L., Lamiaceae	Carnosic acid and carnosol (phenolic diterpenes)	Wang et al. 2014
289.	*Ruta graveolens* L., Rutaceae	Rutin	Ahmed et al. 2010
290.	*Saccharum officinarum* L., Poaceae	Glycon A, B, C, D, and E; ferulic acid (present in this plant)	Ajikumaran and Subramoniam 2005; Chohachi et al. 1985
291.	*Salacia chinensis* L., Celastraceae	Mangiferin; 3β, 22β-dihydroxyoleon-12-en-29-oic acid, tingenone, tingenine B, regeol A, triptocalline A and salasol (a triterpene)	Morikawa et al. 2003; Sellamuthu et al. 2014
292.	*Salacia oblonga* Wall. ex Wight. & Arn., Celastraceae	Salacinol and kotalanol; reported to contain the anti-DM compound mangiferin	Matsuda et al. 1999
293.	*Salacia reticulata* Wight, Celastraceae	Salacinal and kotanol, polyhydroxylated cyclic 13-membered sulfoxide	Ozaki et al. 2008
294.	*Salvia miltiorrhiza* Bunge, Lamiaceae	Abietane-type diterpene metabolites: isotanshinone IIA, dihydroisotanshinone I, and isocryptotanshinone; and anshenol A (triterpene)	Angel de la Fuente and Manzanaro 2003; Jiang et al. 2012
295.	*Salvia officinalis* L., Lamiaceae	Carnosic acid and carnosol; 12-O-methyl carnosic acid and a-linolenic acid; ursolic acid and rosmarinic acid	Hamidpour et al. 2014; Wang et al. 2014
296.	*Sambucus adnata* Wall. ex DC., Caprifoliaceae	Ursolic acid, oleanolic acid and (±)-boehmenan	Sasaki et al. 2011
297.	*Sambucus nigra* L., Adoxaceae	α-Linolenic acid, linoleic acid, and naringenin	Wang et al. 2014
298.	*Sansevieria senegambica* Baker., Agavaceae	Quercetin, kaempferol, (–)-epicatechin, naringenin, (+)-and catechin are reported in water extract of rhizome	Chigozie and Chidinma 2012
299.	*Sarcopoterium spinosum* (L.) Spach, Rosaceae	Catechin and epicatechin	Smirin et al. 2010
300.	*Sarracenia purpurea* L., Sarraceniaceae	7β-O-methylmorroniside, rutin, kaempferol-3-O-rutinoside, kaempferol-3-O-(6”-caffeoylglucoside), morroniside, goodyeroside, and quercetin-3-O-galactoside	Eid and Haddad 2014
301.	*Saururus chinensis* (Lour.) Baill., Saururaceae	Saurufuran A	Wang et al. 2014
302.	*Saussurea lappa* C.B. Clarke, Asteraceae	Betulinic acid, methyl ester of betulinic acid, mokkolactone and dehydrocostuslactone; and chrysophanol and its glucopyranoside	Choi et al. 2009; Wei et al. 2014
303.	*Schisandra arisanensis* Hayata, Schisandraceae	Schiarisanrin A and B	Hsu et al. 2012
304.	*Scoparia dulcis* L., Scrophuilariaceae	Scoparic acid D, a diterpenoid; a glycoside amellin; β-sitosterol	Latha et al. 2009; Saikia et al. 2011

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
305.	*Scrophularia deserti* Del., Scrophulariaceae	Scropolioside-D (iridoid glycosides)	Ahmed et al. 2003
306.	*Scutellaria baicalens* Georgia, Lamiaceae	Baicalein (5,6,7-trihydroxyflavone)	Nishioka et al. 1988
307.	*Selaginella tamariscina* (Beauv.) Spring, Selaginellaceae	Amentoflavone	Jiang et al. 2012
308.	*Senna tora* (L.) Roxb., Fabaceae	Napthopyrone glycoside	Chaurasia et al. 2011
309.	*Sesbania sesban* (L.) Merr., Fabaceae	Oleanolic acid	Gomase 2012
310.	*Siegesbeckia glabrescens* Makino., Asteraceae	Kaurane-type diterpenes	Jiang et al. 2012
311.	*Silybum marianum* (Linn.) Gaertn., Asteraceae	Silymarin (flavonoid); isosilybin A (phenolic); kaempferol and quercetin	Ajikumaran and Subramoniam 2005; McCarty 2005; Wang et al. 2014;
312.	*Siraitia grosvenorii* (Swingle) C. Jeffrey ex. A.M. Lu. and Zhi Y., Cucurbitaceae	Mogrosides (aglycone mogrol and two cucurbitane triterpenoids)	Xiang-Yang et al. 2008
313.	*Smallanthus sonchifolius* (Poepp & Endl.) H. Robinson, Asteraceae	Enhydrin (the major sesquiterpene lactone of yacon); chlorogenic acid, ferulic acid and quercetin	Genta et al. 2010; Pedreschi et al. 2003
314.	*Scrophularia ningpoensis* Hemsl., Scrophulariaceae	Scrophuside and iridoid glycosides ningposide 1 and 2 from the roots	Firdous 2014
315.	*Solanum virginianum* L., Solanaceae	β-Sitosterol, phytosterol	Gupta et al. 2011
316.	*Sonchus oleraceus* L., Asteraceae	Esculetin	Hozayen et al. 2011
317.	*Sorbus commixta* Hedl., Rosaceae	Triterpenes: lupeol and lupenone	Jiang et al. 2012
318.	*Sorbus decora* C.K. Schneid, Rosaceae	Pentacyclic triterpene: 23, 28,-dihydroxylupan-20(29)-ene-3-β-caffeate; catechin and epicatechin	Guerrero-Analco et al. 2010
319.	*Stephania tetrandra* Moore, Menispermaceae	Bis-benzylisoquinoline alkaloid, fangchinoline; and alkaloid, tetrandrine	Lieberman et al. 1992; Tsutsumi et al. 2003
320.	*Stereospermum teteragonum* DC., Bignoniaceae	A novel iridoid glycoside: (1,4a,5,7a-tetrahydro-5-hydroxy-7-(hydroxymethyl)-1-(tetrahydro-6-(hydroxymethyl)-3,4,5-trimethoxy-2H-pyran-2yloxy) cyclopenta[c] pyran-4-carboxylic acid); and a derivative of napthoquinone (5,8-dihydro-7-isopentyl-2,3,5,8-tetramethoxynaphthalene-1,4,6-triol).	Bino Kingsley 2014; Bino Kingsley et al. 2013a
321.	*Stevia rebaudiana* (Bert.) Bertoni, Asteraceae	Stevioside and steviol; rebaudioside; kaempferol-3-O-rhamnoside, quercetin, quercetin-3-O-glucoside, quercetin-3-O-arabinoside, sitosterol and stigmasterol were isolated from leaf	Jeppesen et al. 2002; Madan et al. 2010
322.	*Streblus asper* Lour, Moraceae	α-Amyrin acetate; α-amyrin and β-sitosterol are reported from the bark	Karan et al. 2013; Rastogi et al. 2006
323.	*Styrax japonica* Siebold & Zucc., Styracaceae	Triterpenoids and a sterol	Jiang et al. 2012
324.	*Sutherlandia frutescens* R.Br. var. incana E. Mey., Fabaceae	Pinitol	VanWyk and Albrecht 2008

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
325.	*Swertia bimaculata* (Siebold & Zucc.) C. B. Clarke., Gentianaceae	Corymbiferin	Liu et al. 2013b
326.	*Swertia chirayita* (Roxb. ex Flm.) Krast., Gentianaceae	Swerchirin (1,8 dihydroxy 3,5 dimethoxy xanthone); [Mangiferin and β-sitosterol are present in this plant]	Ajikumaran and Subramoniam 2005; Saxena et al. 1991
327.	*Swertia japonica* (Schult.) Makino., Gentianaceae	Bellidifolin (a xanthone)	Basnet et al. 1994
328.	*Swertia mussotii* Franch, Gentianaceae	Mangiferin; oleanolic acid (present in this plant)	Yang et al. 2005
329.	*Swertia punicea* Hemsl., Gentianaceae	Methylswertianin and bellidifolin	Tian et al. 2010
330.	*Swietenia macrophylla* King, Meliaceae	β-Sitosterol	Hashim et al. 2013
331.	*Symplocos cochinchinsis* (Lour.) S. Moore, Symplocaceae	β-Sitosterol and oleanolic acid (present in the active extract)	Antu et al. 2014
332.	*Symplocos paniculata* (Thunb.) Miq., Symplocaceae	Triterpenes: Ursolic acid, corosolic acid and 2α,3α,19α,23-tetrahydroxyurs-12-en-28-oic acid	Jiang et al. 2012
333.	*Syzigium cordatum* Hoscht. ex. C. Krauss, Myrtaceae	Oleanolic acid and ursolic acid present in the leaf	Mapanga et al. 2009
334.	*Syzygium cumini* (L.) Skeels., Myrtaceae	α-Hydroxy succinamic acid; ferulic acid (phenolic acid); cuminoside; ellagic acid, gallic acid, quercetin, β-sitosterol, kaempferol glycosides and lupeol	Alam et al. 2012; Farswan et al. 2009; Gupta and Saxena 2011; Mandal et al. 2008; Tanwar et al. 2010
335.	*Syzygium malaccense* (L) Merr. & Perr, Myrtaceae	Myricitrin (major active compound in leaf); β-sitosterol and ursolic acid are present in the plant leaf	Arumugam et al. 2014; Ismail et al. 2010
336.	*Syzygium samarangense* (Blume) Merrill and Perry, Myrtaceae	Vescalagin from fruit; 2′,4′-dihydroxy-3′,5′-dimethyl-6′-methoxychalcone and its isomeric flavanone from leaf	Resurreccion-Magno et al. 2005; Shen and Chang 2013
337.	*Tabernaemontana divaricata* (L.) Roemer & Schultes, Apocynaceae	Conophylline, a vinca alkaloid from leaves	Fujij et al. 2009
338.	*Tecoma stans* (L.) Kunth., Bignoniaceae	Tecomine (alkaloid); 5-β-hydroxyskitanthine and boschniakine	Costantino et al. 2003; Singh et al. 2013
339.	*Tectona grandis* L., Verbenaceae	β-Sitosterol (present in this plant)	Nidavani and Mahalakshmi 2014
340.	*Tephrosia purpuria* (L.) Pers, Fabaceae	β-Sitosterol, rutin and quercetin (present in this plant)	Sharma et al. 2013
341.	*Terminalia bellerica* (Gaertn) Roxb., Combrataceae	Gallic acid and gallotannins	Latha and Daisy 2011; Yang et al. 2013
342.	*Terminalia chebula* Retz. or *Terminalia chebula* Retz var. tomentella Kurt, Combretaceae	Reported to contain anti-DM compounds, gallic acid, ellagic acid, and so on	Rathinamoorthy and Thilagavathi 2014
343.	*Terminalia paniculata* Roth, Combretaceae	Gallic acid (ellagic acid, catechin, and epicatechin are also present)	Ramachandran et al. 2013
344.	*Tetracera scandens* (L.) Merr., Dilleniaceae	Flavonoids, genistein-derivatives	Jiang et al. 2012
345.	*Thymus vulgaris* L., Lamiaceae	Carvacrol	Wang et al. 2014

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
346.	*Tinospora cordifolia* (Willd.) Miers. Ex Hook. F. & Thoms., Menispermaceae	Tinosporaside, berberine, β-sitosterol, and γ-sitosterol	Arif et al. 2014; Sankhala et al. 2012
347.	*Tinospora crispa* (L.) Hook. f. & Thomson	Borapetol B	Lokman et al. 2013
348.	*Tithonia diversifolia* (Hemsl.) A. Gray, Asteraceae	Three new germacrane sesquiterpenes	Zhao et al. 2012
349.	*Toona ciliata* var *pubescens* (Franchet) Handel-Mazzetti, Meliaceae	(*Z*)-aglawone from stem bark	Jiang et al. 2012
350.	*Tournefortia hartwegiana* Steud, Boraginaceae	β-Sitosterol, stigmasterol, lupeol, ursolic acid, and oleanolic acid	Ortiz-Andrade et al. 2007
351.	*Trichosanthes kirilowii* Maxim., Cucurbitaceae	Trichosans A (glycan)	Hikino et al. 1989
352.	*Trifolium pratense* L., Fabaceae	Genistein, biochanin A, 6-hydroxydaidzein soflavones, 3′-hydroxygenistein, and so on	Wang et al. 2014
353.	*Trigonella foenum-graecum* L., Leguminoceae	4-Hydroxyisoleucine (2*S*, 3*R*, and 4*S*) from seed; trigonelline (phenolic compound); antihyperglycemic compound named GII from seeds	Al-Khateeb et al. 2012; Moorthy et al. 2010a; Sauvaire et al. 1998
354.	*Urtica pilulifera* L., Urticaceae	Lectin from seed	Kavalal et al. 2003
355.	*Uvaria rufa* Blume, Annonaceae	Isoquercetin and its acetate derivatives	Deepralard et al. 2009
356.	*Vaccinium angustifolium* Ait., Ericaceae	Chlorogenic acid (reported from fruit); anthocyanin: malvidin-3-O-glucoside	Grace et al. 2009; Rodriquez-Mateoz et al. 2012
357.	*Vaccinium arctostaphylos* L., Ericaceae	Anthocyanin: malvidin-3-O-β-glucoside	Nickavar and Amin 2010
358.	*Vaccinium vitis-idaea* L., Ericaceae	Quercetin-3-O-galactoside, quercetin, and quercetin-3-O-glucoside	Eid and Haddad 2014
359.	*Verbesina crocata* Less, Asteraceae	Daucosterol, galegine, and lupiol and lupeol acetate	Marles and Farnsworth 1995
360.	*Vernonia amygdalina* Del., Asteraceae	Chlorogenic acid and luteolin-7-O-glucoside.	Ong et al. 2011
361.	*Viburnum opulus* L., Adoxaceae	Rich in chlorogenic acid, an anti-diabetic compound	Erdogan-Orhan et al. 2011
362.	*Vinca minor* L., periwinkle	Vincamine, an alkaloid	De and Saha 1975; Farahanikia et al. 2011
363.	*Vitex lucens* Kirk, Lamiaceae, syn: *Vitex littoralis* A.Cunn.	Vitexin and p-hydroxy benzoic acid	Ghisalberti 2005
364.	*Vitex negundo* L., Labiatae	1, 2 Di-substituted idopyranose; and iridoid glucoside	Manikandan et al. 2011; Sundaram et al. 2012
365.	*Vitis vinifera* L., Vitaceae	Ellagic acid and epicatechin gallate	Wang et al. 2014
366.	*Wedelia paludosa* DC, Asteraceae (*Acmella brasiliensis* Spreng)	Kaurenoic acid, a diterpene	Bresciani et al. 2004
367.	*Weigela subsessilis* L.H. Bailey, Caprifoliaceae	24-Norursane triterpenes, ilekudinols A and B	Jiang et al. 2012
368.	*Woodfordia fruticosa* (L.) Kurz, Lythraceae	Gallic acid, oleonolic acid and β-sitosterol are present in this plant	Arya et al. 2012
369.	*Xanthium strumarium* L., Compositae	Caffeic acid	Hsu et al. 2000

(*Continued*)

TABLE 2.1 (*Continued*)

Phytochemicals with Anti-Diabetes Mellitus (Anti-DM) Properties

No.	Plant source (Botanical Name and Family Names)	Phytochemicals	References
370.	*Xanthocercis zambesiaca* (Baker) Dumaz, Leguminosae	Fagomine (nitrogen-containing sugar) and related compounds	Nojima et al. 1998
371.	*Zea mays* L., Poaceae	Hirsutrin	Kim et al. 2013
372.	*Zingiber officinale* Roscoe, Zingiberaceae	6-Shogaol and 6-gingerol	Gao et al. 2013; Wang et al. 2014
373.	*Ziziphus jujuba* Mill., Rhamnaceae	Oleanolic (present)	
374.	*Ziziphus rugosa* Lamk., Rhamnaceae	β-Sitosterol, quercetin and quercetin-3-rhamnoside; oleanolic acid (anti-DM phytochemical reported)	Ajikumaran and Subramoniam 2005
375.	*Ziziphus spina-christi* (L.) Willd., Rhamnaceae	Christinin-A (the major saponin glycoside from leaf); rutin, quercetin and quercetin glycosides are also reported	Abdel-Zaher et al. 2005; Asgarpanah and Haghighat 2012

2.2 Phytochemicals with Anti-DM Activities

1. 3-β-O-Acetyl aleuritolic acid

   Plant source: *Macaranga adenantha*

   Anti-diabetes: Triterpene metabolite with protein tyrosine phosphatase 1B inhibitory activity identified as 3β-O-acetyl aleuritolic acid (oleanolic acid, 3β, 28-dihydroxy-12-en-olean; maslinic acid) were obtained from the plant *M. adenantha* (Jiang et al. 2012).

   Other activities: Other reported activities include antibacterial and inhibition of DNA topoisomerase II (Prachayasittikul et al. 2009).

2. Achyrofuran (a prenylated dibenzofuran)

   Plant source: *Achyrocline satureioides*

   Anti-diabetes: Achyrofuran significantly lowered blood glucose levels when administered orally (p.o.) (20 mg/kg) to type 2 diabetic db/db mouse (Carney et al. 2002).

3. Aconitan A, B, C, and D

   Plant source: *Acontium carmichaelii*

   Anti-diabetes: Glycans (aconitans A, B, C, and D) of *A. carmichaelii* roots lowered blood glucose (Konno et al. 1985c).

4. Aegeline (alkaloid)

   Plant source: Aegeline is found in the anti-DM tree *Aegle marmelos*. The chemical structure of the alkaloid aegeline is shown in Figure 2.1.

   Anti-diabetes: Aegeline, N-[2-hydroxy-2-(4-methoxyphenyl) ethyl] cinnamamide, an alkaloid amide from the leaves showed anti-diabetes activity in streptozotocin diabetic rats. The compound also decreased the levels of cholesterol, triglyceride and free fatty acid and increased high-density cholesterol (HDL) cholesterol levels (Narender et al. 2007). Based on pharmacophoric

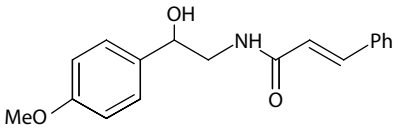


FIGURE 2.1 Structure of aegeline.

hypothesis and three-dimensional quantitative structure–activity relationship models (3D-QSAR model), the authors suggest that the compound might be a β-3-adrenergic receptor (AR) agonist.

Other activities: Aegeline inhibited histamine release from mast cells; this effect was depended on the type of mast cell and involved some mechanisms related to intracellular Ca(2+) signaling (Nugroho et al. 2011).

5. Aglawone [(*Z*)-aglawone, pregnane steroid]

   Plant source: The stem bark of *Toona ciliata* var pubescens yielded (*Z*)-aglawone.

   Anti-diabetes: (*Z*)-aglawone from *T. ciliata* inhibited PTP1B activity in a competitive manner with a half maximal inhibitory concentration (IC_{50}) value of 1.12 μg/mL. It is interesting to note that the (E)-isomer of this compound showed no inhibition of PTP1B (Jiang et al. 2012).

6. Alisol F and Alisol B (protostane-type triterpenes)

   Plant source: *Alisma orientale*, *Alismatis rhizoma*, and so on

   Anti-diabetes: Alisol F and alisol B from rhizome displayed *in vitro* inhibition of α-glucosidase activity (Li and Qu 2012).

   Other activities: It is an inhibitor of the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase; it induced autophagy, endoplasmic reticulum stress, and apoptosis in cultured cells (Law et al. 2010).

7. Allicin (diallylthiosulfinate)

   Plant source: Allicin (diallyl thiosulfinate) is found in garlic (*Allium sativum*). The chemical structure of allicin is shown in Figure 2.2.

   Anti-diabetes: Allicin showed hypoglycemic activity, enhancement of serum insulin levels and increase in glycogen synthesis in alloxan-diabetic animals (Mathew and Augusti 1973). Garlic extract's hypoglycemic action may be due to enhanced insulin production, and allicin has also been shown to protect insulin against inactivation (WHO 1999).

   Other activities: Other reported activities of pure allicin include antimicrobial activity, inhibition of cell proliferation, cholesterol-lowering effect, and blood pressure–lowering effect (Borlinghaus et al. 2014).

8. Alstiphyllanines E and F (picraline type alkaloids)

   Plant source: *Alstonia macraphylla*

   Anti-diabetes: Alstiphyllanines E and F showed moderate Na (+)–glucose cotransporter (SGLT1 and SGLT2) inhibitory activity. 10-Methoxy-N(1)-methylburnamine-17-O-veratrate, a derivative of alstiphyllanines, exhibited potent SGLT inhibitory activity (Arai et al. 2010).

9. Amentoflavone

   Plant source: *Selaginella tamariscina*, *Salaginella rupestris*, *Cnestis ferruginea*, and so on

   Anti-diabetes: From the methanol extract of *S. tamariscina*, amentoflavone was obtained and characterized as a noncompetitive PTP1B inhibitor (IC_{50} value = 7.3 μmol/L). Treatment with the compound of 32D cells over expressing the insulin receptor (IR) resulted in a dose-dependent increase in tyrosine phosphorylation of IR, possibly through inhibition of PTP1B to enhance insulin-induced intracellular signaling (Jiang et al. 2012).

   Other activities: Amentoflavone, like caffeine, caused a concentration-dependent increase in Ca^{2+} release from the heavy fraction of fragmented sarcoplasmic reticulum of rabbit skeletal muscle (Suzuki et al. 1999). Amentoflavone isolated from *C. ferruginea* showed antidepressant and anxiolytic effects in mice (Ishola et al. 2012).

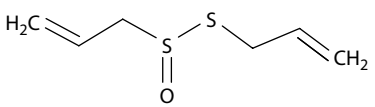


FIGURE 2.2 Structure of allicin.

10. Amorfrutins

    Plant source: Amorfrutins are isoprenoid-substituted benzoic acid derivatives, which were found in *Amorpha fruticosa*, *Glycyrrhiza foetida*, *Glycyrrhiza uralensis*, *Amorpha fruticosa*, and so on.

    Anti-diabetes: A family of natural products, the amorfrutins, from edible parts of two legumes (*G. foetida* and *A. fruticosa*) showed powerful anti-DM activities. Amorfrutins bind to and activate peroxisome proliferator–activated receptor-gamma (PPAR-γ), which results in selective gene expression and physiological profiles markedly different from activation by current synthetic PPAR-γ drugs. In diet-induced obese and db/db mice, amorfrutin treatment strongly improved insulin resistance and other metabolic and inflammatory parameters without concomitant increase of fat storage or other unwanted side effects such as hepatoxicity (Weidner et al. 2012). Amorfrutins lowered blood glucose, fat weight, and dyslipidemia (Wang et al. 2014). Amorfrutin 1 binds to purified PPAR-γ and activates chimeric Gal4-PPAR-γ-dependent reported gene expression as partial agonist; it selectively modulates PPAR-γ gene expression in human adipocytes. It improved insulin resistance without concomitant increase of fat storage in diet-induced obese and db/db nice. Amorfrutin 2 and amorfrutin B also bind to purified PPAR-γ and activates chimeric Gal4-PPAR-γ-dependent reporter gene expression as partial agonist; amorfrutin B induces partial recruitment of several PPAR-γ transcriptional coactivators; in insulin-resistant mice, it showed liver protecting properties and improved insulin sensitivity, glucose tolerance without weight gain (Wang et al. 2014).

    Other activities: In tumor necrosis factor (TNF)-α-stimulated colon cells amorfrutin A reduced significantly the expression and secretion of several inflammation mediators (Fuhr et al. 2015).

11. Amorphastilbol (*trans*-stilbene)

    Plant source: Amorphastilbol was isolated from the seed of *Robinia pseudoacacia*.

    Anti-diabetes: Amorphastilbol exhibited dual PPAR-γ/-α agonist effects. It binds to purified human PPAR-γ and activates human PPAR-γ-dependent luciferase reporter gene expression. It improved glucose and lipid impairment in db/db mice without side effects such as weight gain or hepatomegaly (Wang et al. 2014). In a recent study, anti-diabetic effects of amorphastilbol from *Amorpha fruticosa* were evaluated in high-fat-diet (HFD) mice. HFD-induced blood glucose and insulin levels are significantly reduced in amorphastilbol treatment groups. HFD-induced weight gain was also reduced by the treatment, which was accompanied by reduction of fat mass and adipocyte size and number in white adipose tissues. Furthermore, total cholesterol and low-density lipoprotein–cholesterol levels were decreased in amorphastilbol treated mice. In addition, amorphastilbol improved insulin sensitivity through inhibition of protein tyrosine phosphatase 1B, a negative regulator of the insulin-signaling pathway. Taken together, the data suggest that this compound has beneficial effects on glucose and lipid metabolism. The authors concluded that amorphastilbol can be used as potential therapeutic agents against type 2 diabetes and associated metabolic disorders, including obesity, by enhancing glucose and lipid metabolism (Lee et al. 2015).

12. α-Amyrin, β-amyrin, and α-amyrin acetate (terpenoids)

    Plant sources: α-Amyrin and β-amyrin are present in *Ficus bengalensis* (aerial part), *Hemidesmus indicus* (root), *Protium heptaphyllum*, *Protium heptophyllum*, and so on; α-amyrin acetate is reported from *Ficus racemosa*, *Streblus asper*, *H. indicus*, and so on.

    Anti-diabetes: α-Amyrin acetate isolated from *F. bengalensis* has been reported to have anti-diabetes mellitus activity at 50 mg/kg dose level; it also showed antihyperglycemic activity in normal rats (Singh et al. 2009). In another study, α-amyrin acetate (25–75 mg/kg) from *Strebules asper* showed anti-DM activity in streptozotocin-diabetic rats (Karan et al. 2013). β-Amyrin acetate is a potent inhibitor of α-glucosidase (Wijayabandara et al. 2008). Mice treated with α-, β-amyrin mixture (10–100 mg/kg) from *P. heptaphyllum* have showed significant reduction in streptozotocin-induced increase in blood glucose, total cholesterol, and serum triglycerides (Santos et al. 2012).

    Other activities: Other known pharmacological properties include antinociceptive activity, antimicrobial activity, anti-inflammatory activity, and weak cytotoxicity. The mixture of β-amyrin and α-amyrin produced consistent peripheral, spinal, and supraspinal antinociception in

rodents, especially when assessed in inflammatory models of pain (Otuki et al. 2005; Vazquez et al. 2012).

13. β-Amyrin palmitate

    Plant source: *Hemidesmus indicus* root, *Lobelia inflata*, *Protium heptophyllum*, *Tabernaemontana dichotoma*, and so on contain β-amyrin palmitate (Ajikumaran et al. 2014). The chemical structure of β-amyrin palmitate is shown in Figure 2.3.

    Anti-diabetes: β-Amyrin palmitate isolated from *H. indicus* root showed remarkable antihyperglycemic activity in orally glucose-loaded rats. Furthermore, it exhibited excellent anti-DM activity in both alloxan-diabetic and streptozotocin-diabetic rats at a very low concentration (50 μg/kg). One of the mechanisms of action of β-amyrin palmitate appears to be blocking the entry of glucose from the intestine. Since the drug restored weight of body and liver and liver glycogen content in the diabetic rats, it is likely to have more than one mechanisms of action. In addition to the inhibition of glucose absorption, it may have delayed actions such as insulin like (partial or complete) action and/or sensitization of insulin action. It is also possible that the compound could protect β-cells and/or stimulate the cells to produce more insulin. The authors suggest that one or more of these delayed actions may occur, at least, a few hours after the administration of β-amyrin palmitate. Further studies are required to elucidate its multiple mechanisms of action. β-Amyrin palmitate is very promising to develop a medicine for diabetes for combination therapy and/or monotherapy (Ajikumaran et al. 2014).

    Other activities: The compound has antidyslipidemic activity also (Maurya et al. 2012).

14. Anacardic acid

    Plant source: Anacardic acid is found in nutshell of *Anacardium occidentale*. Chemically, it is a mixture of several closely related organic compounds, each consisting of salicylic acid substituted with an alkyl chain. The chemical structure of anacardic acid is shown in Figure 2.4.

    Anti-diabetes: The phenolic compound, anacardic acid, stimulated glucose uptake into C2C12 myotubes by activation of adenosine monophosphate-activated protein kinase (AMPK) which in tern increased plasma membrane glucose transporters (Tedong et al. 2010). Furthermore, anacardic acid activated AMPK in the myotubes after 6 h of incubation. The compound exerted

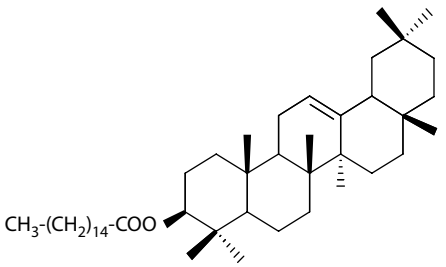
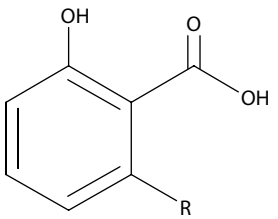


FIGURE 2.3 Structure of β-amyrin palmitate.



R is an alkyl chain of variable length, which may be saturated or unsaturated

FIGURE 2.4 Structure of anacardic acids.

uncoupling of succinate-stimulated respiration in rat liver mitochondria. Activation of AMPK is likely to increase the number of plasma membrane glucose transporters resulting in elevated glucose uptake (Tedong et al. 2010).

Other activities: Other pharmacological activities of this compound and its derivatives include antimicrobial, anticancer, anti-inflammation, antiobesity, and antioxidative stress. Furthermore, anacardic acid was found to be a common inhibitor of several clinically targeted enzymes such as nuclear factor kappa B (NF-κB) kinase, histone acetyltransferase, lipoxygenase, xanthine oxidase, tyrosinase, and ureases (Hemshekhar et al. 2012).

15. Andrographolide

    Plant source: Andrographolide is the principal bioactive phytoconstituent of *Andrographis paniculata*.

    Anti-diabetes: The antihyperglycemic and anti-diabetic properties of andrographolide have been shown in streptozotocin-induced rats (Yu et al. 2003). Mediation of β-endorphin in andrographolide-induced plasma glucose-lowering action in type 1 diabetes-like animals has been reported (Yu et al. 2008). Andrographolide showed hypoglycemic and hypolipidemic effects in high-fat-fructose-fed rats also (Nugroho et al. 2012). In a recent study, andrographolide significantly decreased the levels of blood glucose and improved diabetic rat islet β-cells in streptozotocin-induced type 2 diabetic rats. The treatment could restore decreasing of pancreatic insulin contents in the diabetic rats (Nugroho et al. 2014).

    Other activities: Andrographolide exhibited credible anticancer, anti-inflammatory, angiogenic, antivenom, and antimalarial activities in various investigations around the globe (Deshpande et al. 2014).

16. Anthocyanin

    Plant source: Anthocyanins occur in many plants; examples of these include *Vaccinium arctostaphylos* and *Vaccinium* sp.

    Anti-diabetes: Anthocyanins are flavonoids that occur in plants and are, to a large extent, responsible for their color. Anthocyanin glycoside isolated from *V. arctostaphylos* inhibited pancreatic α-amylase (Nickavar and Amin 2010). The anthocyanin protected β-cells from oxidative stress and increased secretion of insulin; furthermore, it improved insulin resistance (Sancho and Pastore 2012). Studies using cell lines and animal models and human clinical trials suggest that anthocyanins exhibit anti-DM properties (Sancho and Pastore 2012). However, structural diversity of anthocyanins makes it difficult to generalize their actions in DM. Understanding the absorption and metabolism of different anthocyanins is important for their efficacy in DM. Published data suggest that anthocyanins may lower blood glucose by improving insulin resistance, protecting β-cells, enhancing insulin secretion, and inhibiting digestion of sugars in the small intestine (Sancho and Pastore 2012).

    Other activities: Anthocyanins have antioxidant properties. They can neutralize free radicals that cause neurodegenerative disease, cardiovascular disease, and cancer.

17. Araliosides

    Plant source: Araliosides were isolated from the root bark of *Aralia elata*.

    Anti-diabetes: Araliosides prevented diabetic cardiomyopathy in streptozotocin-induced diabetic rats during the early stages. The study suggested that total aralosides of *A. elata* prevents diabetes-induced cardiac dysfunction and pathological damage through upregulating L-type Ca^{2+} channel current in cardiac cells and decreasing connective tissue growth factor expression (Xi et al. 2009).

18. Apigenin-6-C-β-L-fucopyranoside

    Plant source: *Averrhoa carambola* L.

    Anti-diabetes: Apigenin-6-C-β-L-fucopyranoside from *Averrhoa carambola* showed an acute effect on blood glucose lowering in hyperglycemic rats and stimulated glucose-induced insulin secretion (Cazarolli et al. 2009). When muscles were incubated with this compound, a stimulatory effect on glycogen synthesis was observed; this effect was completely nullified by

pre-treatment with insulin signal transduction inhibitors. This study provides evidence for dual effects of apigenin-6-C-β-L-fucopyranoside as an antihyperglycemic (stimulation of insulin secretion) as well as an insulinomimetic agent (Cazarolli et al. 2009).

19. Arecoline (alkaloid)

    Plant source: *Areca catechu* (betel nut)

    Anti-diabetes: Arecoline showed hypoglycemic activity (Chempakam 1993). It increased the translocation of glucose transporter (GLUT4) via PPAR-γ activation and increased 2-deoxy glucose uptake by 3T3-L1 adipocytes (Chempakam 1993; Prabhakar and Doble 2011).

    Other activities: It is an agonist at both muscarinic and nicotinic acetylcholine receptors. It is used in the form of various salts as a ganglionic stimulant, a parasympathomimetic, and a vermifuge, especially in veterinary practice.

20. Asiatic acid (a triterpenoid)

    Plant source: Asiatic acid is one of the main components in the herb *Centella asiatica*.

    Anti-diabetes: Asiatic acid showed anti-diabetic activity in streptozotocin-induced diabetic mice. Administration of the compound resulted in a reduction in blood glucose and stimulation of β-cell proliferation and survival; the treatment activated Akt activity and increased the expression of Bcl-xL (Liu et al. 2010). Besides, asiatic acid exhibited anti-DM activity in rats; the compound improved lipid profile also in the diabetic rats (Ramachandrana et al. 2014).

    Other activities: Asiatic acid showed anti-inflammatory effect by the inhibition of enzymes (indusable nitric oxide synthase [iNOS], cyclooxygenase-2), interleukins (IL-6, IL-1β), TNF-α expression through the downregulation of NF-κB activation in lipopolysaccharide-induced murine macrophage cells. Furthermore, asiatic acid-induced apoptosis in human melanoma cells and colon cancer cells. Asiatic acid showed enhancing learning and memory properties in rats (Dipankar et al. 2013).

21. Aspalathin (dihydrochalcone)

    Plant source: Aspalathin (2′,3,4,4′,6′-pentahydroxy-3′-C-β-D-glucopyranosyl dihydrochalcone) is reported as a major active ingredient in *Aspalathus linearis* and related species. The chemical structure of aspalathin is shown in Figure 2.5.

    Anti-diabetes: Aspalathin, a tea component, dose dependently increased glucose uptake by L6 myotubes at concentrations 1–100 μM. It also increased insulin secretion from cultured RIN-5F β-cells at 100 μM. Inclusion of aspalathin in the diet (0.1% and 0.2%) suppressed the increase in fasting blood glucose levels of db/db type 2 diabetic mice. In intraperitoneal (i.p.) glucose tolerance test, aspalathin improved impaired glucose tolerance at 30, 60, 90, and 120 min in the diabetic db/db mice (Kawano et al. 2009). A mixture of aspalathin and rutin (1:1) at a low dose (1.4 mg/kg), but not the single compounds separately, reduced blood glucose concentrations over a 6 h monitoring period in streptozotocin diabetic rats. The improved hypoglycemic activity of the mixture and the extract showed synergic actions of the polyphenols in mixture (Muller et al. 2012). Remarkably, treatment with aspalathin or nothofagin (another dihydrochalcone found in green rooibos) inhibited high-glucose-mediated vascular

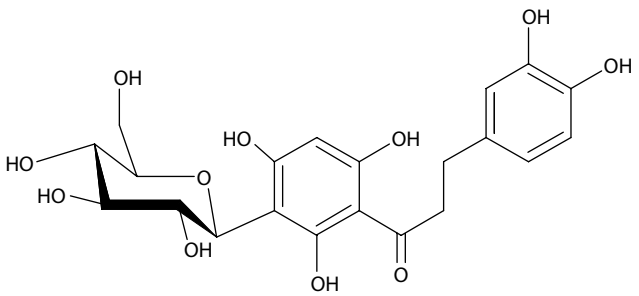


FIGURE 2.5 Structure of aspalathin.

hyperpermeability, adhesion of monocytes toward human umbilical vein endothelial cells, and expression of cell adhesion molecules *in vitro*. In addition, these compounds suppressed the formation of reactive oxygen species (ROS) and the activation of NF-κB. *In vivo* in mice also these compounds suppressed vascular inflammation. Since vascular inflammation induced by high levels of glucose is critical in the development of diabetic complications, the authors suggest that these compounds may have significant benefits in the treatment of diabetic complications (Ku et al. 2015).

Other activities: Other reported activities of aspalathin include antioxidant activity, xanthine oxidase inhibitory activity, and hypouricemic effect. In hyperuricemic mice, treatment with aspalathin significantly suppressed the increased plasma uric acid level in a dose-dependent manner. Aspalathin was found to be a competitive inhibitor of xanthine oxidase (Kondo et al. 2013).

22. Astilbin (flavonoid)

    Plant source: Astilbin is found in plants such as *Hymeneae martiana*, *Astilbe thunbergii*, *Astilbe odontophylla*, *Smilax glabra*, and *Smilax china*.

    Anti-diabetes: Astilbin, a flavonoid compound, isolated from the rhizome of *Smilax* sp. showed beneficial effects to diabetic kidney and heart. Astilbin from *Smilax glabra* inhibited high glucose-stimulated HK-2 cell production of transforming growth factor-beta (TGF-β) and connective tissue growth factor (CTGF) *in vitro*. Intragastric administration of astilbin 2.5 or 5 mg/kg to streptozotocin-diabetic rats significantly ameliorated renal function and it increased body weight and survival time in animals. In addition, there was no significant difference in blood glucose level between the streptozotocin-treated group and the astilbin groups. Furthermore, astilbin ameliorated the pathological progress of renal morphology. Thus, astilbin can exert an early renal protective role to diabetic nephropathy, inhibiting production of TGF-β1 and especially of CTGF. This work provides evidence for astilbin as a new candidate of diabetic nephropathy therapeutic medicine (Li et al. 2009). In another study, treatment of diabetic rats with astilbin (50 mg/kg, intravenous [i.v.] for 14 days) from *S. china* attenuated cardiac remodeling in the model myocardial ischemia and reperfusion injury. These protective effects might be due to block of the myocardial inflammatory cascade via the high-mobility group box protein 1-dependent NF-κB signaling pathway (Diao et al. 2014).

    Other activities: Astilbin showed *in vitro* antibacterial activity. Furthermore, it exhibited burn wound healing property, antinociceptive activity, and antiedematogenic properties (Cechinel-Filho et al. 2000).

23. Astragalin (flavonoid glycoside)

    Plant source: Astragalin (flavonoid glycoside) is found in the leaves of *Eucommia ulmoides*, *Aristolochia indica*, and so on.

    Anti-diabetes: Astragalin (5,7-dihydroxy-2-(4-hydroxyphenyl)-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-(trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one) isolated from the leaves of *E. ulmoides* inhibited advanced glycation end products (AGEs) formation; this activity is comparable to that of aminoguanidine, a known glycation inhibitor (Hy et al. 2004). A study showed that astragalin decreased the overexpression of vascular endothelial growth factor (VEGF) in Müller cells and alleviated the effects caused by high glucose. Thus, astragalin has promising application in preventing and treating diabetic retinopathy caused by DM (Ke et al. 2012).

    Other activities: Other reported activities include anti-inflammatory activity (Kim and Kim 2011).

24. Astragaloside IV (triterpene)

    Plant source: *Celastrus vulcanicola*

    Anti-diabetes: This triterpene compound showed anti-DM activity in HFD-fed streptozotocin diabetic rats. The treatment-reduced blood glucose levels and influenced positively glucose regulating enzymes in the liver of the diabetic rats (Lv et al. 2010).

    Other activities: Astragaloside IV exhibited protective effects on the cardiovascular, immune, digestive, and nervous system. The mechanisms of actions were associated with regulation of the calcium balance, antioxidant, antiapoptosis, and antivirus activities (Ren et al. 2013).

25. Atractans A, B, and C (glycans)

    Plant source: *Atractylodes japonica*

    Anti-diabetes: Atractans A, B, and C (glycans) exerted significant hypoglycemic actions in normal and alloxan-induced hyperglycemic mice (Konno et al. 1985d).

26. Azorellanol and mulinolic acid (diterpenoids)

    Plant source: *Azorella compacta*

    Anti-diabetes: Administration of mulinolic acid or azorellanol to the diabetic rats markedly reduced the hyperglycemia and the effect was comparable to that of chlorpropamide. Azorellanol treatment resulted in elevation of serum insulin levels in the diabetic rats, but mulenic acid did not influence serum insulin levels (Fuentes et al. 2005). Thus, the studies indicated the presence of two anti-DM compounds which act through different mechanisms in *A. compacta*.

    Other activities: These diterpenoids showed relevant gastroprotective activity at low doses in rodents.

27. Bacosine, a triterpene

    Plant source: *Bacopa monnieri*

    Anti-diabetes: Bacosine, from ethanol extract of *B. monnieri*, produced a significant decrease in the blood glucose level in alloxan diabetic rats when compared with the diabetic control rats both in the single administration as well as in the multiple administration study. Repeated administration of the compound reversed the weight loss of the diabetic rats and increased glycogen content in the liver. Furthermore, administration of bacosine decreased the levels of malondialdehyde and increased the levels of reduced glutathione and the activities of superoxide dismutase (SOD) and catalase in the liver of diabetic rats. Bacosine prevented elevation of glycosylated hemoglobin *in vitro* with an IC_{50} value of 7.44 μg/mL. Bacosine increased glucose utilization in the diaphragm of diabetic rats *in vitro*, which is comparable with the action of insulin. Thus, bacosine might have insulin-like activity and its antihyperglycemic effect might be due to an increase in peripheral glucose consumption as well as protection against oxidative damage in alloxanized diabetes (Ghosh et al. 2011).

28. Baicalein (5,6,7-trihydroxyflavone)

    Plant source: *Scutellaria baicalens*

    Anti-diabetes: Baicalein (5,6,7-trihydroxyflavone) inhibited human intestinal sucrase expressed in Caco-2 cells (Nishioka et al. 1988). Furthermore, it is an inhibitor of rat intestinal α-glucosidase; the inhibitory mechanism of baicalein against α-glucosidase was suggested to be a mixed type inhibition (Gao et al. 2004).

    Other activities: Baicalein reduces oxidative stress-induced DNA damage by upregulating the DNA repair system (Kim et al. 2012).

29. Bakuchiol

    Plant source: *Psoralea corylifolia*

    Anti-diabetes: Bakuchiol isolated from *P. corylifolia* seed inhibited PTP1B (Jiang et al. 2012).

    Other activities: other reported activities of this compound include anti-inflammation, antimicrobial activity, antioxidant activity, and antitumor activity (Chen et al. 2010).

30. Baohuoside I (a flavonol)

    Plant source: Baohuoside I is one of the major components of medicinal plants such as *Herba epimedii*, *Cortex periplocae*, and *Epimedium brevicornum*. It is also known as icariside II.

    Anti-diabetes: Baohuoside I, a flavonol from the leaves of *E. brevicornum*, exhibited strong inhibition against the α-glucosidase (Phan et al. 2013).

    Other activities: Baohuoside I (icariside II) exerted anticancer activity by causing apoptosis and influencing multiple signaling pathways in cancer cells (Khan et al. 2015).

31. Bassic acid, an unsaturated triterpene acid

    Plant source: *Bumelia sartorum*, *Mimusops elangii*, and so on.

Anti-diabetes: Bassic acid, isolated from the ethanol extract of the root bark, exhibited a hypoglycemic effect in alloxan-induced diabetic rats. Bassic acid treatment increased plasma insulin levels significantly in alloxan-diabetic rats. The hypoglycemic potential was also demonstrated *in vitro* using isolated rat diaphragm (Naik et al. 1991).

Other activities: Bassic acid showed antileishmanial activity in animal studies (Lala et al. 2006).

32. Bauerenone and bauerenol

    Plant source: *Anthocleista schweinfurthii*

    Anti-diabetes: Bauerenone and bauerenol were found to be highly promising α-glucosidase inhibitors (Mbouangouere et al. 2007).

33. Bellidifolin (a xanthone)

    Plant source: Bellidifolin is found in plants such as *Swertia japonica*, *Swertia randaiensis*, *Gentiana campestris*, *Gentiana karelinii*, *Gentiana algida*, and *Swertia punctata* (Singh 2008).

    Anti-diabetes: Bellidifolin (a xanthone) isolated from the ethyl acetate fraction *S. japonica* showed a potent and dose-dependent hypoglycemic activity in streptozotocin-induced diabetic rats, both in i.p. and p.o. administration (Basnet et al. 1994). Besides, bellidifolin-stimulated glucose uptake in rat fibroblasts (Basnet et al. 1995).

    Other activities: Other reported pharmacological properties include anticholinesterase activity, cerebral vasodilatory effect, and hypolipidemic property (Singh 2008).

34. Benzodioxane, lignin

    Plant source: *Artemisia minor*

    Anti-diabetes: 1,4-Benzodioxane, isolated from the methanol extract of *A. minor*, inhibited PTP1B with an IC_{50} of 1.62 μg/mL (Jiang et al. 2012).

35. Berberine

    Plant source: Berberine alkaloid is present in *Berberis aristatica*, *Berberis brebissima*, *Berberis parkeriana*, *Chelidonium majus*, *Coptin chinensis*, *Phellodendron amurense*, *Tinospora cordifolia*, and so on. Berberine is the main alkaloid of *C. chinensis* (Ma et al. 2010). The chemical structure of berberine is shown in Figure 2.6.

    Anti-diabetes: Several studies have shown the anti-DM and hypolipidemic properties of this alkaloid. It improves insulin action by activating AMP-activated protein kinase, which helps in regulating the cellular uptake of glucose, oxidation of free fatty acids and the synthesis of GLUT4 (Arif et al. 2014). AMPK is a serine/threonine protein kinase; this enzyme is activated by several natural compounds such as berberine, resveratrol, epigallocatechin gallate and quercetin (Hardie 2013). Besides, berberine reduced the expression of the enzymes involved in fatty acid and cholesterol synthesis (Prabhakar and Doble 2011).

    Berberine mimics insulin action by increasing glucose uptake by 3T3-L1 adipocytes and L6 myocytes in an insulin independent manner inhibiting phosphatase activity of PTP1B and increasing phosphorylation of IR, insulin receptor substrate (IRS)1, and Akt in 3T3 L1 adipocytes. It does not increase insulin synthesis and release (Chen et al. 2010). Furthermore, it increases GLP-1

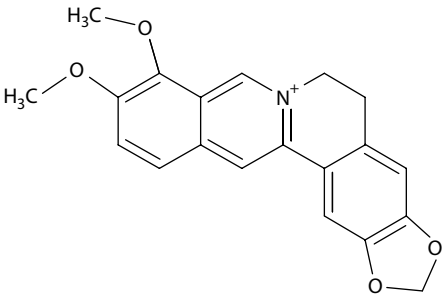


FIGURE 2.6 Structure of berberine.

secretion in streptozotocin-diabetic rats; *in vivo* 5-week treatment with berberine enhanced GLP-1 secretion induced by glucose load-promoted L-cell (GLP-1 secreting cell) proliferation in the intestine (Yu et al. 2010). Inhibition of protein kinase C (PKC) or AMPK inhibited berberine-mediated GLP-1 secretion. Some signaling pathways including PKC-dependent pathways are involved in promoting GLP-1 secretion and biosynthesis (Yu et al. 2010).

Experimentally, berberine was found to inhibit human recombinant DPP-4 *in vitro*. This inhibition is one of the mechanisms that explain the antihyperglycemic activity of berberine (Almasri et al. 2009). Protoberberine-type alkaloid present in the rhizome of *Coptis chinensis* inhibited rat lens aldose reductase activity (Jung et al. 2008).

A meta-analysis study suggests that berberine per se does not show glycemic control in type 2 diabetic patients. Berberine had a mild antidyslipidemic effect on patients. Combination treatment with other oral hypoglycemic agents showed better glycemic control than either treatment alone (Chang et al. 2013).

Other activities: Other reported activities include antiarthritis, anti-inflammation, and antiangiogenic activities (Wang et al. 2014).

36. Bergenicin and bergelin

    Plant source: In a recent study, two new compounds bergenicin and bergelin were isolated from aerial parts of *Bergenia himalaica* (Siddiqui et al. 2014).

    Anti-diabetes: Reduction in blood glucose levels was observed at 1 h (1.0 mg/kg) and 2 h (0.5 mg/kg), after bergenicin administration to streptozotocin- and nicotinamide-induced diabetic rats; and at 2 h (1.0 mg/kg) and 3 h (0.5 mg/kg), after bergelin administration. Bergenicin, but not bergelin, enhanced glucose-stimulated insulin secretion in isolated pancreatic islets (Siddiqui et al. 2014).

37. Bergenin

    Bergenin has been isolated from different parts of a number of plants. For example, bergenin is a major constituent of *Caesalpinia digyna*.

    Anti-diabetes: Bergenin from *C. digyna* roots exhibited significant anti-diabetic, hypolipidemic, and antioxidant activity in streptozotocin- and nicotinamide-induced type 2 DM in rats. Histopathological studies suggest the regenerative effect of bergenin on pancreatic β-cells. However, bergenin showed no significant effect on liver glycogen at all doses studied (Kumar et al. 2012b).

    Other activities: Bergenin exhibited antiviral, antifungal, antitussive, antiplasmodial, anti-inflammatory, antihepatotoxic, antiarrhythmic, antitumor, antiulcerogenic, and wound healing properties (Bajracharya 2015).

38. Betavulgaroside (glucuronide saponin)

    Plant source: *Beta vulgaris*

    Anti-diabetes: Betavulgaroside (glucuronide saponin), isolated from the root and leaves of *B. vulgaris*, showed hypoglycemic effects in rats (Yoshikawa et al. 1996a).

39. Betulin (triterpene)

    Plant source: Betulin (lup-20(29)-ene-3β,28-diol) is an abundant, naturally occurring triterpene. It can be converted to betulic acid (the alcohol group replaced by an acid group), which is biologically more active than betulin itself. Examples of plants containing betulin include *Betula papyrifera* (bark) and *Euclea undulata* (root and bark).

    Anti-diabetes: Betulin decreases blood glucose levels and inhibits α-glucosidase activity (Deutschlander et al. 2011). In another study, betulin specifically inhibited the maturation of sterol regulatory element-binding proteins (SREBP) by inducing interaction of SREBP cleavage activating protein. Inhibition of SREBP by betulin decreased the biosynthesis of cholesterol and fatty acid. *In vivo*, betulin ameliorated diet-induced obesity, decreased the lipid contents in serum and tissues, and increased insulin sensitivity. Furthermore, betulin reduced the size and improved the stability of atherosclerotic plaques (Tang et al. 2011).

    Other activities: Studies have shown that betulin (3β-lup-20(29)-en-3,28-diol) was effective against a variety of tumors. It induces apoptosis in cancer cells. Betulinic acid has gained a lot of attention

since it exhibited pharmacological properties such as anticancer activity, anti-HIV (human immunodeficiency virus) activity, antibacterial effect, and antimalarial activity (Moghaddam et al. 2012).

40. Betulinic acid

    Plant source: Betulinic acid is a naturally occurring pentacyclic lupine type triterpenoid. This compound is widely distributed in plants. The birch tree (*Betula* spp.) is a rich source of this compound. Other examples of betulinic acid containing plants include *Ziziphus* spp., *Diospyros* spp., and *Saussurea lappa* (Moghaddam et al. 2012).

    Anti-diabetes: Activity-guided fractionation of methanol extract of the root of *S. lappa* led to the isolation of four compounds (betulinic acid, methyl ester of betulinic acid, mokkolactone, and dehydrocostuslactone), which inhibit protein tyrosine phosphatase 1B (PTP1B). The authors suggest that betulinic acid is a potential lead molecule for the development of new PTP1B inhibitors to treat diabetes (Choi et al. 2009).

    Other activities: The reported medicinal properties of betulinic acid include inhibition of HIV, antibacterial, antimalarial, anti-inflammatory, anthelmintic, anticancer, and antinocicepive activities (Moghaddam et al. 2012).

41. Biochanin A

    Plant source: Biochanin A is found in red clover (*Trifolium pretense*), *Origanum vulgare*, *T. pretense*, and many other plants.

    Anti-diabetes: Biochanin A, isolated from the leaves of this plant-activated PPAR-γ *in vitro* (Mueller et al. 2008).

    Other activities: Biochanin A-inhibited fatty acid amide hydrolase both *in vitro* and peripherally *in vivo*. Furthermore, limited evidence suggests possible efficacy of red clover containing biochanin A in maintenance of bone health and improvement of arterial compliance, a risk factor for atherosclerosis (Thors et al. 2010).

42. Bixin

    Plant source: The carotenoids bixin and norbixin are present in the seeds of *Bixa orellana*.

    Anti-diabetes: Bixin and norbixin from *B. orellana* regulated mRNA expression involved in adipogenesis and enhanced insulin sensitivity in 3T3-L1 adipocytes through PPAR-γ activation (Wang et al. 2014). Norbixin showed hyperglycemic effect on rats and mice. But, toxicity of this compound to mice, but not to rats, was detected (Fernandes et al. 2002). Detailed studies are required to understand the species-dependent toxicity of this compound. Interestingly in a recent study bixin and norbixin showed opposite effects (Roehrs et al. 2014). Bixin treatment to streptozotocin-induced diabetic rats prevented protein oxidation, nitric oxide production, and restored superoxide dismutase activity. Norbixin treatment did not change these parameters, and at the highest dose, it increased low-density cholesterol (LDL) cholesterol and triglycerides levels and showed prooxidant action (increased protein oxidation and nitric oxide levels). These findings suggest that bixin could have an antihyperglycemic effect, could improve lipid profiles, and protect against damage induced by oxidative stress in the diabetic state. Because norbixin is a water-soluble analog of bixin, the authors proposed that lipophilicity is crucial for the protective effect of annatto carotenoids against streptozotocin-induced diabetes (Roehrs et al. 2014).

    Other activities: Administration of bixin to rats during and after whole-body radiation resulted in reduction in the levels of long collagen hydroxyproline and liver and serum lipid peroxide levels. Furthermore, bixin inhibited the activity of immunoglobulin (Ig) E in rat lymphocytes suggesting a possible antiallergic effect. In another study, bixin-induced liver monooxygenases in female rats (De-Oliveira et al. 2003).

43. Borapetol B

    Plant source: *Tinospora crispa*; the chemical structure of borapetol B is shown in Figure 2.7.

    Anti-diabetes: Acute oral administration of borapetol improved glucose tolerance in normoglycemic rats and spontaneously type 2 diabetic Gato-Kakizaki rats. Furthermore, borapetol B increased plasma insulin levels by twofold in the treated normoglycemic and spontaneously

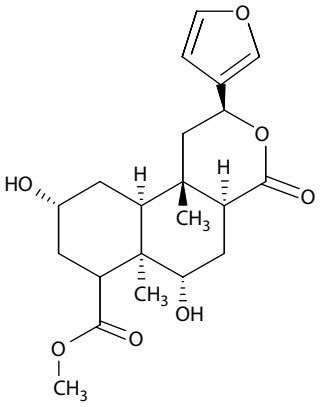


FIGURE 2.7 Structure of borapetol B.

type 2 diabetic rats at 30 min. Besides, this compound dose dependently increased insulin secretion from isolated islets obtained from normal and type 2 DM rats at 3.3 mM and 16.7 mM glucose. Thus, borapetol B exerts its DM activity by stimulating insulin secretion (Lokman et al. 2013). In a follow-up study, borapetol B-stimulated insulin release at both low and high glucose in islets from normoglycemic rats and spontaneously type 2 diabetic Goto-Kakizaki rats. The opening of K-adenosine triphosphate (ATP) channels by adding diazoxide inhibited insulin release from the islets at high glucose levels. Furthermore, the effect of borapetol B was partly dependent on pertussis toxin-sensitive G_e protein. Therefore, the major stimulatory effect of this compound might be on the exocytosis (Lokman et al. 2013).

44. Borapetosides

    Plant source: Three major diterpenoids (borapetosides A, B, and C) were isolated from ethanol extract of *Tinospora crispa* vines. Borapetoside A and C are active ingredients for lower plasma glucose.

    Anti-diabetes: Borapetoside C reduced plasma glucose levels and increased plasma insulin levels in normal and type 2 diabetic mice. The hypoglycemic effect was associated with increase of glucose utilization in peripheral tissue and reduction of gluconeogenesis in liver (Lam et al. 2012). In another study, this compound increased glucose utilization, delayed the development of insulin resistance, and enhanced insulin sensitivity in diabetic mice. Acute treatment with borapetoside C (5 mg/kg, i.p.) attenuated the elevated plasma glucose induced by oral glucose in normal and type 2 DM mice. Compared to the effect of injected insulin (0.5 IU/kg), borapetoside C caused a more prominent increase of glycogen content in skeletal muscle of type 2 DM mice, but a less increase in type 1 DM mice. Combined treatment of a low-dose borapetoside C (0.1 mg/kg, i.p.) plus insulin enhanced insulin-induced lowering of the plasma glucose level and insulin-induced increase of muscle glycogen content. Continuous treatment with 5 mg/kg borapetoside C (twice daily) for 7 days increased phosphorylation of insulin receptor (IR) and protein kinase B (Akt) as well as the expression of GLUT2 in type 1 DM mice. Combined treatment of a low-dose borapetoside C (0.1 mg/kg, twice daily) plus insulin for 7 days enhanced insulin-induced IR and Akt phosphorylation and GLUT2 expression in the liver of type 1 DM mice (Ruan et al. 2012). Borapetoside A was shown to increase the glycogen content and decrease the plasma glucose concentration in a concentration or dose-dependent manner *in vitro* and *in vivo*. The hypoglycemic effects in the normal mice and the mice with diet-induced type 2 diabetes mellitus were associated with the increases of the plasma insulin levels. Borapetoside A not only attenuated the elevation of plasma glucose induced by an i.p. glucose tolerance test, but also increased the glycogen synthesis of IL-6-treated C2C12 cells. Moreover, the elevated protein expression levels of phosphoenolpyruvate carboxykinase in the diabetic mice were reversed after borapetoside A treatment twice a day for 7 days (Ruan et al. 2013).

45. Boswellic acid

    Plant source: Boswellic acid is found in the gum resin of *Boswellia serrata*.

    Anti-diabetes: Under *in vitro* conditions boswellic acid isolated from gum resin of *B. serrata* inhibited aldose reductase in rat lens homogenate. Furthermore, boswellic acid (10 mg/kg) inhibited formation of AGEs in diabetic rats (Rao et al. 2013).

    Other activities: Major pharmacological activities of boswellic acid include induction of apoptosis, anti-inflammatory effects and antitumor activity. The efficacy of boswellic acids in the management of leukotriene-mediated inflammatory conditions has been established (Jing et al. 1999).

46. Brazilin (7,11b-dihydrobenz[b]indeno-[1,2-d] pyran-3,6a,9,10 (6H)- tetrol)

    Plant source: Brazilin (7,11b-dihydrobenz[b]indeno-[1,2-d]pyran-3,6a,9,10(6H)-tetrol) is a major and active compound found in *Caesalpinia sappan* heartwood.

    Anti-diabetes: Brazilin from *C. sappan* was found to have hypoglycemic action and increase glucose metabolism in experimental diabetic animals. Brazilin increased basal glucose transport in 3T3-L1 fibroblasts and adipocytes. However, insulin-stimulated glucose transport was not influenced by the compound. Autophosphorylation of the partially purified insulin receptor was not affected by brazilin treatment in 3T3-L1 fibroblasts. However, brazilin decreased the PKC activity in 3T3-L1 fibroblasts and adipocytes (Kim et al. 1995). Besides, brazilin exhibited antioxidant activity and inhibited adipocyte differentiation (Liang et al. 2013).

    Other activities: Pharmacological activities of this compound include antioxidant, antibacterial, anti-inflammatory, antiphotoaging, hypoglycemic, vasorelaxant, hepatoprotective, and antiacne activities (Nirmal et al. 2015).

47. Breviscapine (flavonoid)

    Plant source: Breviscapine is a flavonoid extracted from *Erigeron breviscapus*.

    Anti-diabetes: Breviscapine at a dose of 10 and 25 mg/kg/day (p.o.) exerted protective effects in the pathogenesis of cardiomyopathy induced by high glucose levels in streptozotocin diabetic rats via the PKC/NF-κB/c-fos signal transduction pathway (Wang et al. 2009). Furthermore, the compound (10 and 25 mg/kg/day; p.o.) ameliorated cardiac dysfunction and regulated myocardial calcium cycling proteins in streptozotocin diabetic rats (Wang et al. 2010). It was shown that treatment with breviscapine attenuated renal injury in the diabetic rats. Furthermore, the combination of enalapril and breviscapine conferred superiority over monotherapies on renoprotection in diabetic rats. The mechanism of action may be, at least partly, correlated with synergetic suppression of increased oxidative stress and PKC activities as well as overexpression of TGF-β1 in renal tissue (Xu et al. 2013).

    Other activities: Other reported activities include antioxidant activity in cerebral ischemia–reperfusion in rats, protection against apoptosis induced by transient focal cerebral ischemia in rats, induction of apoptosis of human hepatocellular carcinoma cell line HepG2, and so on (Wu et al. 2010; Yiming et al. 2008).

48. Bruceine D and E (quassinoids)

    Plant source: *Brucea javanica*

    Anti-diabetes: Butanol extract of *B. javanica* contained blood glucose-lowering quassinoids bruceine D and E (Shahida et al. 2011).

    Other activities: Quassinoids isolated from *B. javanica* are reported to have cytotoxic activity *in vitro*. Bruceantin was tested in phase I clinical cancer trials, but no tumor regression was observed (WHO 1999).

49. Caffeic acid

    Plant source: Caffeic acid (3,4-dihydroxycinnamic acid) is phenolic acid present in many plants and occurs in the diet as part of fruits, tea, coffee, and wine.

    Anti-diabetes: Caffeic acid occurs naturally in many agriculture products. After an i.v. injection of caffeic acid (from the fruit of *X. strumarium*) into diabetic rats of both streptozotocin-induced

and insulin-resistant models, a dose-dependent decrease of plasma glucose was observed. However, a similar effect was not produced in normal rats (Hsu et al. 2000). Furthermore, this compound reduced the elevation of plasma glucose level in insulin-resistant rats receiving a glucose tolerance test. Also, glucose uptake into the isolated adipocytes was raised by caffeic acid in a concentration-dependent manner (Hsu et al. 2000). Caffeic acid isolated from the aerial parts of *A. minor* was found to be a tyrosine phosphatase 1B (PTP1B) inhibitor with an IC_{50} value of 3.06 μmol/L (Jiang et al. 2013).

Other activities: Caffeic acid has a broad spectrum of pharmacological properties including antioxidant activity, hepatoprotective activity, anti-inflamatory activity, and immunomodulatory property. Interestingly, a study demonstrated that caffeic acid improved memory and interfered with the cholinergic signaling (Anwar et al. 2012).

50. Caffeoylquinic acid (polyphenol)

    Plant source: *Ipomoea batatas*

    Caffeoylquinic acid isolated from the leaf extract of *I. batatas* enhanced GLP-1 secretion *in vitro* (Nagamine et al. 2014). The leaf extract containing caffeoylquinic acid enhanced GLP-1 levels in type 2 diabetic mice (Nagamine et al. 2014).

51. Calystegines (alkaloids)

    Plant source: The polyhydroxylated nortropane alkaloids called calystegines occur in many plants of the Convolvulaceae, Solanaceae, and Moraceae families including many dietary fruits and vegetables.

    Anti-diabetes: Calystegine B2 is a potent inhibitor of β-glucosidases and β-galactosidases (Griffiths et al. 1996). Calystegines A3 and B2 selectively inhibited the rat liver β-glucosidase activity. It also showed potent inhibitory effect on mammalian β-glucosidase and α-galactosidase activities *in vitro*. This raises the possibility of toxicity in humans consuming large amounts of plants that contain these compounds (Asano et al. 1997). However, the glucosidase inhibitors have a potential for the treatment of diabetes because they reduce diet-induced hyperglycemia and endogenous insulin secretion (Gaikwad et al. 2014).

52. Capsaicin

    Plant source: Capsaicin in a pungent alkaloid found primarily in the fruits of *Capsicum* spp. such as *Capsicum annum*.

    Anti-diabetes: The effect of dried red chili pepper at 1% and 2% and the pure capsaicin at 0.015% in the diet were studied in HFD-fed alloxan diabetic rats. Blood serum glucose levels were markedly reduced in the diabetic group fed HFD + 0.015% capsaicin compared to diabetic control animals. The decrease was less in the red chili fed groups compared to that in capsaicin fed diabetic rats. The HDL concentration for the groups fed with red chili or capsaicin were significantly higher than that in diabetic control rats fed with HFD (Magied et al. 2014).

    Other activities: Capsaicin has many biological activities including binding to its receptor (vanilloid 1 receptor) present primarily in the sensory neurons; it participates in release of somatostatine, endotheline, and so on; it reduces adipose tissue in rodents by stimulating energy and lipid metabolism; it is used topically to treat pain syndromes; and it causes substance P depletion (Reyes-Escogido et al. 2011).

53. Carnosic acid and carnosol (phenolic diterpenes)

    Plant source: Carnosol and carnosic acid (phenolic diterpene compounds) are found in plants such as *Rosmarinus officinalis* and *Salvia officinalis*.

    Anti-diabetes: Carnosic acid and carnosol from *R. officinalis* activated the human PPAR-γ (Wang et al. 2014).

    Other activities: Carnosol and carnosic acid, two major components of rosemary extracts, have shown activity for cancer prevention and therapy including antiangiogenic properties (Lopez-Jimenez et al. 2013). These compounds inhibited microsomal prostaglandin E_2 synthase 1 also (Bauer et al. 2012).

54. Carvacrol

    Plant source: Carvacrol is a monoterpenic phenol produced by an abundant number of aromatic plants, including *Thymus vulgaris*.

    Anti-diabetes: Carvacrol, a component of thyme oil, activated PPAR-α and -γ and suppressed COX-2 expression (Wang et al. 2014). Furthermore, *in vivo* studies are required to establish its anti-DM property.

    Other activities: Results from *in vitro* and *in vivo* studies show that carvacrol possess a variety of biological and pharmacological properties including antioxidant, antibacterial, antifungal, anti-cancer, anti-inflammatory, hepatoprotective, spasmolytic, and vasorelaxant (Suntres et al. 2015).

55. Castanospermine (alkaloid)

    Plant source: Castanospermine (1*S*,6*S*,7*R*,8*R*,8a*R*—1,6,7,8-tetrahydroxyindolizidine) is an indolizine alkaloid; it was firstly isolated from the seeds of the monotypic Australian species *Castanospermum australe*.

    Anti-diabetes: The seed of *C. australe* contains the alkaloid castanospermine; this compound exhibited hypoglycemic activity and inhibited intestinal maltase and sucrose activity in normal and streptozotocin-treated rats (Ghisalberti 2005; Peng et al. 2014).

    Other activities: In addition to diabetes, castanospermine has been found to have tremendous potential in viral infection, immunosuppressive deficiencies, and tumor metastasis (Peng et al. 2014).

56. Casuarines (alkaloids)

    Plant source: Casuarines are found in *Casuarina equisetifolia* L.

    Anti-diabetes: Casuarine 6-O-α-glucoside showed anti-diabetes activity (Gaikwad et al. 2014). Casuarine was a much more potent inhibitor of α-D-glucosidases [rice α-D-glucosidase (IC_{50}: 1.2 (μM) and rat intestinal maltase (IC_{50}: 0.7 μM)] than casuarine-6-O-α-glucoside [rice α-D-glucosidase (IC_{50}: 440 μM) and rat intestinal maltase (IC_{50}: 260 μM)]. In contrast, casuarine-O-α-glucoside from almond was a more active inhibitor of β-D-glucosidase (IC_{50}: 7.0 μM). Both compounds were potent inhibitors of amyloglucosidase from *Aspergillis niger* (Ritthiwigrom and Pyne 2012).

57. Catechin

    Plant source: Catechin and related phytochemicals are reported from *Camellia sinensis*, *Nelumbo nucifera*, *Cinnamomum* sp., *Eriobotrya japonica*, *Euclea undulate*, and *Pterocarpus marsupium nucifera*, *Prunus amygdalus.* This compound is present in many other plants also. Of all the catechins found in *C. sinensis* leaf [(–)-epicatechin-3-gallate, (–)-epigallocatechin, (–)-epicatechin and (–)-epigallocatechin-3-gallate] (–)-epigallocatechin-3-gallate is the most abundant and powerful (see under epicatechin).

    Anti-diabetes: In an *in vitro* study, catechin promoted adipocyte differentiation in human bone marrow mesenchymal stem cells through PPAR-γ activation (Wang et al. 2014). Catechin has α-amylase inhibitory activity also (Liu et al. 2014).

    Other activities: Thus far, numerous pharmacological activities regulating disease-specific molecular targets have been reported *in vitro* for (–)-epigallocatechin-3-gallate concentrations in the micromolar range, which are physiologically irrelevant (Mak 2012).

58. Catharanthine (alkaloid)

    Plant source: Catharanthine is found in *Catharanthus rosus*. Catharanthine is a precursor of the antitumor drugs vinblastine and vincristine, formed by dimerization of catharanthine with vindoline.

    Anti-diabetes: Catharanthine (methyl (18β)-3,4-didehydroibogamine-18-carboxylate) and related compounds lowered blood glucose levels in normal and streptozotocin-induced diabetic rats (Gaikwad et al. 2014).

    Other activities: Catharanthine itself is an inhibitor of tubulin self-assembly into microtubules, although not so potent as vinblastine or vincristine. Catharanthine has anticholinergic activity. It showed muscarinic antagonism and fully inhibited nicotinic receptor-mediated diaphragm contractions.

59. Centellsapogenol A, a triterpene

    Plant source: *Centella asiatica*

    Anti-diabetes: Centellsapogenol A, a triterpene, from *C. asiatica* inhibited aldolase reductase (Matsuda et al. 2001).

60. Chalcomoracin

    Plant source: *Morus alba*

    Anti-diabetes: Chalcomoracin, moracin C, moracin D, and moracin M isolated from *M. alba* inhibited α-glucosidase activity (Firdous 2014).

61. Chalepin

    Plant source: Chalepin is found in plants like *Clausena lansium* and *Ruta angustifolia*.

    Anti-diabetes: Chalepin and imperatorin were the major anti-DM constituents of *C. lansium*. Chalepin increased *in vitro* insulin release (138%) (Adebajo et al. 2008).

    Other activities: Chalepin isolated from *R. angustifolia* leaves inhibited hepatitis C virus replication (Wahyuni et al. 2014).

62. Charantin (steroidal saponins)

    Plant source: Charantin is present in *Momordica charantia*, bitter guard, an important anti-DM medicinal herb. Charantin is a typical cucurbitane type triterpenoid. It is a mixture of two closely related compounds, sitosteryl-3-O-β-glycoside, and stigmasteryl glucoside (Pitiphanpong et al. 2007). Chemical structure of sitosteryl-3-O-β-glycoside is shown in Figure 2.8.

    Anti-diabetes: A few studies have established the hypoglycemic and anti-DM properties of charantin (Joseph and Jini 2013). In one study, in fasting rabbits, charantin gradually lowered blood sugar within one to four hours and recovered slowly to initial level. At an oral dose of 50 mg/kg, blood sugar level was declined by 42% at the fourth hour. The average blood sugar fall during 5 h was 28%. Charantin was found to be more potent than tolbutamide; however, both compounds produced similar patterns of blood sugar change. The hypoglycemic activity of charantin in depancreatized cats was less, indicating a pancreatic as well as extrapancreatic action (Desai and Tatke 2015). Various extracts and compounds of *M. charantia* are believed to exert their hypoglycemic effects by different mechanisms. Probable mechanisms of action of charantin include increase in the release of insulin and slowing down glucogenesis (Ng et al. 1986). There are many compounds related to charantin and anti-DM activity has been shown in some of them (Lee et al. 2009).

    Other activities: The effect of charantin on cardiovascular system was studied. At the dose of 800 mg/kg, 5–10% of blood pressure lowering of anaesthetized cat was observed. The contraction of isolated heart of frog was increased at dose of 5–10 mg and the same dose was effective to terminate action of acetylcholine. Antisialogogue activity was also reported. Charantin at dose of 10–15 mg/kg delayed the onset of tremors but did not affect salivation produced by tremorine (Desai and Tatke 2015).

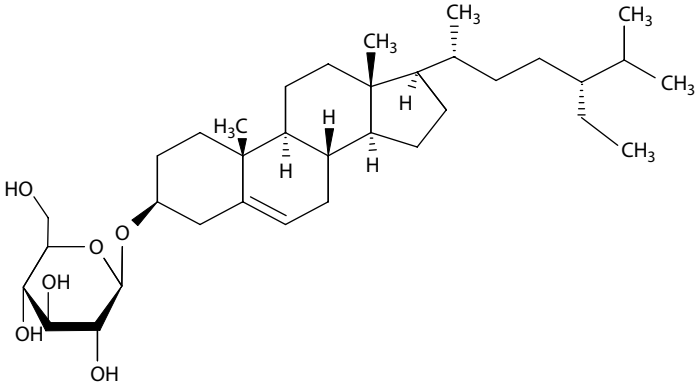


FIGURE 2.8 Structure of a component of charantin (sitosteryl-3O-β-D-glycoside).

63. Chicoric acid

    Plant source: Chicoric acid is found in plants such as *Ocimum gratissimum* and *Cichorium intybus*.

    Anti-diabetes: Chicoric acid (phenolic compound) isolated from *O. gratissimum* leaf reduced the glycemic level of streptozotocin-induced diabetic mice at 2 mg/kg level (Casanova et al. 2014). In another study, daily intraperitoneal (i.p.) administrations of a natural chicoric acid extract from *C. intybus* for 4 days to rats improved i.p. glucose tolerance in a dose-dependent manner mainly via an insulin sensitizing effect. The antihyperglycemic effect was essentially due to a peripheral effect on muscle glucose uptake (Azay-Milhau et al. 2013).

    Other activities: L-chicoric acid is an inhibitor of HIV-1 integrase *in vitro* and of HIV-1 replication in tissue culture. Furthermore, chicoric acid positively regulated behavioral and biochemical alterations induced by chronic stress in experimental albino mice (Kour and Bani 2011).

64. Chlorogenic acid (3-caffeoylquinic acid)

    Plant source: Chlorogenic acid is present in many plant sources. These include *Artemisia herba-alba*, *Carissa edulis*, *Cerepia obtusifolia* (rich in this compound), *Coffea arabica*, *Exostema paniculata*, *Eriobotrya japonica*, *Ficus carica*, *Hintonia latiflora*, *Ilex paraguariensis*, *Lonicerae japonica*, and *Perilla frutescens*. Chlorogenic acid is a polyphenol and the ester of caffeic acid and quinic acid. The chemical structure of chlorogenic acid is shown in Figure 2.9.

    Anti-diabetes: Chlorogenic acid is a major component of coffee, and it is present in many other plants and is being recognized as an important anti-diabetic compound. This phenolic compound stimulated glucose uptake in insulin-resistant and sensitive 3T3 adiposites. It reduces glucose-6-phosphate levels (Cetto and Heinrich 2005; Meng et al. 2013).

    Chlorogenic acid has been shown to delay intestinal glucose absorption and inhibit gluconeogenesis. It inhibits glucose-6-phosphate translocase 1 and reduces the sodium gradient-driven apical glucose transport. Besides, *in vitro* and animal studies on chlorogenic acid and its derivatives showed that these substances can decrease the hepatic glucose output through inhibition of glucose-6-phospatase. Furthermore, chlorogenic acid exerts antioxidant effects also. This may have beneficial effects on glucose metabolism as oxidative stress plays a role in the development of insulin resistance and type 2 diabetes. Chlorogenic acid can act as a metal chelator, and chlorogenic acid changed the soft tissue mineral composition (e.g., increased magnesium concentrations in the liver) in rats. This change in mineral composition may have improved glucose tolerance (Bisht and Sisodia 2010).

    In db/db mice, a significant decrease in fasting blood sugar was observed 10 min after the i.p. administration of 250 mg/kg chlorogenic acid and the effect persisted for another 30 min after the glucose challenge. Besides, chlorogenic acid stimulated and enhanced both basal and insulin-mediated glucose transports in soleus muscle. In L6 myotubes, chlorogenic acid caused a dose- and time-dependent increase in glucose transport. Chlorogenic acid was found to phosphorylate AMPK, consistent with the result of increased AMPK activities. Chlorogenic acid did not appear to enhance association of IRS1 with p85. However, activation of Akt by chlorogenic acid was observed. These parallel activations in turn increased translocation of GLUT4

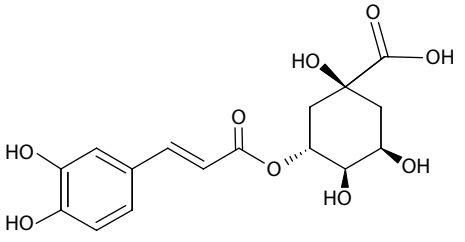


FIGURE 2.9 Structure of chlorogenic acid (3-caffeoylquinic acid).

to plasma membrane. At 2 mmol/L, chlorogenic acid did not cause any significant changes in viability or proliferation of L6 myotubes. Chlorogenic acid stimulated glucose transport in skeletal muscle via the activation of AMPK. It appears that chlorogenic acid may contribute to the beneficial effects of coffee on type 2 diabetes mellitus (Ong et al. 2012).

3,5-Dicaffeoylquinic acid from *Ilex paraguariensis* significantly elevated serum GLP-1 levels in ddY mice. However, the compound did not inhibit DPP-1 activity. This suggests that the compound increases GLP-1 production (Chang et al. 2013).

Other activities: Chlorogenic acid has potential antioxidant and chemopreventive activities. Chlorogenic acid scavenges free radicals, which inhibits DNA damage and may protect against the induction of carcinogenesis. In addition, this agent may upregulate the expression of genes involved in the activation of the immune system and enhances activation and proliferation of cytotoxic T-lymphocytes, macrophages, and natural killer cells. Chlorogenic acid also inhibits the activity of matrix metalloproteinases. The evidence from published randomized clinical trials suggests that chlorogenic acid intake causes statistically significant reductions in systolic and diastolic blood pressures. The size of the effect is moderate (Onakpoya et al. 2015).

65. Christinin-A (saponin glycoside)

    Plant source: Christinin is present in *Ziziphus spina-christi*; the chemical structure of christinin-A is shown in Figure 2.10.

    Anti-diabetes: Pretreatment with *Z. spina-christi* leaf butanol extract (100 mg/kg) or christinin-A, the major saponin glycoside of the leaves, potentiated glucose-induced insulin release in normal rats. In type 2 but not in type 1 diabetic rat, pretreatment with the butanol extract or christinin-A improved the oral glucose tolerance and potentiated glucose-induced insulin release. Treatment either with butanol extract (100 mg/kg) or christinin-A reduced the serum glucose level and increased the serum insulin level of nondiabetic and type 2 diabetic rats but not of type 1 diabetic rats. Pretreatment of nondiabetic normal and type 2 diabetic rats either with 100 mg/kg butanol extract or christinin-A also enhanced the glucose lowering and insulinotropic effect of glibenclamide. The hyperglycemic and hypoinsulinemic effects of 30 mg/kg diazoxide in nondiabetic control and type 2 diabetic rats were inhibited and antagonized respectively by pretreatment with the butanol extract or christinin-A. The safe insulinotropic and subsequent hypoglycemic effects of christinin-A may be due to a sulfonylurea-like activity (Abdel-Zaher et al. 2005).

66. Chrysoeriol

    Plant source: Chrysoeriol is a flavonoid compound found in several tropical *medicinal* plants. For example, chrysoeriol is found in *Hyphaene thebaica*, *Eurya cilliata*, *Otostegia persica*, and *Urena lobata*

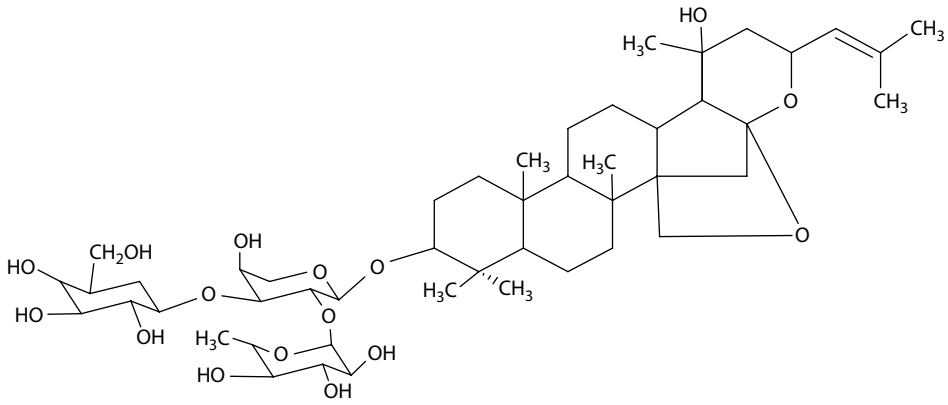


FIGURE 2.10 Structure of christinin A.

Anti-diabetes: Chrysoeriol (7-O-β-D-galactopyranosyl (1-2)-α-L-arabinofuranoside) isolated from the epicarp of *H. thebaica* fruit significantly reduced serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatine levels in the diabetic rats, indicating improvement in liver and kidney functions (Salib et al. 2013).

Other activities: Chrysoeriol exhibited potent antioxidant activity comparable with vitamin E and butylated hydroxytoluene (BHT) (Tofighi et al. 2014). Chrysoeriol isolated from *E. cilliata* leaves protected MC3T3-E1 cells against hydrogen peroxide-induced inhibition of osteoblastic differentiation (Kim et al. 2010).

67. Chrysophanol

Plant source: *Saussurea lappa*, *Rheum rhabarbarum*, and so on.

Anti-diabetes: Chrysophanol and its glucopyranoside derivatives with PTP1B inhibitory activity were obtained from the ethanol extract of the root (Jiang et al. 2012). Chrysophanol-8-O-β-D-glucopyranoside up to 25 μM dose dependently activated glucose transport in insulin-stimulated myotubes. Chrysophanol up to 100 μM exerted mild glucose transport activity and elevated the tyrosine phosphorylation of IR via tyrosine phosphatase 1B inhibition in myotubes; GLUT4 mRNA expression was also significantly increased by 100 μM chrysophanol. Therefore, these two anthraquinones from rhubarb (*R. rhabarbarum*) rhizome, chrysophanol-8-O-β-D-glucopyranoside and chrysophanol, have anti-diabetic properties and could play metabolic roles in the insulin-stimulated glucose transport pathway (Lee and Sohn 2008). There is an urgent need to carry on *in vivo* studies.

Other activities: Chrysophanol showed anti-inflammatory activity through the suppression of NF-kappaB/caspase-1 activation *in vitro* and *in vivo* (Kim et al. 2010).

68. Cinchonain Ib

Plant source: *Eriobotrya japonica*

Anti-diabetes: Cinchonain Ib enhanced significantly insulin secretion from INS-1 cells. Cinchonain Ib at a dose of 108 mg/kg enhanced plasma insulin levels in rats for as long as 240 min after oral administration, but it did not induce any change in blood glucose levels (Qadan, et al. 2009).

69. Cinnamaldehyde

Plant source: Cinnamaldehyde is found in the bark of *Cinnamomum* sp. The bark is used as a spice.

Anti-diabetes: Cinnamaldehyde (20 mg/kg, daily for 4 weeks) showed antihyperglycemic and antihyperlipidemic actions in C57BLKS/J db/db mice. Furthermore, the treatment decreased mRNA expression of TNF-α in adipose tissue (Li et al. 2012). In another study, oral administration of cinnamaldehyde produced significant antihyperglycemic effect in streptozotocin diabetic rats. Furthermore, the treatment lowered both total cholesterol and triglyceride levels and, at the same time, increased HDL in the diabetic rats. This investigation revealed the potential of cinnamaldehyde for use as a natural oral agent, with both hypoglycemic and hypolipidemic effects (Subash-Babu et al. 2007). Furthermore, cinnamaldehyde protected streptozotocin-induced pancreatic β-cells damage in Wistar rats via antioxidative and antiperoxidative effects (Subash-Babu et al. 2014).

Other activities: Pharmacological properties of cinnamaldehyde include antimicrobial activity; stimulation of histamine release and increase in cell-mediated immunity; and inhibition of nitric oxide (NO) production in RAW 269.4 cells (Lee et al. 2002).

70. Cinnamtannin B1

Plant source: Cinnamtannin B1 is a double-linked flavan-3-ol trimer known as A-type proanthocyanidin. Cinnamtannin B1 is reported from *Cinnamomum cassia*, *Cinnamonum zylanicum*, and other related species. The chemical structure of cinnamtannin B1 is shown in Figure 2.11.

Anti-diabetes: Actions of cinnamtannin B1 include a reduction in postprandial intestinal glucose absorption by inhibiting the activity of enzymes involved in carbohydrate metabolism

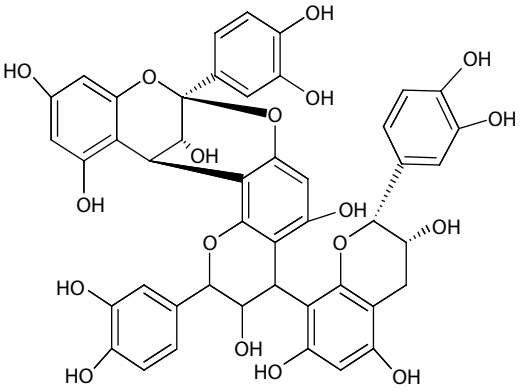


FIGURE 2.11 Structure of cinnamtannin B1.

(pancreatic α-amylase and α-glucosidase); stimulation of cellular glucose uptake by translocation of GLUT4 to the membrane; stimulation of glucose metabolism and glycogen synthesis; inhibition of gluconeogenesis by influencing key regulatory enzymes; and stimulation of insulin release and potentiation of insulin signaling (Bandara et al. 2012). *In vitro* studies were carried out on the activity on cinnamtannin B. The compound promoted 3T3-L1 cell proliferation approximately twofold at 48 h after treatment. Addition of cinnamtannin B1 into the culture of 3T3-L1 adipocyte increased glucose consumption up to 32%. Cinnamtannin B1 stimulated phosphorylation of insulin receptor subunit. There was no phosphorylation of insulin receptor observed in 3T3-L1 preadipocytes. The activity of cinnamtannin B1 in stimulating glucose uptake and phosphorylation were inhibited by Wortmannin and cytochalasin B. The results demonstrated that activity of cinnamtannin B1 mimics insulin action. They acted directly on insulin receptor subunit and activation of phosphoinositide 3 (PI3)-kinase that stimulates glucose transporter-4 (GLUT4) translocation. Stimulation of GLUT4 translocation stimulates glucose uptake leading to glucose disposal process in adipocytes (Taher 2005).

Other activities: Cinnamtannin B1 is a potent antioxidant.

71. Clausenacoumarine

    Plant source: Clausenacoumarine is a compound isolated from the leaves of *Clausena lansium*, which grows widely in South China.

    Anti-diabetes: Clausenacoumarine, isolated from the leaves of *C. lansium* (200 mg/kg for 3 days p.o.), lowered blood glucose level in normal mice and alloxan-induced diabetic mice and antagonized the elevation of blood glucose caused by injecting adrenaline in normal mice. No effect on blood lactic acid was observed (Shen et al. 1989).

72. Coagulin L

    Plant source: Coagulin L is a withanolide present in *Withania coagulans* and certain other plants of the Solanaceae family.

    Anti-diabetes: Coagulin L (a withanolide) has shown potential to inhibit adipogenesis significantly, which can be therapeutically exploited for treatment of obesity and metabolic syndrome. The study showed that coagulin-L reduces the expressions of PPAR-γ and CCAAT/enhancer-binding protein α (C/EBPα), the major transcription factors orchestrating adipocyte differentiation. Detailed analysis further proved that early exposure of coagulin-L is sufficient to cause significant inhibition during adipogenesis. Coagulin-L inhibited mitotic clonal expansion by delayed entry in G1 to S phase transition and S-phase arrest. This mitotic clonal expansion blockade was caused apparently by decreased phosphorylation of C/EBPβ, modulation in expression of cell cycle regulatory proteins, and upregulation of Wnt/β-catenin pathway, the early stage regulatory proteins of adipogenic induction (Beg et al. 2014).

Other activities: Withanolides have shown a wide range of pharmacological activities including immunomodulatory, anti-inflammatory, antiarthritic, angiogenesis inhibition, anticholinesterase, antioxidant, antibacterial, and antitumor activities (Singh et al. 2010).

73. Commipheric acid

    Plant source: Commipheric acid is isolated from the gum of the tree *Commiphora mukul*.

    Anti-diabetes: Commipheric acid, isolated from the ethyl acetate extract of the gum of the tree, activated PPAR-α and PPAR-γ that may contribute to the anti-diabetic activity of guggulipid in Lep(ob)/Lep(ob) mice (Wang et al. 2014).

74. Conglutin-γ (glycoprotein)

    Plant source: *Lupinus mutabilis*

    Anti-diabetes: A lupin seed glycoprotein known as conglutin-γ was found to causes significant plasma glucose reduction when orally administered to rats in a glucose tolerance test. The glucose-lowering effect of this protein is comparable to that of metformin (Magni et al. 2004). Conglutin- γ in its native conformation is unusually resistant to proteolysis by trypsin. *In vitro* studies, in cultured myoblastic C2C12 cells, have shown that conglutin-γ stimulation of cells results in the persistent activation of protein synthetic pathway kinases and increase in glucose transport, and GLUT4 translocation to the membrane. It appears to stimulate the same insulin-signaling pathways (Terruzzi et al. 2011). Furthermore, lupin seed conglutin-γ lowered blood glucose in hyperglycemic rats and increased glucose consumption of HepG2 cells. When the glycoprotein (conglutin-γ) was administered for 28 days at a daily p.o. dose of 28 mg/kg to rats in which hyperglycemia was induced by providing drinking water with 10% glucose, the treatment attenuated the rise in the levels of plasma glucose and insulin. Besides, fasting insulin levels and insulin resistance were decreased in conglutin-γ treated rats. Moreover, conglutin-γ increased glucose consumption by HepG2 cells under cell culture conditions. In this *in vitro* model conglutin-γ potentiated the activity of insulin and metformin (Lovati et al. 2012). In another study, γ-conglutin-enriched preparation was tested in a glucose overload trial with both murine models and adult healthy volunteers. The results with rats showed a dose-dependent decrease of blood glucose concentration, which confirmed previous findings obtained with the purified protein. Moreover, three test product doses equivalent to 630, 315, and 157.5 mg γ-conglutin, orally administered 30 min before the carbohydrate supply, showed a relevant hypoglycemic effect in human trials. Insulin concentrations were not significantly affected. This is the first report on the glucose-lowering effect of lupin γ-conglutin in human subjects (Bertoglio et al. 2011).

75. Conophylline (alkaloid)

    Plant source: Sources of canophylline include *Ervatamia microphylla*, *Tabernaemontana divaricate*, and *Tabernaemontana bufalina*. The chemical structure of canophylline is shown in Figure 2.12.

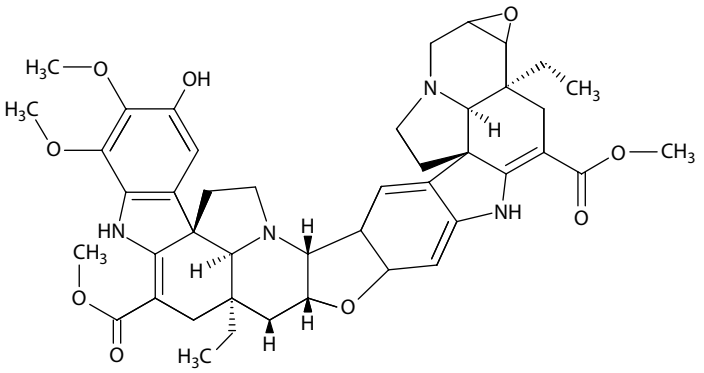


FIGURE 2.12 Structure of conophylline.

Anti-diabetes: Conophylline isolated from *E. microphylla* is known to induce the differentiation of pancreatic precursor cells (progenitor) cells to insulin-producing β-cells *in vitro*. The compound promoted β-cell differentiation in fetal and neonatal rat pancreas (Ogata et al. 2004). In another study, this alkaloid decreased the blood glucose level and increased the plasma insulin level in streptozotocin-induced diabetic rats after repetitive administration (0.11 and 0.46 mg/kg/day for 15 days). Conophylline also decreased the fasting blood glucose level in Goto-Kakizaki rats in a dose-dependent manner after daily administration for 42 days. These results suggest that the extract from conophylline-containing leaves may be useful as a functional food for the treatment of type 2 diabetes mellitus (Chang et al. 2013; Fujij et al. 2009).

Other activities: Conophylline downregulates the expression of the TNF-α receptors on the cell surface. It was found to inhibit TNF-α-induced NF-κB activation.

76. Corosolic acid (α-hydroxy ursolic acid)

    Plant source: Corosolic acid is reported from *Eriobotrya japonica*, *Lagerstroemia speciosa*, *Symplocos paniculata*, *Vitex leucoxylon*, and so on. The chemical structure of corosolic acid is shown in Figure 2.13.

    Anti-diabetes: Corosolic acid, triterpene acid, from *S. paniculata* inhibited PTP1B activity and the IC_{50} value was 7.2 μM (Nazaruk and Borzym-Kluczyk 2014). This compound containing gel (Glucosol TM) has been patented for weight loss and lowering glucose (US patent No: US 7713546 B1; Udell and Hari 2001). A number of studies in animals and human subjects using purified corosolic acid indicate that this compound enhanced cellular uptake of glucose, improved insulin sensitivity, decreased gluconeogenesis and inhibited intestinal hydrolysis of sucrose. These effects may be mediated by PPAR-γ, MAPK, NF-κB, and other signal transduction factors. No adverse effects have been observed in animal studies or controlled human clinical trials (Stohs et al. 2012).

    Other activities: Corosolic acid also exhibits antihyperlipidemic, antioxidant, antiinflammatory, antifungal, antiviral, antineoplastic and osteoblastic activities (Stohs et al. 2012). It is an important molecule for drug development.

77. Corymbiferin (pentaoxygenated xanthone)

    Plant source: *Swertia bimaculata*

    Anti-diabetes: Dichloromethane extract of *S. bimaculata* and corymbiferin (the most abundant component of dichloromethane extract) displayed remarkable anti-diabetic effects in high-fat and sucrose-fed and low-dose streptozotocin-induced diabetic rats (Liu et al. 2013). The insulin sensitivity was improved on the basis of increased expressions of insulin-receptor substrate-2, phosphatidylinositol 3-kinase, and Ser/Thr kinase AKT2. The treatments decreased fasting blood glucose levels, increased serum insulin levels and improved oral glucose tolerance. Furthermore, the treatments improved lipid profile, improved insulin sensitivity and decreased oxidative stress in the diabetic rats; corymbiferin exhibited improvement of histopathology of livers and pancreatic β-cells also (Liu et al. 2013).

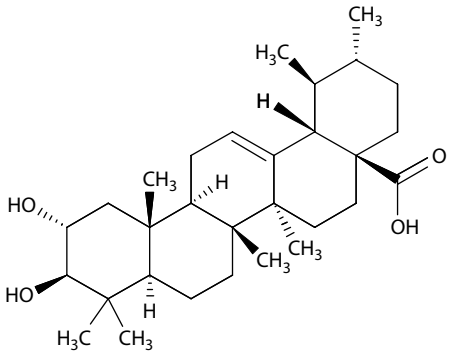


FIGURE 2.13 Structure of corosolic acid.

78. Costunolide

    Plant source: *Costus speciosus*

    Anti-diabetes: Eremanthin and costunolide isolated from *C. speciosus* root showed anti-DM and antihyperlipidemic activities in streptozotozin-induced diabetic rats (Eliza et al. 2009a, 2009b).

    Other activity: Protective effect of costunolide and eremanthin from oxidative stress has been shown (Eliza et al. 2010).

79. Coutareagenin (neoflavonoid)

    Plant source: Coutareagenin is a neoflavonoid (5-hydroxy-7-methoxy-4-(3,4-dihydroxyphenyl)-2H-benzo-1-pyran-2-on) isolated from *Hintonia latiflora*.

    Anti-diabetes: The anti-diabetic effect of *H. latiflora* extract was shown in various animal species with hyperglycemia induced by different methods. In a study, a blood sugar-lowering effect of oral or intragastric administration of *H. latiflora* cortex extract or intragastric administration of pure coutareagenin from the extract was demonstrated in streptozotocin-induced diabetic rats (Korec et al. 2000).

80. Cryptolepine (alkaloid)

    Plant source: Cryptolepine is the major alkaloid of the West African shrub, *Cryptolepis sanguinolenta*

    Anti-diabetes: Using an ethnobotanical approach in combination with *in vivo* activity guided fractionation cryptolepine was isolated as an antihyperglycemic component of *C. sanguinolenta*. The hydroiodide, hydrochloride, and hydrotrifluoromethanesulfonate (hydrotriflate) salts of cryptolepine were synthesized, and a comparison of their *in vitro* activities in a 3T3-L1 glucose transport assay was made. Cryptolepine and its salt forms lowered blood glucose in rodent models of type 2 diabetes. This is the first report on the antihyperglycemic properties of cryptolepine (Bierer et al. 1998).

    Other activities: Cryptolepine has been shown to inhibit nitric oxide production and DNA binding of NF-κB following inflammatory stimuli *in vitro.* Furthermore, it exhibited anti-inflammatory activity in carrageenan-induced paw edema in rats (Olajide et al. 2009).

81. Cucurbitacins

    Plant source: Cucurbitacin and its derivatives are a class of highly oxidized tetracyclic triterpenoids. They are widely distributed in the plant kingdom, particularly in Cucurbitaceae.

    Anti-diabetes: Recently, a new cucurbitacin from *M. charantia*, 5β,19-epoxycucurbit-23-en-7-on-3β,25-diol and 3 already known cucurbitacins showed concentration-dependent inhibition of glucose production from liver cells (Chan et al. 2015). Cucurbitane-type triterpene glycosides activated PPAR-γ (Joseph and Jini 2013; Wang et al. 2014). Cucurbitacin B and cucurbitacin I were suggested as a new strategy to treat metabolic diseases and implicate STAT3 as a new target for the development of functional foods and drugs (Seo et al. 2014).

    Other activities: Cucurbitacins possess strong pharmacological properties, such as antitumor, anti-inflammatory, and hepatoprotective effects (Chen et al. 2012).

82. Cuminoside (phenolic glycoside)

    Plant source: *Syzygium cumini*

    Anti-diabetes: Cuminoside isolated from the seed of *S. cumini* exhibited anti-DM activity in rats. Cuminoside (50 mg/kg, p.o.) was studied for its hypoglycemic and antioxidant potential Cuminoside caused a significant decrease in fasting blood sugar level, lipidperoxidation level, and improvement in the levels of antioxidant enzymes (reduced glutathione, superoxide dismutase, and catalase) in streptozotocin-induced type 2 diabetic rats (Farswan et al. 2009).

83. Curcumin

    Plant source: Curcumin is the major active principle present in the rhizome of *Curcuma longa*. The chemical structure of curcumin is shown in Figure 2.14.

    Anti-diabetes: Curcumin, the principal constituent of the rhizomes of *C. longa*, was found to inhibit PTP1B. The compound improved insulin and leptin sensitivity in the liver of rats; it

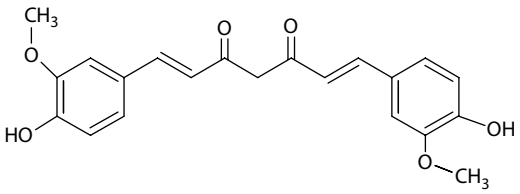


FIGURE 2.14 Structure of curcumin.

prevented hypertriglyceridemia and hepatic steatosis in fructose-fed rats (Li et al. 2010). Active principles such as curcumin, demethoxycurcumin, sesquiterpenoids, bisdemethoxycurcumin, and ar-turmerone, act via PPAR-γ ligand-binding activity (Arun and Nalini 2002; Kuroda et al. 2005; Nishiyama et al. 2005). Furthermore, curcumin can prevent some of the diabetic complications primarily due to its antioxidant and anti-inflammatory properties. Curcumin (150 mg/kg, p.o.) prevented diabetic nephropathy in streptozotocin-induced diabetic rats by inhibiting the activation of Sphk1-S1P signaling pathway (Huang et al. 2013). Besides, curcumin (100 mg/kg; p.o.) prevented diabetic cardiomyopathy in streptozotocin-induced diabetic rats (Soetikno et al. 2012).

Other activities: Curcumin has potentiality to prevent carcinogenesis and suppress certain types of cancer growth. Curcumin is known to induce apoptotic cell death. However, it can prevent oxidative stress-mediated apoptosis due to its antioxidant property (Ashok and Meenakshi 2004; Labban 2014). Other reported activities include anti-inflammatory activity, hypolipidemic activity, antiviral activity, wound healing, hepatoprotection from toxic chemicals and protective property on the cardiovascular system (Labban 2014).

84. Cyclonoside A

    Plant source: *Cyclocarya paliurus*

    Anti-diabetes: A naphthoquinone derivative, cyclonoside A from *C. paliurus* inhibited the activity of PTP1B (Jiang et al. 2012).

85. Daidzein

    Plant source: Daidzen, an isoflavone, is found in soybean (*Glycine max*), *Pueraria thomsonii*, and so on.

    Anti-diabetes: Bioassay-guided fractionation resulted in the isolation of daidzein from *P. thomsonii* as the PPAR-activating compound (Shen et al. 2006a). The blood glucose and HbA(1c) levels were significantly lower in daidzein treated groups than in the control type 2 diabetic db/db mice. The daidzein supplements increased the insulin/glucagon ratio in the type 2 diabetic animals. Furthermore, daidzein supplements improved the plasma total cholesterol, triglyceride, HDL cholesterol/total cholesterol, free fatty acid and hepatic triglyceride concentrations in db/db mice. These results suggest that daidzein exerts anti-diabetic effect in type 2 diabetic conditions by enhancing the glucose and lipid metabolism (Ae-Park et al. 2006).

    Other activities: Reported pharmacological activities of daidzein include antithrombotic and antiallergic activities (Choo et al. 2002).

86. Dammarane derivatives

    Plant source: *Gynostemma pentaphyllum*

    Anti-diabetes: Dammarne derivatives isolated from *G. pentaphyllum* inhibited PTP1B (Jiang et al. 2012).

87. Danshenols A (triterpene)

    Plant source: *Salvia miltiorrhiza* (root and rhizome)

    Anti-diabetes: Danshenols A (triterpene) was isolated from the root and rhizome of *S. miltiorrhiza*. This compound inhibited lens aldose reductase (Angel de la Fuente and Manzanaro 2003).

88. Dehydrocostuslactone

    Plant source: *Saussurea lappa*

Anti-diabetes: Dehydrocostuslactone (sesquiterpene lactone) was isolated from methanol extract of *S. lappa* root. This compound inhibited PTP1B. The authors suggest that this compound also is a potential lead molecule for the development of new PTP1B inhibitors to treat diabetes (Choi et al. 2009).

Other activities: Dehydrocostus lactone inhibited LPS-induced NO production *in vitro*. Furthermore, dehydrocostus lactone can be considered as neuroleptics by resemblance of their pharmacological activities to chlorpromazine (Okugawa et al. 1996).

89. Dehydrocrotonin

Plant source: *Croton cajucara*

Anti-diabetes: *Trans*-dehydrocrotonin, a nor-clerodane diterpene, isolated from *C. cajucara* exhibited hypoglycemic activity in alloxan-induced diabetic rats and glucose fed normal rats (Farias et al. 1997). In another study, treating rats with *trans*-dehydrocrotonin (50 mg/kg) significantly reduced streptozotocin-induced increases in blood glucose levels as well as ethanol-induced increases in blood triglycerides (Silva et al. 2001a). *Trans*-dehydrocrotonin (50 mg/kg) showed reduction of hyperglycemia in streptozotocin-diabetic rats and reduction of triglyceride in ethanol-induced hypertriglyceridemic rats. Thus, the compound has anti-DM potential (Silva et al. 2001b).

Other activities: Other reported activities include the gastroprotective, hypoglycemic, and hypolipidemic effects, antitumor activity, antiulcer activity, anti-inflammatory, and antinociceptive activities. Hypotensive and bradycardia effects of this compound have also been reported (Silva et al. 2005).

90. Demethoxycapillarisin and 2,4-dihydroxy-4-methoxy dihydrochalcone (polyphenolic compounds)

Plant source: Demethoxycapillarisin and 2,4-dihydroxy-4-methoxy dihydrochalcone are two phenolic compounds isolated from *Artemisia dracunculus*. The chemical structure of demethoxycapillarisin is shown in Figure 2.15.

Anti-diabetes: Two polyphenolic compounds that inhibited phosphoenolpyruvate carboxykinase (PEPCK) mRNA levels were isolated and identified as 6-demethoxycapillarisin and 2,4-dihydroxy-4-methoxy dihydrochalcone with IC_{50} values of 43 and 61 μM, respectively. The PI3 kinase (PI3K) inhibitor LY-294002 showed that 6-demethoxycapillarisin exerts its effect through the activation of the PI3K pathway, similarly to insulin. The effect of 2,4-dihydroxy-4-methoxy dihydrochalcone is not regulated by PI3K and is dependent on activation of the AMPK pathway (Govorko et al. 2007). Furthermore, 6-demethoxycapillarisin and 2′,4′-dihydroxy-4-methoxydihydrochalcone isolated from *A. dracunculus* inhibited aldose reductase, a key enzyme involved in diabetic complications (Logendra et al. 2006). When combined with labrasol, 2′,4′-dihydroxy-4-methoxy dihydrochalcone was at least as effective as metformin at doses of 200–300 mg/kg/day (Ribnicky et al. 2009).

91. Deoxyelephantopin

Plant source: *Elephantopus scaber*

Anti-diabetes: Deoxyelephantopin from *E. scaber* has been reported to function as a selective partial agonist against of PPAR-γ. It binds to purified PPAR-γ, but not to PPAR-α; it enhanced the transcriptional activity of full-length PPAR-γ and Gal4–PPAR-γ chimera as a partial agonist (Wang et al. 2014).

Other activities: Wound healing activity of the leaf extracts and deoxyelephantopin isolated from *E. scaber* showed wound healing activity (Singh et al. 2005). Several studies have reported

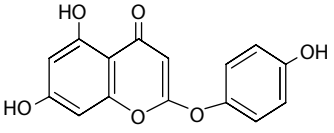


FIGURE 2.15 Structure of demethoxycapillarisin.

the anticancer/antitumor activity of deoxyelephantopin. For example, it inhibited the growth of lung adenocarcinoma cells (Kabeer et al. 2013).

92. Deoxynojirimycin (alkaloid)

    Plant source: The root barks extract and leaves of *Morus nigra*, *Morus multicaulis*, *Ramulus mori*, and so on, contain deoxynojirimycin, an alkaloid. Young mulberry (*M. nigra*) leaves, taken from top part of branches in summer, contained the highest amount of deoxynojirimycin. The chemical structure of 1-deoxynojirimycin is shown in Figure 2.16.

    Anti-diabetes: Deoxynojirimycin is a potent α-glycosidase inhibitor and helpful to establish greater glycemic control in type 2 diabetes. In a study on diabetic models of rats, 1-deoxynojirimycin treatment showed significant anti-diabetic effects in Otsuka Long–Evans Tokushima fatty rats, with significant improvements in fasting blood glucose levels and glucose tolerance and, especially, increased insulin sensitivity. Furthermore, there was significant loss of body weight. Deoxynojirimycin also showed significant antihyperglycemic effects in streptozotocin- and HFD-induced hyperglycemic rats. Its efficacy and dose profiles were better than those of acarbose, a typical α-glucosidase inhibitor in clinical use. Furthermore, a substantial fraction of deoxynojirimycin was absorbed into the bloodstream within a few minutes of oral administration. Deoxynojirimycin was also detected in the urine. These findings suggest that its postprandial hypoglycemic effect in the gastrointestinal tract is a possible but insufficient mechanism of action underlying the anti-diabetic effects of deoxynojirimycin (Kong et al. 2008).

    In a human study, 1-deoxynojirimycin enriched powder of mulberry leaves significantly suppressed elevation of postprandial glucose. The authors conclude that newly developed deoxynojirimycin enriched powder can be used as a dietary supplement for preventing diabetes mellitus (Kumar and Chauhan 2008).

    Other activities: Treatment by 1-deoxynojirimycin of HIV-infected lymphocyte cultures inhibited virus spread. Furthermore, 1-deoxynojirimycin blocked HIV envelope glycoprotein-mediated membrane fusion at the C-X-C motif chemokine receptor type 4 (CXCR4) binding step (Papandreou et al. 2002).

93. Desmethoxysenegin II (triterpenoid glycoside)

    Plant source: *Polygala senega* (rhizome)

    Anti-diabetes: Desmethoxysenegin II from *P. senega* decreased blood glucose levels in normal and KK-Ay mice (Kako et al. 1997).

94. Dihydroxychromone

    Plant source: *Daphniphyllum macropodum* fruit

    Anti-diabetes: 5,7-dihydroxychromone from *D. macropodum* fruit showed promising PPAR-γ agonist activity. The compound potently induced the differentiation of mouse 3T3-L1 preadipocytes. Furthermore, it increased PPAR-γ and liver X receptor-α mRNA expression levels. Furthermore, the compound-rich fraction from *D. macropodum* reduced serum glucose, total cholesterol and triglyceride levels in streptozotocin-/HFD-induced type 2 DM mice (Koo et al. 2014).

95. Dihydroxy gymnemic triacetate

    Plant source: Dihydroxy gymnemic triacetate (saponin) was isolated from the leaves of *Gymnema sylvestre*.

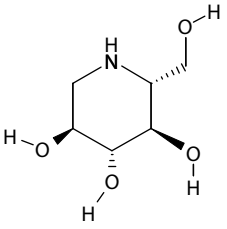


FIGURE 2.16 Structure of deoxynojirimycin.

Anti-diabetes: Dihydroxy gymnemic triacetate (20 mg/kg for 45 days) showed hypoglycemic and hypolipidemic activities in streptozotocin diabetic rats (Daisy et al. 2009b; Sugiharo et al. 2000). Mechanism of action includes stimulation of insulin secretion, regeneration of β-cells, enhanced peripheral utilization of glucose, and reduction in sugar absorption (Daisy et al. 2009b).

Molecular docking studies show interaction of this compound with insulin receptor (Daisy et al. 2012).

Other activities: In a recent study, treatment of dihydroxy gymnemic triacetate resulted in a dose-dependent inhibition of growth of PC-3 cells. The cell cycle arrest was observed at the G2/M phase and accumulation of apoptotic cells was observed in the treated prostate cancer cell lines (Nivedha et al. 2015).

96. 6,7-Dimethoxy-2H-1-benzopyran-2-one

Plant source: *Cuscuta reflexa*

Anti-diabetes: This phenolic compound inhibited α-glucosidase (Anis et al. 2002).

97. Diosgenin (a phytosterol)

Plant source: Diosgenin, a steroidal sapogenin, is found in *Dioscorea bulbifera*, *Dioscorea nipponoca*, *Solanum incanum*, *Solanum xanthocarpum*, and *Trigonella foenum-graecum*.

The chemical structure of diosgenin is shown in Figure 2.17.

Anti-diabetes: Diosgenin inhibited α-amylase activity. Kinetic studies confirmed the uncompetitive mode of binding of diosgenin to α-amylase (Ghosh et al. 2014). Diosgenin from *T. foenum-graecum* improved glucose metabolism by promoting adipocyte differentiation and inhibiting inflammation in adipose tissue (Uemura et al. 2010). Diosgenin supplementation to diabetic rats significantly decreased lactase and maltase activities compared to the diabetic control group. It also decreased the activity of the transaminases compared to the normal and diabetic control rats. Effects of diosgenin on fasting blood glucose and intestinal α-amylase in streptozotocin-induced diabetic rats were studied. There was a significant increase in the activity of α-amylase in the proximal region of the small intestinal mucosa of diabetic rats treated with diosgenin. In another study, plasma glucose decreased significantly in diabetic rats fed the commercial diosgenin (1%) diet compared to the diabetic control. Diosgenin significantly decreased glucose-6-phosphatase activity compared to the diabetic control. The activities of ATP-citrate lyase, pyruvate kinase, and glucose-6-phosphate dehydrogenase were significantly reduced in the liver of diabetic rats compared to normal control. Supplementation of the diet with commercial diosgenin did not significantly alter ATP citrate lyase and pyruvate kinase activities but significantly increased glucose-6-phosphate dehydrogenase activity in the liver compared to control diabetic rats. Plasma glucose and glucose-6-phosphatase levels decreased significantly in diabetic rats fed with diosgenin as compared to the diabetic control (Patel et al. 2012). Diosgenin improved glucose metabolism by promoting adipocyte differentiation and inhibiting inflammation in adipose tissue (Chang et al. 2013).

Other activities: Dioscorea root contains diosgenin, which has antifatigue, anti-inflammatory, antistress, hypocholesterolemic, and estrogenic effects. It is also able to prevent bone loss to the same extent as that of estrogen. It shows antihepatitis C viral activity *in vitro* (Patel et al. 2012).

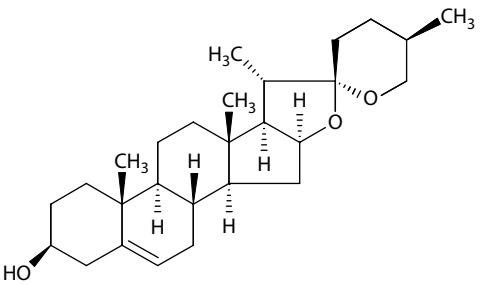


FIGURE 2.17 Structure of diosgenin.

98. Diphenyl amine

    Plant source: *Allium cepa*, *Camella sinensis*, and so on.

    Anti-diabetes: Diphenyl amine is an antihyperglycemic agent present in onion, tea, and so on. (Karawya et al. 1984).

    Other activities: Diphenyl amine and related compounds exhibit antioxidant and antimicrobial activities.

99. Eclalbasaponin VI

    Plant source: *Eclipta alba*

    Anti-diabetes: A bioactivity guided isolation approach based on α-glucosidase inhibition led to the isolation of four echinocystic acid glycosides from *E. alba*, of which eclalbasaponin VI was found to be the most potent (IC_{50} 54.2 ± 1.3 μM) (Kumar et al. 2012).

100. Elatoside A, E, G, H, and I (saponins)

    Plant source: Elatosides are present in *Gymnema sylvestre* (root), *Aralia elata*, and so on. The chemical structure of elatoside E is shown in Figure 2.18.

    Anti-diabetes: Elatosides (oleanolic acid monodesmosides) from *G. sylvestre* showed hypoglycemic activity in oral glucose tolerence test in rats. The mechanism of action may be due to inhibition of hepatic gluconeogenesis or glycogenolysis. Elatosides E isolated from the root cortex of *A. elata* inhibited α-glucosidase activity. Elatosides E was shown to lower the elevation of plasma glucose level in oral sugar tolerance test in rats (Yoshikawa et al. 1994a).

    Elatosides G, H and I from *A. elata* were also found to exhibit potent hypoglycemic activity in oral glucose tolerance test (Yoshikawa et al. 1995).

    Other activities: Elatosides A and B from the bark of *A. elata* exhibited potent inhibition of ethanol absorption in rats (Yoshikawa et al. 1993).

101. Eleutheroside E

    Plant source: Eleutheroside E is a principal component of *Eleutherococcus senticosus*. The chemical structure of eleutheroside E is shown in Figure 2.19.

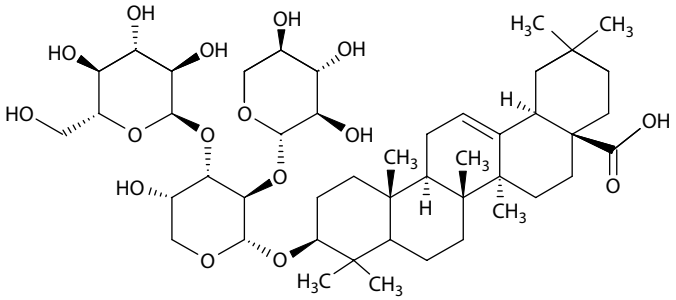


FIGURE 2.18 Structure of elatoside E.

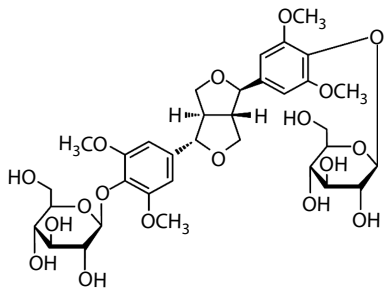


FIGURE 2.19 Structure of eleutheroside E.

Anti-diabetes: The effect of eleutheroside E containing *E. senticosus* extracts as well as eleutheroside E on hyperglycemia and insulin resistance in db/db mice was studied. When 5-week-old db/db mice were fed a diet consisting of the plant extract or eleutheroside E for 5 weeks, serum lipid profiles improved and blood glucose levels decreased. The extract and the compound effectively attenuated homeostatic model of assessment-insulin resistance (HOMA-IR). Glucose tolerance and insulin tolerance tests showed that the compound increased insulin sensitivity. Immunohistochemical staining indicated that eleutheroside E and the extract protected pancreatic α- and β-cells from diabetic damage. In addition, the extract and the compound improved hepatic glucose metabolism by upregulating glycolysis and downregulating gluconeogenesis in obese type 2 diabetic mice (Ahn et al. 2013). Eleutheroside E increased the insulin-provoked glucose uptake in C2C12 myotubes. Moreover, the compound improved TNF-α-induced suppression of glucose uptake in 3T3-L1 adipocytes (Ahn et al. 2013).

Other activities: Eleutheroside E from *E. senticosus* has anti-inflammatory and protective effects in ischemia heart (Ahn et al. 2013).

102. Ellagic acid

Plant source: Ellagic acis is reported from many plants. Examples of these include *Myrciaria dubia*, *Phyllanthus emblica* (fruit), and *Thespesia populnea*. The chemical structure of ellagic acid is shown in Figure 2.20.

Anti-diabetes: Ellagic acid from *M. dubia* inhibited aldose reductase (Ueda et al. 2004). In another study, ellagic acid (50 and 100 mg/kg, p.o. for 35 days) restored the altered levels of serum glucose, blood glycalated hemoglobin, hexokinase activity, plasma insulin, and plasma C-peptide to near normal levels in streptozotocin diabetic rats. Thus, ellagic acid exhibited potent anti-DM activity in streptozotocin diabetic rats (Malini et al. 2011). Furthermore, ellagic acid ameliorated renal function in experimental diabetic nephropathy (Ahad et al. 2014).

Other activities: Other reported activities of ellagic acid include inhibition of NF-κB activity and hepatoprotective activity against antituberculosis drugs (Stephan Ambrose et al. 2013).

103. Ellagitannins

Plant source: Ellagitannins are polyphenols present in some fruits, nuts and seeds, such as pomegranates, black raspberries, raspberries, strawberries, walnuts, and almonds.

Anti-diabetes: Ellagitannins from the fruit of *T. chebula* inhibited α-glucosidase activity (Gao et al. 2007). Ellagitannin from pomegranate flowers (Punicatannin A) showed potent inhibition of α-glucosidase and lipogenic gene expression (Yuan et al. 2012).

Other activities: Anticancer cell proliferation and apoptosis-inducing activities of ellagitannins have been demonstrated (Landete 2011).

104. Enhydrin (sesquiterpene lactone)

Plant source: *Smallanthus sonchifolius*

Anti-diabetes: Enhydrin, the major sesquiterpene lactone of yacon leaves, was also effective in reducing postprandial glucose and useful in the treatment of diabetic animals (minimum dose: 0.8 mg/kg) (Genta et al. 2010).

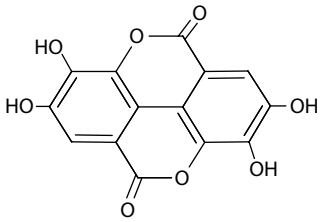


FIGURE 2.20 Structure of ellagic acid.

Other activities: Other known pharmacological properties of enhydrin include chemopreventive activity (Siriwan et al. 2011), promising antimicrobial activity and trypanocidal activity (Frank et al. 2013).

105. Ephedrans A, B, C, D, and L (glycans)

Plant source: *Ephedra distachya*

Anti-diabetes: The hypoglycemic effect of *E. distachya* has been investigated to show that the hydroalcoholic extract produced long-lasting hypoglycemia in mice following transient hyperglycemia. Activity-guided fractionation resulted in the isolation of five active glycans ephedrans A, B, C, D, and E, which significantly reduced blood glucose levels in normal and alloxan-induced diabetic mice (Konno et al.1985a).

106. Ephedrine (alkaloid)

Plant source: *Ephedra distachya* and other *Ephedra* spp.

Anti-diabetes: Ephedrine alkaloid from *E. distachya* showed antihyperglycemic activity in streptozotocin-induced diabetic mice. The alkaloid not only suppressed hyperglycemia in the diabetic mice, but also promoted the regeneration of pancreas islets following atrophy induced by streptozotocin. It is suggested that this compound may regenerate atrophied pancreatic islets (Xiu et al. 2001).

107. Epicatechin and epigallo-catechin gallate

Plant source: Epicatechin and related compounds (epigallo-catechin gallate; (−)-3-O- galloylepicatechin and (−)-3-O-galloylcatechin) are reported from *Nelumbo nucifera*, *Cinnamomum* sp., *Eriobotrya japonica*, *Euclea undulata*, *Pterocarpus marsupium*, *Prunus amygdalus*, and so on. Epigallo-catechin gallate is a major compound in *Camella sinensis* (leaf); (−)-3-O-galloylepicatechin and (−)-3-O-galloylcatechin are present in *Bergenia ciliata*. These compounds are present in many other plants also. The chemical structure of epicatechin is shown in Figure 2.21.

Anti-diabetes: Insulin release was enhanced by approximately 44–70 folds when isolated rat islets were exposed to epicatechin (0.8 mmol/L). (−) Epicatechin (0.8 mmol/L) inhibited $^{45}Ca^{2+}$ efflux in the presence and absence of extracellular $^{45}Ca^{2+}$. In the presence of 20 mmol/L glucose, both the short-term (5 min) and steady state (30 min) $^{45}Ca^{2+}$ uptake were significantly increased by (−)epicatechin (Hii and Howell 1985). The authors suggest that the compound may, at least in part, exert their effects on insulin release via changes in Ca^{2+} metabolism (Hii and Howell 1985). Epicatechin influenced glucose transporters in cardiac tissue and peripheral nerves in type 2 diabetes (Gonzalez 2014). Epigallo-catechin gallate isolated from *C. sinensis* leaf lowered hepatic glucose production (Waltner-Law et al. 2002). Furthermore, epigallo-catechin gallate supplementation prevented progression to glucose intolerance in db/db mice. Furthermore, the compound alleviated diabetes in rodents (Chang et al. 2013).

Other activities: Catechins have been reported to have many pharmacological properties such as antioxidant activity, anti-inflammatory, anticarcinogenic, antiultraviolet radiation, and reduction of blood pressure, glucose, and cholesterol levels. Besides, epicatechin increased the testosterone secretion by rat Leydig cells via the enzyme activities of 17β-hydroxysteroid dehydrogenase (Yu et al. 2010). Furthermore, epicatechin is useful in the treatment of gastric ulcers.

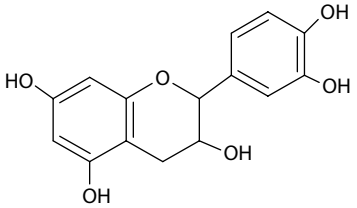


FIGURE 2.21 Structure of epicatechin.

It provides gastroprotection through reinforcement of the mucus barrier and neutralization of gastric juice (Rozza et al. 2012).

108. 13-Epitorulosol, diterpene labdane derivative

Plant source: *Larix laricina*

Anti-diabetes: 13-Epitorulosol potentiated adipogenesis (EC_{50} 8.2 μM) of 3T3-L1 cells (Shang et al. 2012). A new triterpenoid and the diterpene labdane derivative 13-epitorulosol, isolated from *L. laricina*, had the most prominent adipogenic effect (3.7- and 2.7-fold increase in accumulation of lipids, when compared to vehicle control) (Eid and Haddad 2014).

109. Eremanthin

Plant source: *Costus speciosus*

Anti-diabetes: Eremanthin and costunolide isolated from *C. speciosus* root showed anti-DM and antihyperlipidemic activities in streptozotozin-induced diabetic rats (Eliza et al. 2009a, 2009b).

Other activities: Acute toxicity test in rodents revealed the nontoxic nature of eremanthin and costunolide. Eremanthin and costunolide showed excellent protective effect against oxidative stress (Eliza et al. 2010).

110. Eremophilane sesquiterpene

Plant source: *Ligularia fischeri*, *Eremophila mitchelli*, and so on.

Anti-diabetes: From the roots of *L. fischeri*, an eremophilane sesquiterpene was isolated; this sesquiterpene exhibited PTP1B inhibitory activity with IC_{50} value of 1.3 μmol/L (Jiang et al. 2012).

111. Eremophilanolide sesquiterpenes (3-hydroxycacalolide and epi-3-hydroxycacalolide)

Plant source: *Psacalium decompositum*

Anti-diabetes: *In vivo* bioassay guided fractionation of a water extract of the roots of *P. decompositum* led to the isolation of two new eremophilanolides, 3-hydroxycacalolide, and epi-3-hydroxycacalolide. A 1:1 mixture of these compounds exhibited antihyperglycemic activity when tested at a dose of 1.09 mmol/kg in ob/ob type 2 DM mice. The known furanoeramophilane cacalol was isolated from CH_2Cl_2 extract of the plant roots and also possessed antihyperglycemic activity (Inman et al. 1999). A novel hypoglycemically active eremophilanolide, sesquiterpenes, obtained from the roots of *P. decompositum*, have been patented for their use as hypoglycemic agents in the treatment of diabetes (Inman et al. 1998). Cacalol, cacalone epimer mixture, and cacalol acetate blocked adenosine triphosphate-sensitive potassium channels in a similar way to the anti-diabetic drug glibenclamide (Campos et al. 2009).

112. Erigeroflavanone

Plant source: *Erigeron annuus*

Anti-diabetes: A novel 2,3-dioxygenated flavanone, erigeroflavanone, isolated from ethyl acetate-soluble extract of the flowers of *E. annuus*, inhibited advanced glycation end products formation and rat lens aldose reductase activity. This property may be useful in attenuating complications of DM (Yoo et al. 2008). Furthermore, erigeroflavanone provided a protective effect against oxidative stress-induced cell death in mesangial cells that is associated with its antioxidant action and inhibition of mitogen-activated protein kinases (MAPKs) and caspase-3. These results suggest that erigeroflavanone has potential as a therapeutic agent in the treatment of renal diabetic complications (Kim et al. 2009).

Other activities: Cytoprotection and antioxidant activities (Kim et al. 2009).

113. Erinidine (alkaloid)

Plant source: *Hunteria umbellata*

Anti-diabetes: An *in vitro* study showed the antihyperglycemic action of erinidine, isolated from *H. umbellata*; this effect may be, to some extent, mediated via a α-glucosidase inhibition mechanism. However, erinidine (50 mg/kg, p.o.) attenuated the increase in blood glucose levels in an oral glucose tolerance test in normal and alloxan-induced hyperglycemic rats. Its

antiglycemic mechanism may be inhibition of intestinal glucose absorption; biotransformation in the gut may enhance its inhibitory activity (Adejuwon et al. 2013). However, other *in vivo* mechanism of action may also be involved.

114. Escins II A and II B (triterpine oligoglycosides)

    Plant source: *Aesculus hippocastanum*

    Anti-diabetes: Escins (triterpine oligoglycosides) or aescins present in the seeds of *A. hippocastanum* (horse chestnut) have been shown to have hypoglycemic activity in glucose tolerance tests in rats (Yoshikawa et al. 1994b, 1996b).

    Other activities: Studies suggest that escin is a potent anti-inflammatory drug with long-lasting anti-inflammatory effects and without any immunosuppressive effects (Wang et al. 2009). It has vasoprotective effects also.

115. Esculetin (Aesculetin)

    Esculetin (6,7-dihydroxycoumarin) is found in plants such as *Cichorium intybus* and *Sonchus oleraceus*. The chemical structure of esculetin is shown in Figure 2.22.

    Anti-diabetes: The effect of oral administration of esculetin (6 mg/kg) for 4 weeks on oral glucose tolerance, insulin secretory response, serum lipid profile and oxidative stress in streptozotocin-induced diabetic rats was evaluated. The treatment with esculetin resulted in a marked amelioration of the impaired glucose tolerance in the diabetic rats; the treatment lowered insulin and C-peptide levels. The impoverished liver glycogen content and elevated liver glucose-6-phosphatase and serum AST and ALT activities of fasting diabetic rats were profoundly corrected as a result of the treatment. Also, the treatment led to decrease in serum total lipid, total cholesterol, triglyceride, LDL, and very-low-density lipoprotein (VLDL) levels and increase in HDL level. The antioxidant defense system was potentially improved in diabetic rats as a result of the treatment (Hozayen et al. 2011).

    Other activities: Esculetin exerted protective effects against oxidative stress-induced cell damage via scavenging ROS (Kim et al. 2008). In a recent study, esculetin showed analgesic activity in acute noninflammatory pain and acute inflammatory pain models in rats. Furthermore, it inhibited 5-lipoxygenase (Rzodkiewicz et al. 2015).

116. Fagomine (nitrogen-containing sugar)

    D-fagomine is an iminosugar originally isolated from seeds of buckwheat (*Fagopyrum sculentum*). Fagomine is also reported from *Morus* sp., and so on. The chemical structure of D-fagomine is shown in Figure 2.23.

    Anti-diabetes: Fagomine potentiated glucose-induced insulin secretion from isolated rat pancreatic islets in response to glucose. The suggested mechanism is through acceleration of some step(s) after the formation of glyceraldehyde 3-phosphate in the glycolytic pathway (Taniguchi

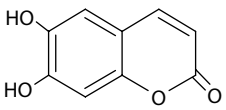


FIGURE 2.22 Structure of esculetin.

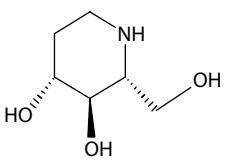


FIGURE 2.23 Structure of D-fagomine.

et al. 1998). D-fagomine occurs naturally in buckwheat grain and traditional buckwheat-based foods; D-fagomine could help diabetics keep their blood glucose levels well-managed (Amezqueta et al. 2013). In another report, in rats, D-fagomine lowered postprandial blood glucose levels in a dose-dependent manner without stimulating insulin secretion. D-fagomine may be used as a dietary ingredient or functional food component to reduce the health risks associated with an excessive intake of fast-digestible carbohydrates (Gomez et al. 2012).

Other activities: D-fagomine modulated selectively bacterial adhesion; it (0.14 mM) agglutinated 60% of Enterobacteriaceae (*Escherichia coli* and *Salmonella enterica* serovar, Typhimurium) (Gomez et al. 2012). The compound is reported to be useful for the control of inflammatory processes related to an overactivation of the humoral immune response (Pumarola et al. 2014).

117. Falcarindiol (polyyne)

Plant source: *Aegiceras corniculatum*

Anti-diabetes: Falcarindiol isolated from *A. corniculatum* inhibited PTP1B at a low concentration (IC_{50} = 9.1 μmol/L) (Jiang et al. 2012).

Other activities: Falcarindiol has been shown to have anti-inflammation, antibacterial, and anticancer activities, as well as protective effects against hepatotoxicity. These beneficial effects occur at nontoxic concentrations. Falcarindiol preferentially killed colorectal cancer cells and inhibited tumor growth (Jin et al. 2012).

118. Falcarinol (polyacetylene)

Plant source: *Daucus carota*, *Panax ginseng*, and so on.

Anti-diabetes: In a recent study, falcarinol (polyacetylene) isolated from carrot stimulated glucose uptake in normal and insulin-resistant primary porcine myotubes. This effect was attenuated in the presence of indinavir (GLUT4 inhibitor) and Wortmannin (PI3K and MAPK inhibitor) indicating a dependence on GLUT4 activity as well as PI3K and/or p38MAPK activity. Furthermore, falcarinol-stimulated glucose uptake was independent of AMPK activity. Besides, falcarinol enhanced phosphorylation of TBC 1 domain family member (TBC1D1) suggesting that this compound enhanced translocation of GLUT4-containing vesicles and thereby glucose uptake via a TBC1D1-dependent mechanism (Bhattacharya et al. 2014).

Other activities: It was shown that falcarinol acts as a covalent cannabinoid receptor type one inverse agonist. It showed some level of anticancer activity; it inhibited the growth of Caco-2 cells (cancer cells originated from intestinal epithelial cells) above 1 μg/mL level (Purup et al. 2009).

119. Fangchinoline (alkaloid)

Plant source: *Stephania tetrandra*

Anti-diabetes: In streptozotocin-induced diabetic mice, the water extract of *S. tetrandra* reduced blood glucose in a dose-dependent manner in the range of 0.48–16 mg/kg, which is due to fangchinoline. The main bis-benzylisoquinoline alkaloid, fangchinoline (0.3–3 mg/kg) significantly brought down the blood glucose level of the diabetic mice in a dose-dependent manner. The effect of fangchinoline was 3.9-fold greater than that of water extract of *S. tetrandra* (Tsutsumi et al. 2003).

Other activities: Fangchinoline-induced autophagic cell death via p53/sestrin2/AMPK signaling in human hepatocellular carcinoma cells (Wang et al. 2011).

120. Ferulic acid (phenolic)

Plant source: Ferulic acid is present in many plants, including edible plant parts. Examples of these include *Coffea arabica*, *Ficus carica*, *Musa sapientum*, *Opuntia ficus-indica*, *Syzygium cumini*, and *Curcuma longa*. The chemical structure of ferulic acid is shown in Figure 2.24.

Anti-diabetes: Ferulic acid at 0.01% and 0.1% of basal diet suppressed significantly blood glucose levels in streptozotocin-induced type 1 diabetic mice. In type 2 DM model, KK-Ay mice also 0.05% ferulic acid suppressed effectively blood glucose levels. In addition, ferulic acid inhibited the lipid peroxidation in brown adipose tissue of diabetic mice (Ohnishi et al. 2004).

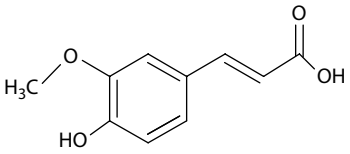


FIGURE 2.24 Structure of ferulic acid.

Another study suggests that ferulic acid have protective and therapeutic effects on diabetic nephropathy in a rat model of obese type 2 DM by reducing oxidative stress and inflammation (Choi et al. 2011). It has been reported that ferulic acid interacted synergistically with metformin and thiazolidinedione drugs in streptozotocin-induced diabetic rats (Prabhakar et al. 2013). Recent studies have revealed that ferulic acid presents pharmacological properties beyond those related to its antioxidant activity, such as the ability to competitively inhibit hepatic 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase and activate glucokinase, contributing to reduce hypercholesterolemia and hyperglycemia, respectively (Paiva et al. 2013).

Other activities: Ferulic acid presents antioxidant activity and a wide range of potential therapeutic effects useful in the treatments of cancer, lung and cardiovascular diseases, liver diseases and neuroprotective effects. Besides, the compound showed antimicrobial and anti-inflammatory activities (Paiva et al. 2013).

121. Formononetin (isoflavone)

Plant source: *Astragalus membranaceus*

Anti-diabetes: Formononetin isolated from the ethanol extract of *A. membranaceus* activated PPAR-γ (Wang et al. 2014).

Other activities: Formononetin exhibited neuroprotective effects against *N*-methyl-D-asparate-induced apoptosis in primary cultured cortical neurons (Tian et al. 2013). Besides, recent studies have shown that formononetin could inhibit enterovirus replication by regulating cyclo-oxygenase-2 (COX-2)/ prostaglandin E2 (PGE_2) expression (Wang et al. 2015).

122. Forskolin (diterpene)

Plant source: *Coleus forskohlii*

Anti-diabetes: Forskolin stimulated insulin release and increased cyclic AMP content in rat pancreatic islets (Wiedenkeller et al. 1983).

Other activities: Forskolin directly stimulates adenylyl cyclase and has been used extensively to increase cyclic adenosine monophosphate (cAMP) and to elicit cAMP-dependent physiological responses. Besides, forskolin has been shown to inhibit a number of membrane transport proteins and channel proteins through a mechanism that does not involve the production of cAMP (Laurenza et al. 1989).

123. Fraxisecoside (coumarin-secoiridoid hybrid glycoside)

Plant source: *Fraxinus rhynchophylla*

Anti-diabetes: Fraxisecoside exhibited moderate PTP1B inhibition activity (Xiao et al. 2008).

Other activity: It showed inhibition activity against B- and T-cell proliferation, without cytotoxicity (Xiao et al. 2008).

124. Friedelane triterpenoids (7β-hydroxy-3-oxo-D:A-friedooleanan-28-oic acid and 7β,29-dihydroxy-3-oxo-D:A-friedoolean-ane)

Plant source: *Celastrus vulcanicola* and *Maytenus jelskii*

Anti-diabetes: Insulin's effect on IR phosphorylation was clearly mimicked by treatment of human hepatic cells (Huh7 cells) with compounds 7β-hydroxy-3-oxo-D:A-friedooleanan-28-oic acid and 7β,29-dihydroxy-3-oxo-D:A-friedoolean-ane. Furthermore, 7β-hydroxy-3-oxo-D:A-friedooleanan-28-oic acid, but not 7β,29-dihydroxy-3-oxo-D:A-friedoolean-ane, showed a very potent effect in enhancing insulin-mediated IR tyrosine phosphorylation. These studies

suggest that these friedelane triterpenoids have potential therapeutic use in insulin-resistant states (Ardiles et al. 2012).

125. Galactomannans

Plant source: Galactomannans are found in many plants. Examples of these plants include *Cyamopsis tetragonolobus*, *Amorphophallus konjac*, and *Trigonella foenum-graecum*.

Anti-diabetes: Galactomannans (unabsorbable carbohydrate) decreased postprandial hyperglycemia in humans (Gaikwad et al. 2014). Guar gum is shown to have hypolipidemic and hypocholesterolemic properties (Frias and Sgarbieri 1998; Srivastava et al. 1987). In another study, the increase in blood glucose levels found in diabetic rats was significantly suppressed in the fenugreek galactomannan-treated group than those in the diabetic control rats. Moreover, the galactomannan exhibited a prominent selective inhibitory effect against intestinal lipase activity. It was found to significantly delay the absorption of LDL cholesterol and triglycerides and the increase in HDL cholesterol. In addition, fenugreek galactomannan efficiently protects the hepatic function as judged from serum marker enzymes for liver function. The beneficial effects of fenugreek galactomannan were also evidenced by their capacity to inhibit diabetes-induced kidney injury through lowering the urea and creatinine content in plasma (Hamden et al. 2010).

126. Galegine

Plant source: *Galega officinalis*

Anti-diabetes: The water extract of *G. officinalis* leaves contains guanidine and galegine as major chemical components. Studies demonstrated that galegine and other guanidine derivatives reduce blood sugar levels. These compounds, although having an anti-diabetic effect, are too toxic for clinical use. Studies on guanidine and galegine analogs for anti-diabetic activity culminated in the discovery of metformin, introduced as glucophage in 1957 (Sterne 1957).

127. Gallic acid

Plant source: *Mangifera indica* (mango fruit peel), *Citrullus lanatus*, *Cyamopsis tetragonoloba*, *Musa sapientum*, *Opuntia ficus-indica*, *Phyllanthus emblica,* and so on.

Anti-diabetes: Gallic acid isolated from *Terminalia* species stimulated insulin secretion (Latha and Daisy 2011). Gallic acid is shown to have antihyperglycemic, antilipid peroxidative, and antioxidant effects in streptozotocin-induced diabetic rats (Punithavathi et al. 2011).

Other activities: Gallic acid has been shown to be beneficial for the treatment of myocardial damage associated with type 1 diabetes. Furthermore, it protected liver from oxidative stress (Patel and Goyal 2011).

128. Genistein (flavonoid)

Plant source: Genistein is an isoflavone found in *Glycine max* (soybean), *Genista tinctoria*, and so on. The chemical structure of genistein is shown in Figure 2.25.

Anti-diabetes: Several studies have demonstrated that genistein has anti-diabetic effects, in particular, direct effects on β-cell proliferation, glucose-stimulated insulin secretion, and protection against apoptosis, independent of its functions as an estrogen receptor agonist, antioxidant, or tyrosine kinase inhibitor. While there are limited data on the effects of genistein consumption in humans with diabetes, there are a plethora of animal and cell culture studies that demonstrate, at physiologically relevant concentrations (<10 μM), a direct effect of genistein on β-cells. The effects appear to involve cAMP/PKA signaling and there are some studies that suggest an

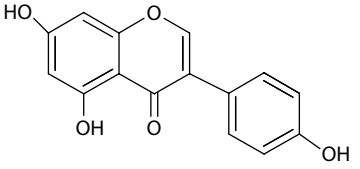


FIGURE 2.25 Structure of genistein.

effect on epigenetic regulation of gene expression (Gilbert and Liu 2013). Genistein showed hypoglycemic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 246.7 cells (Mezei et al. 2003). In a recent histological and immunohistochemical study, genistein showed protective effects on pancreatic β-cells damage, possesses the ability to regenerate β-cells and improved serum levels of insulin and glucose in streptozotocin-induced diabetic rats in a dosage-dependent manner (El-Kordy and Alshahrani 2015). A detailed study has shown that genistein promoted viability, inhibited apoptosis, and reduced caspase-3 activity of INS1 β-cells and human and mouse islets chronically exposed to palmitate (0.5 mM) and high glucose (20 mM). In addition, exposure of β-cells to genistein activated PI3K/Akt signaling and upregulated antiapoptotic protein Bcl-2 expression. The antiapoptotic effect of genistein is independent of classical estrogen receptor-mediated signaling machinery, but it may be achieved through the G-protein-coupled receptor GPR30-mediated activation of cAMP signaling. Oral administration of genistein (50 mg/kg/day) improved hyperglycemia, glucose tolerance, and blood insulin levels in wide-type obese diabetic mice, but these effects were abolished in GPR30 null mice. These findings demonstrate that genistein exerts anti-diabetic effect and promotes β-cell survival via GPR30-mediated signaling pathway (Wang et al. 2014).

Other activities: Molecular and cellular biological experiments strongly suggest that genistein could provide health benefits in various types of diseases such as osteoporosis, cardiovascular diseases, and menopausal symptoms. Genistein's actions occur largely through estrogen receptors (Suther et al. 2001).

129. Geranin

Plant source: *Nephelium lappaceum*, *Phyllanthus amarus*

Anti-diabetes: Geranin isolated from the rind waste of *N. lappaceum* showed antihyperglycemic activity in experimental animals (Palanisamy et al. 2011). The geranin-enriched ethanolic extract of *N. lappaceum* has been shown to be effective in inhibiting the carbohydrate hydrolyzing enzymes, α-glucosidase and α-amylase, at a much more significant level than the drug acarbose. In addition, the geranin-enriched ethanolic extracts were able to inhibit the key enzyme in the polyol pathway, aldose reductase (EC_{50}: 0.04 μg/mL), and prevent the formation of AGE by 43% (Palanisamy et al. 2014).

Other activities: Geranin and its metabolites possess a range of bioactive properties including being anti-infective, anticarcinogenic, and antihypertensive. However, the compounds have limited gastrointestinal absorption due to its polarities (Elendran et al. 2015).

130. Geraniol

Plant source: Geraniol, a monoterpene alcohol, found in the essential oils of citrus fruits and other plants (e.g., *Cymbopogon citratus*).

Anti-diabetes: The whole essential oil, geraniol, and myrcene showed insulin secretagogue action. Geraniol demonstrated most potent insulin secretagogue action both in *in vivo* and *in vitro* studies (Bharti et al. 2013).

Other activities: Geraniol, a monoterpene alcohol, has the verity of pharmacological activities reported in preclinical studies. Geraniol has antibacterial, antiseptic, anti-inflammatory, *in vivo* and *in vitro* anticancer activity against in leukemia, hepatoma, melanoma, and pancreatic cancer cell lines, and activity on lipid metabolisms and mevalonate metabolisms (Madankumar and Devaki 2015).

131. Ginsenoside Re, ginsenoside Rh2

Plant source: Although ginsenosides are present in *Panax* sp., the composition of different types of ginsenosides differs in different species and in different chemotypes of the same species. The chemical structure of ginsenoside Re (Figure 2.26) and ginsenoside Rh2 (Figure 2.27) are shown below.

Anti-diabetes: Studies demonstrated that ginsenoside Re plays a significant role in antihyperglycemic action. Unlike the berry extract, the anti-diabetic effect of ginsenoside Re was not associated with body weight changes, suggesting that other constituents in the extract have

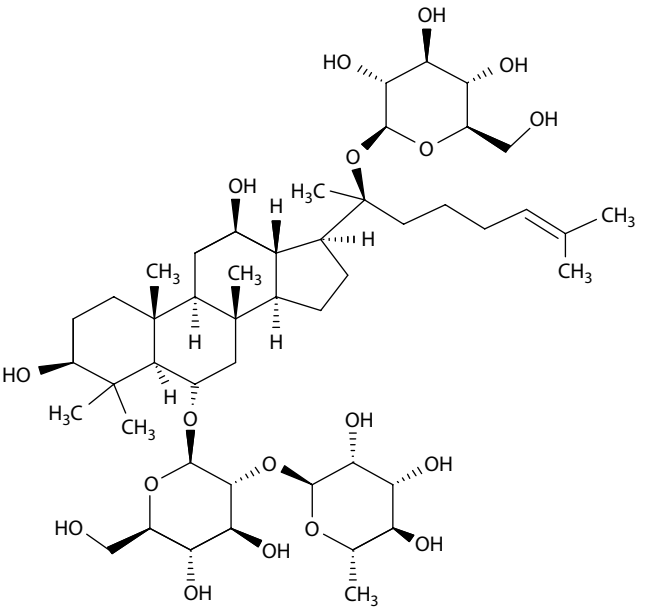


FIGURE 2.26 Structure of ginsenoside Re.

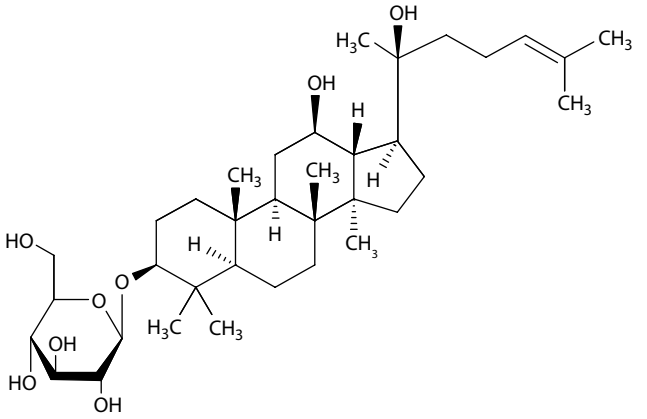


FIGURE 2.27 Structure of ginsenoside Rh2.

distinct pharmacological mechanisms on energy metabolism (Attele et al. 2002). In another study, the antioxidant and antihyperlipidemic efficacies of ginsenoside Re was shown in streptozotocin-diabetic rats. In addition to lowering glucose and lipid levels, ginsenoside Re decreased the levels of TNF and IL-6 involved in inflammation (El-Khayat et al. 2011). A study suggests that the compound can protect the diabetic rats from oxidative stress-mediated microvasculopathy in the eye, kidney, and so on (Cho et al. 2006). Ginsenoside Re exhibited anti-diabetic activity by reducing insulin resistance through activation of PPAR-γ pathway by increasing the expression of PPAR-γ and its responsive genes and inhibiting TNF-α production in 3T3-L1 adipocytes (Gao et al. 2013).

Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in Wister rats has been reported (Lee et al. 2006). In a cell culture system, ginsenoside Rh2 effectively inhibited adipocyte differentiation via PPAR-γ inhibition. Interestingly, ginsenoside Rh2 significantly

activated AMPK in 3T3-L1 adipocytes. Furthermore, ginsenoside Rh2 effectively induced lipolysis and this induction was abolished by AMPK inhibitor treatment (Hwang et al. 2007).

Malonyl ginsenosides, from the root of *Panax ginseng*, lowered fasting blood glucose level, improved insulin sensitivity, and improved lipid profile in type 2 diabetic rats induced by HFD and streptozotocin (Liu et al. 2013). Compound K (one of the ginsenosides) enhanced insulin secretion with beneficial metabolic effects in db/db mice (Kan et al. 2007). In an *in vitro* study, 20(S)-gingenoside Rg3 enhanced glucose-stimulated insulin secretion and activated AMPK (Park et al. 2008a). Another study suggests that the antiobesity effect of red ginseng–rich constituent ginsenoside Rg3 also involves the AMPK signaling pathway and PPAR-γ inhibition (Hwang et al. 2009).

Other activities: Ginsenoside Rh2 is one of the ginsenosides that exerts anti-inflammatory and anticancer effects (Wen et al. 2015).

132. Gingerol (6-gingerol)

Plant source: Gingerol is found in the rhizome of *Zingiber officinale*.

Anti-diabetes: Gingerol was shown to attenuate sodium nitrite-induced type 2 DM. This attenuation is related to islet-cell protection and increased insulin-receptor signaling (Chang et al. 2013). Both 6-Shogaol and 6-gingerol, the pungent of ginger, inhibited TNF-α-mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes (Wang et al. 2014).

Other activities: Other reported activities include antioxidant and anti-inflammatory activities (Dugasani et al. 2010). Furthermore, gingerol, a cardiotonic agent, has been shown to stimulate the Ca^{2+}-pumping activity of sarcoplasmic reticulum of rabbits in a concentration-dependent manner. Furthermore, gingerols represent a novel class of naturally occurring VR1 (vanilloid) receptor agonists that may contribute to the medicinal properties of ginger (Dedov et al. 2002).

133. Globularin, an iridoid glucoside

Plant source: *Globularia alypum*, *Globularia vulgaris*, and so on

Anti-diabetes: Globularin, an iridoid glucoside, was isolated from the leaves of *G. alypum*. In normal and streptozotocin diabetic rats, single (i.p.) administration of globularin (100 mg/kg) produced significant decrease of blood glucose levels. In the prolonged treatment study, the repeated (i.p.) administration of globularin decreased significantly the blood glucose levels when compared to the diabetic control rats. In addition, the daily injection of globularin reduced serum levels of total cholesterol and triglycerides in the diabetic rats. The acute toxicity test demonstrated that globularin is not lethal up to an i.p. dose of 1 g/kg injection (Merghache et al. 2013).

134. Glyceollins (phytoalexins)

Plant source: *Glycine max*

Anti-diabetes: Glyceollins are produced under fungal stress by *G. max*. Under *in vitro* conditions, glyceollins improved insulin-stimulated glucose uptake in 3T3-L1 adipocytes without activating the PPAR-γ agonist. They decreased triacylglycerol accumulation in adipocytes. In addition, glyceollins slightly improved glucose-stimulated insulin secretion without palmitate treatment in Min6 cells, and they potentiated insulinotropic actions when 500 μM palmitate was used to induce β-cell dysfunction. This was associated with decreased β-cell apoptosis because of the attenuation of endoplasmic reticulum stress, as determined by mRNA levels of X-box binding protein-1 (XBP-1), activating transcription factor-4 (ATF-4), activating transcription factor-4 (ATF-6), and C/E BP homologous protein (CHOP). Glyceollins also potentiated GLP-1 secretion to enhance insulinotropic actions in enteroendocrine cells' insulin sensitivity and exerted insulinotropic actions (Park et al. 2010).

Other activities: Glyceollins has anticancer and estrogenic activities. It inhibited angiogenesis (Lee et al. 2013) and inhibited the growth of human prostate cancer cells *in vitro* (Payton-Stewart et al. 2009).

135. Glycyrin and glycyrrhizin

Plant source: *Glycyrrhiza glabra*, *Glycyrrhiza uralensis*

Anti-diabetes: Glycyrin was found to suppress the increased blood glucose level in mice after sucrose loading during the oral sucrose tolerance test. Glycyrin exhibited a potent PPAR-γ ligand binding activity and therefore reduced the blood glucose level in knockout diabetic mice (KK-Ay). This finding is of much significance as licorice has also been traditionally used as an artificial sweetening agent and could be helpful in insulin resistance syndrome prevalent in modern society (Kuroda et al. 2004). Glycyrrhizin has also exhibited anti-diabetic activity in noninsulin-dependent diabetic models (Takii et al. 2000).

Other activities: Glycyrrhizin has a potential hepato protective activity. It has a capacity to regenerate the liver cell and inhibit fibrosis. Glycyrrhizin, an already known anti-inflammatory compound, has also been found as the first plant-based inhibitor of thrombin. Glycyrrhizin has a prominent antiviral activity, as it does not allow the virus cell binding (Sharma and Agrawal 2013).

136. Gossypin

Plant source: Gossypin is a pentahydroxy flavone glucoside found in the flowers of *Hibiscus vitifolius*.

Anti-diabetes: Oral administration of gossypin (20 mg/kg, daily for 30 days) to streptozotocin-induced diabetic rats improved glucose tolerance. Furthermore, the treatment increased blood glucose and HbA1c levels and the reduced plasma insulin and hemoglobin levels in diabetic rats were significantly reversed to near normal levels. Furthermore, the glycogen content of the liver and muscles was significantly improved after gossypin treatment. The data obtained in gossypin-treated rats were comparable with those obtained following gliclazide treatment of diabetic rats (Venkatesan and Pillai 2012).

Other activities: Gossypin has many biological properties, including antioxidant activity, anti-inflammatory, anticancer activities, antiallergic property, antinociceptive effect and neuroprotective activity (Bhaskaran et al. 2013; Chandrashekhar et al. 2013).

137. Gyaianolide (lactucin-8-O-methylacrylate)

Plant source: *Parmentiera edulis*

Anti-diabetes: Hypoglycemic activity-guided fractionation led to the isolation of a gyaianolide (lactucin-8-O-methylacrylate) from the chloroform extract of the dried fruits of *P. edulis*. The compound lowered blood glucose levels in alloxan diabetic mice (Perez et al. 2000).

138. Gymnemic acids

Plant source: *Gymnema sylvestre* leaf contains triterpene saponins gymnemic acids, gymnemasaponins, and gymnemasides. Gymnemic acids are at least nine closely related acidic glucosides. The basic molecular structure of gymnemic acids is shown in Figure 2.28.

Anti-diabetes: Gymnimic acids are a complex mixture of at least 9 closely related compounds (Kanetkar et al. 2007). Gymnemic acids have, in general, anti-diabetes and antisweetner activities. The triterpene glycoside, gymnemic acid IV (3.4–13.4 mg/kg) showed potent blood glucose-lowering activity in streptozotocin diabetic mice (Sugihara et al. 2000), whereas some other components (gymnemic acids I to III) possessed little activity (Sugihara et al. 2000). Gymnic acid V (saponin from leaves) showed hypoglycemic activity and was found to enhance endogenous insulin release (Kanetkar et al. 2007).

Gymnemic acid helped regeneration of β-cell, increased secretion of insulin, increased phosphorylase activity, increased gluconeogenic enzymes and decreased sorbitol dehydrogenase. Furthermore, gymnemic acid stimulated the utilization of glucose by insulin-dependent pathways (Kanetkar et al. 2007). It inhibited glucose absorption from the intestine also (Yoshikawa et al. 1997a).

Other activities: Gymnemic acids have antisweetener and anti-inflammatory activities (Kanetkar et al. 2007).

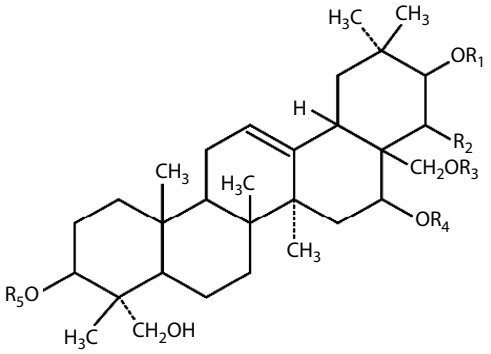


FIGURE 2.28 Basic structure of gymnemic acids.

139. Gymnorrhizol

    Plant source: *Bruguiera gymnorrhiza*

    Anti-diabetes: Gymnorrhizol, a novel, unusual 15-membered macyrocylic polydisulfide, isolated from the *B. gymnorrhiza,* showed potent inhibitory activity against PTP1B (Jiang et al. 2012).

140. Gypenosides

    Plant source: *Gynostemma pentaphyllum*

    Anti-diabetes: In a study, supplementation of ethanol extract of *G. pentaphyllum* leaf containing standardized concentrations of gypenosides in the diet (0.01%) lowered the blood glucose level by altering the hepatic glucose metabolic enzyme activities in C57BL/KSJ-db/db mice. The plasma insulin concentrations of the extract supplemented mice were elevated compared to the control group. The histology of the pancreatic islets revealed that the insulin-positive β-cell numbers were higher in the high-dose extract of *G. pentaphyllum* treated db/db mice (Yeo et al. 2008). The anti-diabetic effect of the standardized extract contained 98% gypenosides was associated with the stimulation of insulin release from the islets. The standardized extract-induced insulin release is partly mediated via K-ATP and L-type Ca^{2+} channels, the PKA system, and also dependent on pertussis toxin-sensitive G_e-protein (Lokman et al. 2015).

141. Harmane, norharmane (alkaloids)

    Plant source: *Peganum harmala* and so on

    Anti-diabetes: The β-carbolines harmane, norharmane (harman, norharman), and pinoline increased insulin secretion two- to threefold from isolated human islets of Langerhans. The effects of harmane and pinoline were dose-dependent and these agents also blocked the inhibitory effects of the potassium channel agonist, diazoxide, on glucose-induced insulin release. Stimulation of insulin secretion by harmane was glucose-dependent but, unlike the imidazoline I receptor agonist efaroxan, it increased the rate of insulin release beyond that elicited by 20 mM glucose. Stimulation of insulin secretion by harmane was attenuated by the imidazoline I receptor antagonist KU14R (2 (2-ethyl 2,3-dihydro-2-benzofuranyl)-2-imidazole) and was reduced when islets were treated with efaroxan for 18 h, prior to the addition of harmane. The results reveal that β-carbolines can potentiate the rate of insulin secretion from human islets and suggest that these agents may be useful prototypes for the development of novel insulin secretagogues (Cooper et al. 2003).

142. Harmine

    Plant source: Harmine is the major alkaloid of *Peganum harmala*. It is also present in plants such as *Banisteriopsis caapi* and *Tribulus terrestris*. The chemical structure of harmine is shown in Figure 2.29.

    Anti-diabetes: Harmine is the major anti-diabetic compound of *P. harmala*. Harmine regulated the expression of PPAR-γ and is reported that it mimics the effect of PPAR-γ ligands on insulin

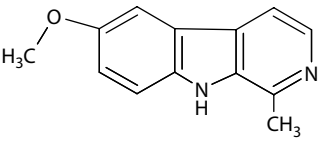


FIGURE 2.29 Structure of harmine.

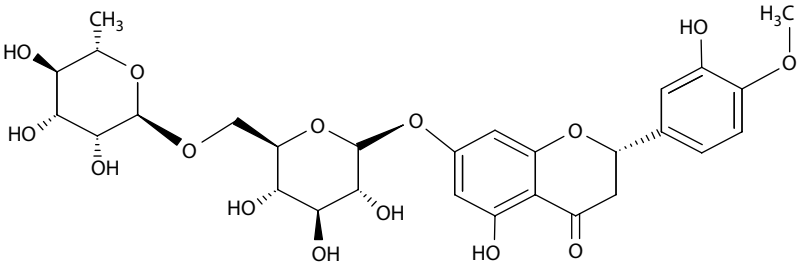


FIGURE 2.30 Structure of hesperidin.

sensitivity and adipocyte gene expression without showing the side effects of thiazolidinedione drugs such as weight gain (Moloudizargari et al. 2013; Waki et al. 2007).

Other activities: Harmine has psychoactive effects. Harmine is a monoamine oxidase inhibitor. The inhibitory effects at 5-HT_{2A} and imidazoline receptors and inhibition of dual-specific tyrosine phosphorylation regulated kinase 1A and the dopamine transporter may explain its psycho-pharmacological effects (Brierley and Davidson 2012).

143. Hesperidin (flavonoid)

Plant source: Hesperidin, a citrus bioflavonoid, is found in *Citrus lemon* and related species. The chemical structure of hesperidin is shown in Figure 2.30.

Anti-diabetes: Hesperidin (0.2 g/kg diet) supplementation significantly reduced blood glucose levels in C57BL/KsJ-db/db mice, an animal model for type 2 diabetes compared with the control diabetic group. Hepatic glucokinase activity and glycogen concentration were both significantly elevated in the hesperidin- and the naringin-supplemented groups compared with the control group. Plasma insulin, C-peptide, and leptin levels in the db/db mice from the two bioflavonoid-supplemented groups were significantly higher than those of the control group. Furthermore, plasma leptin was positively correlated with plasma insulin level and body weight and was inversely correlated with the blood glucose level. The study suggests that hesperidin and naringin both play important roles in preventing the progression of hyperglycemia, partly by increasing hepatic glycolysis and glycogen concentration and/or by lowering hepatic gluconeogenesis (Jung et al. 2004). In another study, the effect of the citrus flavonoids hesperidin and naringin on glucose and lipid regulation in C57BL/KsJ-db/db mice was investigated. Hesperidin and naringin both significantly increased the glucokinase mRNA level, while naringin also lowered the mRNA expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in the liver. In addition, the hepatic glucose transporter 2 protein expression was significantly reduced, while the expression of adipocyte glucose transporter 4 and hepatic and adipocyte PPAR-γ were elevated in the hesperidin and naringin groups when compared with the control group. The two flavonoids also led to a decrease in the plasma and hepatic cholesterol levels that may have been partly due to the decreased HMG-CoA reductase and acyl CoA: cholesterol acyltransferase activities and increased fecal cholesterol excretion (Jung et al. 2006).

Other activities: Both hesperidin and its aglycone hesperetin have been reported to possess a wide range of pharmacological properties. These include antioxidant activity, anti-inflammatory

property, antihypertensive effects, inhibition of bone loss and reduction in lipids in ovary -ectomized mice (Garg et al. 2001).

144. Hirsutrin (Hesperetin 7-rutinoside)

Plant source: *Zea mays*, *Lespedeza cuneata*, and so on

Anti-diabetes: Hirsutrin, from the kernel of purple corn, showed potent competitive inhibition of aldose reductase (IC_{50}: 4.78 μ M). Furthermore, hirsutrin inhibited galactitol formation in rat lenses and erythrocytes incubated with a high concentration of galactose; this finding indicates that hirsutrin may effectively prevent osmotic stress in hyperglycemia. Therefore, hirsutrin derived from *Z. mays* may be a therapeutic agent against diabetes complications (Kim et al. 2013).

Other activities: Hirsutrin (10 μM) showed hepatoprotective activity against injury by t-BHP in HepG2 cells. The observed hepatoprotective effect of hirsutrin showed a high correlation with radical scavenging activity (Kim et al. 2011).

145. Honokiol

Plant source: *Magnolia officinalis*

Anti-diabetes: The natural product honokiol from *M. officinalis* bark was *in silico* predicted to bind into the PPAR-γ ligand binding pocket as dimer. Honokiol indeed directly bound to purified PPAR-γ ligand-binding domain and acted as partial agonist in a PPAR-γ-mediated luciferase reporter assay. While honokiol stimulated basal glucose uptake to a similar extent as pioglitazone, it did not induce adipogenesis in contrast to pioglitazone. In diabetic KK-Ay mice, oral application of honokiol prevented hyperglycemia and suppressed weight gain (Atanasov et al. 2013). Honokiol is a dual agonist of PPAR-γ and RXR; it bound to purified human PPAR-γ and activated PPAR-γ-dependent reporter gene expression as partial agonist; induced glucose uptake but not adipogenesis in 3T3-L1 cells (Wang et al. 2014).

Other activities: Recent studies have demonstrated anti-inflammatory, antiangiogenic, antioxidative and anticancer properties of honokiol *in vitro* and in preclinical models. Honokiol targets multiple signaling pathways including NF-κB, signal transducers and activator of transcription, epidermal growth factor receptor and mammalian target of rapamycin, which have great relevance during cancer initiation and progression (Arora et al. 2012).

146. Hydnocarpin and isohydnocarpin (flavonolignans)

Plant source: *Hydnocarpus wightiana*

Anti-diabetes: Acetone extract of the seed hulls of *H. wightiana* showed strong free radicals scavenging activity, inhibition of α-glucosidase activity and moderate *N*-acetyl-β-D-glucosaminidase inhibitory activities. Hydnocarpin, luteolin, and isohydnocarpin were isolated from the acetone extract. All the three compounds also showed varying degrees of α-glucosidase and *N*-acetyl-β-D-glucosaminidase inhibitory activities (Reddy et al. 2005).

Other activities: Hydnocarpin and isohydnocarpin showed varying levels of antioxidant activity (Reddy et al. 2005). Hydnocarpin is reported to exhibit antimicrobial and anticancer activity (Sahoo et al. 2014).

147. Hydrangeic acid (stilbenoid)

Plant source: Hydrangeic acid was isolated from *Hydrangea macrophylla*. The chemical structure of hydrangeic acid is shown in Figure 2.31.

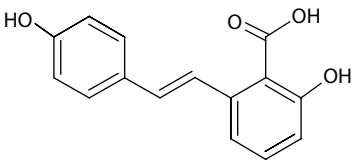


FIGURE 2.31 Structure of hydrangeic acid.

Anti-diabetes: Hydrangeic acid (3–100 μM), a stilbene constituent of the processed leaves of *H. macrophylla* promoted adipogenesis of 3T3-L1 cells. Hydrangeic acid significantly increased the amount of adiponectin released into the medium, the uptake of 2-deoxyglucose into the cells, and the translocation of GLUT4. Hydrangeic acid also increased mRNA levels of adiponectin, PPAR-γ2, GLUT4, and fatty acid-binding protein (aP2) while it decreased the expression of TNF-α mRNA. However, it did not activate PPAR-γ in a nuclear receptor cofactor assay system. Furthermore, hydrangeic acid significantly lowered blood glucose, triglyceride, and free fatty acid levels after its administration for 2 weeks at a dose of 200 mg/kg/day (p.o.) to KK-A(y) mice (Zhang et al. 2009).

148. Hydroxyapigenin (scutellarein)

Plant source: Origanum *majorana* (leaf)

Anti-diabetes: One of flavonoids, 6-hydroxyapigenin (scutellarein) isolated from leaves of *O. majorana* inhibited rat intestinal α-glucosidase. 6-Hydroxyapigenin exhibited IC_{50} value of 12 μM for sucrose hydrolysis by rat intestinal α-glucosidase (Kawabata et al. 2003).

149. Hydroxybenzoic acid

Plant source: *Pandanus odorus*, rice hull and so on

Anti-diabetes: 4-hydroxybenzoic acid from the root of *P. odorus* exhibited hypoglycemic effect in normal rats (Peungvicha et al. 1998a). It increased peripheral glucose consumption (Peungvicha et al. 1998b).

Other activity: 4-Hydroxybenzoic acid has antimcrobial activity (Cho et al. 1998).

150. Hydroxycacalolide and epi-3-hydroxycacalolide (eremophilanolides)

Plant source: *Psacalium decompositum*

Anti-diabetes: Eremophilanolides (epi-3-hydroxycacalolide and 3-hydroxycacalolide) showed antihyperglycemic activity (Inman et al. 1999). In a study, cacalol, cacalone epimer mixture (3-hydroxycacalolide and epi-3-hydroxycacalolide), and cacalol acetate compounds blocked K(ATP) channels in a similar way to glibenclamide in rat aorta. However, controversial data indicate that *P. decompositum* sesquiterpenoids are less effective than glibenclamide in lowering plasma glucose levels, suggesting that cacalol and cacalone epimer mixture, as well as cacalol acetate, may display a higher affinity to SUR2 subunit of K(ATP) channels in aortic smooth muscle than to SUR1 subunit in pancreatic β-cells (Campos et al. 2009).

151. Hydroxyisoleucine

Plant source: 4-Hydroxy isoleucine found in *Trigonella foenum-graecum* (fenugreek) seed is an atypical branched-chain amino acid. The chemical structure of 4-hydroxy isoleucine is shown in Figure 2.32.

Anti-diabetes: Antidyslipidemic and antihyperglycemic activity of 4-hydroxyisoleucine isolated from fenugreek seeds was shown in hamster model (Narender et al. 2006). Fenugreek seeds contain 4-hydroxy isoleucine in two diastero isomers: the major one being the (2*S*, 3*R*, and 4*S*) configuration and the minor one being the (2*R*, 3*R*, and 4*S*) configuration. The ability of the major isomer to stimulate glucose-induced insulin secretion from perfused pancreas *in vitro* in micro molar concentrations was shown (Sauvaire et al. 1998). The major isomer of 4-hydroxyisoleucine is responsible for the activity of fenugreek seed on glucose and lipid metabolism. Also, 4-Hydroxyisoleucine was demonstrated to stimulate glucose-dependent insulin secretion by a direct effect on pancreatic islets. In addition to stimulating insulin

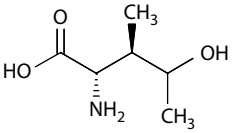


FIGURE 2.32 Structure of hydroxyisoleucine.

secretion, 4-hydroxyisoleucine reduced insulin resistance in muscle and/or liver by activating insulin receptor substrate-associated PI3K activities. Furthermore, 4-Hydroxyisoleucine reduced body weight in diet-induced obese mice. The decrease in body weight was associated with a marked decrease in both plasma insulin and glucose levels, both of which are elevated in this animal model. Besides, 4-hydroxyisoleucine decreased elevated plasma triglyceride and total cholesterol levels in a hamster model of diabetes. Based on the beneficial metabolic properties that have been demonstrated, 4-hydroxyisoleucine may represent an attractive new candidate for the treatment of type 2 diabetes, obesity and dyslipidemia, all key components of metabolic syndrome (Jette et al. 2009). The semisynthetic derivatives of this compound were reported to have more anti-diabetic activity than the parental compound (Sridevi et al. 2014).

Other activities: 4-hydroxyisoleucine may have hepatoprotective property also (Haeri et al. 2009).

152. Hydroxy 4-methoxy benzoic acid

Plant source: *Hemidesmus indicus*

Anti-diabetes: 2-Hydroxy 4-methoxy benzoic acid showed anti-DM activity in streptozotozin-diabetic rats and increased insulin secretion (Mahalingam and Krishnan 2009). Oral administration of 2-hydroxy 4-methoxy benzoic acid isolated from the root of *H. indicus* showed anti-DM activity against streptozotocin diabetic rats. At an oral dose of 500 μg/kg body weight, the compound normalized the elevated levels of glycosylated hemoglobin, total cholesterol and LDL cholesterol found in the diabetic animals. The levels of plasma insulin and liver glycogen content were also restored in the drug treated diabetic rats (Gayathri and Kannabiran 2009). Furthermore, 2-hydroxy 4-methyl benzoic acid ameliorated liver, kidney and pancreas injury in streptozotocin-induced diabetic rats (Gayathri and Kannabiran 2010). In another study, administration of 2-hydroxy-4-methoxy benzoic acid improved the antioxidant defense and reduced the free radial production, lipid peroxidation and the glycosylation of hemoglobin in streptozotocin-diabetic rats (Gayathri and Kannabiran 2012).

Other activities: 2-Hydroxy-4-methoxy benzoic acid exhibited antioxidant effect and provided protection against ethanol-induced hepatotoxicity in rats (Saravanan et al. 2007).

153. Hydroxymethyl xylitol

Plant source: *Casearia esculenta* (root)

Anti-diabetes: A novel compound, 3-hydroxymethyl xylitol was isolated from the root of *C. esculenta*. The compound showed anti-DM activity in streptozotocin diabetic rats (Indian Patent: Chandramohan et al. 2007). Also, 3-Hydroxymethyl xylitol decreased blood glucose levels, increased insulin levels and regulated carbohydrate-metabolizing enzymes in streptozotocin-diabetic rats (Chandramohan et al. 2011). In another study, the effect of 3-hydroxymethyl xylitol (40 mg/kg for 45 days) on plasma and tissue lipid profiles in streptozotocin-induced diabetic rats was determined. Total cholesterol, triglyceride, and free fatty acid levels increased in plasma and tissues significantly, whereas plasma HDL cholesterol significantly decreased and LDL cholesterol and VLDL cholesterol increased in diabetic rats. Treatment with 3-hydroxymethyl xylitol or glibenclamide reversed the above-mentioned changes and improved toward normalcy. Histological study of liver also confirmed the biochemical findings (Chandramohan et al. 2010).

Other activity: Other reported activities include antioxidant activity.

154. Hypoglysin A and hypoglysin B

Plant source: *Blighia sapida*

Anti-diabetes: Two unusual amino acids hypoglysin A and hypoglysin B were isolated from unripe fruit of this plant; these compounds possess antihyperglycemic activity. Hypoglycin A is more potent than hypoglycin B in inducing hypoglycemia. The injection of hypoglycin A forms a metabolite called methylene cyclopropane acetyl CoA, which inhibits several enzymes that are essential for metabolism of lipids, gluconeogenesis, and so on. This toxin induces hypoglycemia; depletion of glucose reserves and inability of cells to regenerate glucose (Atolani et al. 2009). Possibly, these two toxic compounds can serve as lead molecules for synthetic transformation into useful compounds including beneficial anti-DM drugs.

155. Icarin (icariin)

Plant source: The bioactive flavonol glycoside is found in *Epimedium brevicornum*.

Anti-diabetes: Icariin (icariin) isolated from *Epimedium brevicornum* leaf reduced mitochondrial oxidative stress and improved cardiac function in streptozotocin-diabetic rats (Bao and Chen 2011). Furthermore, icarin (5 mg/kg/day; p.o.) ameliorated streptozotocin-induced diabetic retinopathy in rats (Xin et al. 2012). The compound (80 mg/kg; i.g.) protected streptozotocin-diabetic rats from renal damage in the early stage of nephropathy via modulating transforming growth factor β1 and type IV collagen expression (Qi et al. 2011).

Other Activities: Icariin is pharmacologically active and demonstrates extensive therapeutic capacities such as osteoprotective effect, neuroprotective effect, cardiovascular protective effect, anticancer effect, anti-inflammation effect, and immunoprotective effect. Particularly, the significant osteogenic effect of icariin made it a promising drug candidate in bone tissue engineering (Li et al. 2015).

156. Ilekudinols

Plant source: *Weigela subsessilis*

Anti-diabetes: Ilekudinol A and ilekudinol B isolated from *Weigela subsessilis* leaf inhibited PTP1B with IC_{50} values of about 29 and 5 μM, respectively. Kinetic studies suggested that both 1 and 2 are noncompetitive inhibitors of PTP1B (Na et al. 2010). Ilekudinol B produced enhancement of glucose uptake both in basal- and insulin-stimulated L6 muscle cells by 1.6- and 2.9-fold, respectively. No cytotoxicities were observed for ilekudinol B in myoblasts. It may enhance glucose uptake by acting as insulin mimics and as insulin sensitizers *in vivo* (Lee and Thuong 2010).

Other activities: Ilekudinols A–C isolated from *Ilex kudincha* inhibited acyl CoA cholesteryl acyl transferase activity (Nishimura et al. 1999). Ilekudinol B isolated from *W. subsessilis* suppressed cyclooxygenase-2 expression in colonic epithelial cells (Park et al. 2006).

157. Imperatorin

Plant source: *Clausena lansium*

Anti-diabetes: Imperatorin and chalepin from methanol extract of stem bark of *C. lansium* increased *in vitro* insulin release to 170.3% and 137.9%, respectively, after 60 min. In glucose-loaded rats, imperatorin containing methanol extract of *C. lansium* showed antihyperglycemic activity and an increase in plasma insulin at 60 min, compared to control (Adebajo et al. 2009).

Other activities: Imperatorin showed antitrichomonal activity (Adebajo et al. 2009). Imperatorin inhibited hepatic microsomal drug-metabolizing enzymes (Shin and Woo 1986). Liver lesions were observed in chalepin-treated animals and were characterized by very mild necrosis of hepatocytes. No lesions were observed in the livers of rats treated with imperatorin (Emerole 1981).

158. Iridoid glycoside

Plant source: The iridoid glycoside (1,4a,5,7a-tetrahydro-5-hydroxy-7-(hydroxymethyl)-1-(tetrahydro-6-(hydroxymethyl)-3,4,5-trimethoxy-2H-pyran-2yloxy) cyclopenta[c]pyran-4-carboxylic acid) was isolated for the first time from *Steriospermam tetragonum*, a wild tree (Bino Kingsley et al. 2013). The chemical structure of the iridoid glycoside is shown in Figure 2.33.

Anti-diabetes: One of the anti-DM principles present in the root was identified as a novel iridoid glycoside (1,4a,5,7a-tetrahydro-5-hydroxy-7-(hydroxymethyl)-1-(tetrahydro-6-(hydroxymethyl)-3,4,5-trimethoxy-2H-pyran-2yloxy) cyclopenta[c]pyran-4-carboxylic acid). *In silico* docking studies showed binding sites in PPAR-γ for this compound (Bino Kingsley 2014). The mechanism of action of the anti-diabetic molecule appears to be inhibition of glucose absorption from the gut as well as activating PPAR-γ and GLUT4 (Bino Kingsley et al. 2014).

159. Isocryptotanshinone (abietane diterpene)

Plant source: *Salvia miltiorrhiza*

Anti-diabetes: PTP1B acts as a negative regulator of insulin signaling, and selective inhibition of PTP1B has served as a potential drug target for the treatment of type 2 diabetes. Isocryptotanshinone isolated from the root of *S. miltiorrhiza* inhibited PTP1B with 50% inhibitory concentration values of 56.1 ± 6.3 μM (Han et al. 2005).

Other activities: Isocryptotanshinone induced apoptosis and activated MAPK signaling in human breast cancer MCF-7 cells (Zhang et al. 2015).

160. Isohumulone

Isohumulone is present in *Humulus lupulus* (hops). It is a dietary ingredient from this plant. The chemical structure of isohumulone is shown in Figure 2.34. Isohumulones present in *H. lupulus* are primarily composed of isohumulone, isocohumulone, and isoadhumulone.

Anti-diabetes: Studies in multiple cell lines, animal model systems, and human intervention trials have consistently shown that isohumulones, bitter acids from the flower of *H. lupulus*, reduce insulin resistance and have a positive impact in dyslipidemia and obesity (Bland et al. 2015). Isohumulones from the flower of *H. lupulus* activated both PPAR-α and PPAR-γ and reduced insulin resistance (Yajima et al. 2004). Dietary isohumulones from *H. lupulus* raised plasma HDL-cholesterol and reduced liver cholesterol and triacyl glycerol accumulation similar to PPAR-α-activation in C57BL/6 mice (Miura et al. 2005). In another study, dietary isomerized *H. lupulus* extract containing isohumulones prevented diet-induced obesity in rodents (Yajima et al. 2005). Isohumulones modulate blood lipid state favorably through the activation of PPAR-α (Shimura et al. 2005).

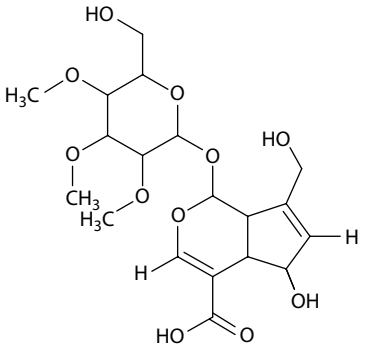


FIGURE 2.33 Structure of the iridoid glycoside.

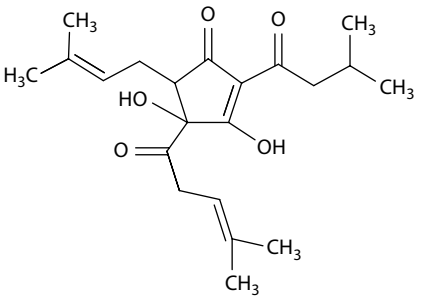


FIGURE 2.34 Structure of isohumulone.

Other activities: The isohumulones have been found to reduce metabolic inflammation and have a positive impact on dyslipidemia and obesity (Bland et al. 2015).

161. Isomeric C12-alkamides

Plant source: The isomeric C12-alkamides were found in *Echinacea purpurea* (root and cone flower)

Anti-diabetes: Two novel isomeric dodeca-2E,4E,8Z,10E/Z-tetraenoic acid 2-methylbutylamides were isolated from the active fraction of *E. purpurea* root. The isomeric C12-alkamides were found to activate PPAR-γ, to increase basal and insulin-dependent glucose uptake in 3T3-L1 adipocytes in a dose-dependent manner, and to exhibit characteristics of a PPAR-γ partial agonist (Kotowska et al. 2014). In another report, docking studies were performed to determine possible binding modes of the novel isomeric C12-alkamides within the PPAR-γ ligand binding domain. The weak activation of PPAR-γ as well as the results of docking mode of the novel isomeric C12-alkamides suggest that these compounds exhibit characteristics of a PPAR-γ partial agonist indicating that they may represent a chemical scaffold for the development of novel compounds with insulin sensitizing potential. Partial PPAR-γ agonists are associated with fewer side effects but still may maintain the effect on insulin resistance. The primary target for the currently used thiazolidinediones is PPAR-γ. However, critical side effects of thiazolidinediones can occur, as they are full PPAR-γ agonists (El-Houri et al. 2014).

162. Isoorientin (flavonoid)

Plant source: *Cecropia obtusifolia*, *Gentiana olivieri* and so on. The chemical structure of the isoorientin is shown in Figure 2.35.

Anti-diabetes: Isoorientin is a plant C-glycosylflavonoid with anti-diabetic properties. Through *in vivo* bioassay-guided fractionation processes isoorientin, a known C-glycosylflavone, was isolated from the ethylacetate fraction of *G. olivieri* as the main hypoglycemic ingredient from the plant. Isoorientin (15 mg/kg) administration to streptozotocin-diabetic rats resulted in significant hypoglycemic and antihyperlipidemic effects (Sezik et al. 2005). Isoorientin (flavonoid) activated the insulin signaling pathway and reverted the insulin resistance (Alonso-Castro et al. 2012). Nontoxic concentration of this compound stimulated 2-2-(N-(7-nitrobenz-2-oxa-1, 3-diazol-4-yl) amino)-2-deoxy-D-glucose uptake by murine 3T3-F442A and human adipocytes. The mechanism of action studies under cell culture conditions showed that isoorientin exerted its anti-DM effects by activating the insulin signaling pathways in adipocytes, reverting the insulin resistance caused in these cells by TNF-α by stimulating phosphorylation of proteins in the signaling pathway, and inducing expression of genes encoding these proteins (Alonso-Castro et al. 2012).

Other activities: Isoorientin was shown to possess significant antinociceptive in p-benzoquinone-induced writing test in rats and anti-inflammatory activities in carrageenan-induced hind paw edema model in mice without inducing any apparent acute toxicity as well as gastric damage (Kupeli et al. 2004).

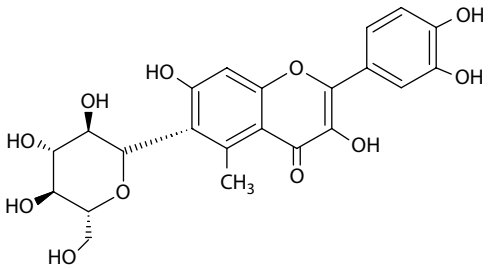


FIGURE 2.35 Structure of isoorientin.

163. Isotanshinone IIA and dihydroisotanshinone I (diterpenes)

Plant source: *Salvia miltiorrhiza*

Anti-diabetes: In the course of screening for PTP1B inhibitory natural products, the methanol extract of the dried root of *Salvia miltiorrhiza* was found to exhibit significant inhibitory effect. Bioassay-guided fractionation and purification afforded three related abietane-type diterpene metabolites, isotanshinone IIA, dihydroisotanshinone I, and isocryptotanshinone, which non-competitively inhibited PTP1B activity with 50% inhibitory concentration values of 11.4, 22.4, and 56.1 μM, respectively (Han et al. 2005).

Other activities: Studies suggest that the protective action of dihydroisotanshinone I against menadione-induced hepatotoxicity is attributed to its antioxidant properties including the free radical scavenging activity and inhibition of lipid peroxidation (Ip et al. 2002).

164. Jatrorrhizine (alkaloid)

Plant source: Jatrorrhizine is a protoberberine alkaloid isolated from *Tinospora cordifolia*, *Enantia* chlorantha and other species.

Anti-diabetes: It was found that jatrorrhizine (50 and 100 mg/kg) could markedly decrease blood glucose levels in a dose- and time-dependent manner in both normal and alloxan-diabetic mice. The treatment increased the activity of liver lactate dehydrogenase (LDH). Jatrorrhizine could significantly reduce the content of liver glycogen in normal mice. The hypoglycemic activity of jatrorrhizine may be attributed to the enhancement of aerobic glycolysis (Yan et al. 2005).

Other activities: Other reported activities include protective activity against amyloid-induced neurotoxicity, antioxidant activity, gastrointestinal modulatory activity, and antihypercholesterolemic effect. Besides, jatrorrhizine-elicited spontaneous contractions in rat ileum longitudinal muscles are mediated by activation of acetylcholine receptors, mostly the M(3) receptor (Yuan et al. 2011).

165. Kaempferol and kaempferol glycoside (flavonoids)

Plant source: Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a flavonoid found in many edible plants (e.g., tea, broccoli, cabbage, kale, beans, black gram, endive, leek, tomato, strawberries, grapes, almond, and cinnamum). The chemical structure of kaempferol is shown in Figure 2.36.

Anti-diabetes: The anti-diabetic effects of a kaempferol glycoside-rich fraction from leaves of soybean and kaempferol (an aglycone of kaempferol glycoside) were determined in genetically type 2 diabetic KK-A(y) mice. The glycated hemoglobin level was decreased and tended to be decreased respectively by feeding kaempferol glycoside and kaempferol. The area under the curve in the oral glucose tolerance test tended to be decreased by feeding kaempferol and kaempferol glycoside. The liver triglyceride level and fatty acid synthase activity were both decreased in the mice fed with kaempferol glycoside and kaempferol when compared to those parameters in the control diabetic mice. These results suggest that

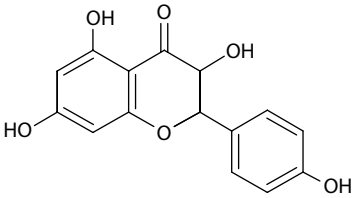


FIGURE 2.36 Structure of kaempferol.

kaempferol glycoside and kaempferol would be useful to improve the diabetes condition (Zang et al. 2011). Recently, the antiobesity and anti-diabetic effects of kaempferol glycoside fractions which were composed of four kaempferol glycosides purified from unripe soybean leaves were studied in C57BL/6J mice. HFD mice treated with 0.15% dietary kaempferol glycosides for 92 days had reduced body weight, adipose tissue and TG levels compared to the HFD control group. Kaempferol glycoside treatment also decreased fasting blood glucose, serum HbA1c levels and improved insulin resistance. Gene expression analysis of the liver showed that kaempferol glycoside decreased PPAR-γ and SREBP-1c expression (Zhang et al. 2015).

Other activities: Numerous preclinical studies have shown that kaempferol and some glycosides of kaempferol have a wide range of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, neuroprotective, antiosteoporotic, estrogenic/antiestrogenic, anxiolytic, analgesic, and antiallergic activities (Calderon-Montano et al. 2011).

166. Kaempferitrin (flavonoid)

Plant source: Kaempferitrin is found in the leaves of *Hedyotis verticillata*, *Onychium japonicum*, *Bauhinia forficata*, and certain other plants.

Anti-diabetes: Kaempferitrin exhibited insulinomimetic effects on glycemia and on ^{14}C-glucose uptake in rat soleus muscle. Kaempferitrin was found to have an acute lowering effect on blood glucose in diabetic rats and to stimulate the glucose uptake, as efficiently as insulin in muscle from normal rats. This compound did not have any effect on glucosuria or on protein synthesis in muscle from normal and diabetic animals (Jorge et al. 2004). In another study, kaempferitrin treatment resulted in an upregulated level of phosphorylation on insulin receptor and insulin receptor substrate 1, and ser473 site in PKB/akt in 3T3-L1 adipocytes. Inhibitor of PI3-K Wortmannin abolished PKB/akt phosphorylation and GLUT4 translocation. GLUT4 translocated to membrane and GLUT4 protein level increased upon kaempferitrin stimulation. Kaempferitrin also stimulated more sustained adiponectin secretion than insulin did. This study provided evidence of the dual effects of kaempferitrin. It improved insulin resistance by the activation of the classical insulin transduction pathway, and increased adiponectin secretion (Tzeng et al. 2009). However, another study showed that kaempferitrin inhibits insulin-stimulated GLUT4 translocation and glucose uptake in 3T3-L1 adipocytes at least by two different mechanisms, one by interfering with the insulin signaling pathway and the other by a possible competition with glucose during the transport (Vishnuprasad et al. 2009). Further studies are required to clear the picture.

167. Kaikasaponin III (triterpene saponin)

Plant source: *Pueraria thunbergiana*, *Pueraria lobata*, *Abrus cantoniensis*, and so on.

Anti-diabetes: Kaikasaponin III from the flowers of *Pueraria thunbergiana* (10 mg/kg, i.p., for 7 days) showed potent hypoglycemic and hypolipidemic effects in the streptozotocin-induced diabetic rat. The compound protected Vero cell from injury by hydrogen peroxide (Lee et al. 2000).

Other activities: Kaikasaponin III showed potent antimutagenic and antilipid peroxidative effects (Park et al. 2002). Furthermore, this compound showed the antihepatotoxic activity against CCl4 toxicity to hepatocytes *in vitro* (Miyao et al.1998). Kaikassaponin-III prolonged the bleeding time and plasma clotting time in streptozotocin-treated rats and increased the tissue factor activity, suggesting that this compound has antithrombosis activity. It also inhibited the formation of malondialdehyde and hydroxy radicals in serum and liver, while promoted superoxide dismutase activity (Choi et al. 2004).

168. Kakonein (flavonoid)

Plant source: *Pueraria lobata* (root)

Anti-diabetes: Kakonein (a flavonoid) isolated from root of this plant exhibited blood glucose-lowering effect in alloxan- or adrenaline-induced diabetic mice (Shen and Xie 1985).

169. Kalopanaxsaponin A (a glycoside)

Plant source: *Kalopanax pictus* (inactive kalopanaxsaponin B from bark is converted into active kalopanaxsaponin A in the human intestine by microflora).

Anti-diabetes: The anti-diabetic evaluation of chemical isolates from the stem bark of *K. pictus* in the streptozotocin-induced diabetic rats showed that kalopanaxsaponin A has a potent anti-diabetic activity in contrast to a mild activity of hederagenin. In addition, significant hypocholesterolemic and hypolipidemic activities of kalopanaxsaponin A and hederagenin were observed (Park et al. 1998). Human intestinal microflora metabolized kalopanaxsaponin B to kalopanaxsaponin A, hederagenin 3-O-α-L-arabinopyranoside and hederagenin. Kalopanaxsaponin H was metabolized to kalopanaxsaponin A and I, hederagenin 3-O-α-L-arabinopyranoside and hederagenin. Among kalopanaxsaponins, kalopanaxsaponin A showed the most potent anti-diabetic activity, followed by hederagenin. Kalopanaxsaponin A (25 mg/kg, i.p.) significantly reduced blood levels of glucose, cholesterol, total lipids and triglycerides in streptozotocin-induced diabetic rats (Kim et al. 1998).

Other activities: Kalopanaxsaponin A potently inhibited NF-κB activation in lipopolysaccharide-stimulated peritoneal macrophages during a screening program for anticolitis agents from natural products. Its anti-inflammatory mechanism involves inhibition of interleukin-1 receptor-associated kinase-1 (IRAK-1) activation in the NF-κB and MAPK pathways (Joh and Kim 2011).

170. Karanjin

Plant source: *Pongama pinnata*

Anti-diabetes: Karangin isolated from the fruits of *Pongamia pinnata* (100 mg/kg) possessed significant antihyperglycemic activity in streptozotocin-induced diabetic rats and type 2 diabetic db/db mice. Inhibition of PTP1B may be the possible mechanism of its activity (Tamrakar et al. 2008). Karanjin inhibited significantly the activity of PTP-ase 1B in an *in vitro* system (Akanksha et al. 2010).

Other activities: Behavioral responses to karanjin include reduced sensitivity to sound and touch, but animals had normal muscle tone and grip and were not sedated (Mahli et al. 1989). However, karanjin inhibited 50% and 74% of ulcers induced by swim stress at 10 and 20 mg/kg, respectively. Gastric mucin was protected up to 85% in case of swim stress, whereas only 47% mucin recovery was seen in ethanol stress-induced ulcers (Vismaya et al. 2011).

171. Kaurenoic acid (*ent*-kaurenoic acid)

Plant source: Kaurenoic acid (*ent*-kaur-16-en-19-oic acid) is a diterpene present in several plants including *Copaifera langsdorffi*, *Smallanthus sonchifolius*, *Sphagneticola trilobata*, and *Wedelia paludosa* (*Acmela brasiliensis*).

Anti-diabetes: The pharmacological evaluation showed that kaurenoic acid (ent-16-kauren-19-oic acid) is responsible, at least in part, for the hypoglycemic potential detected in *W. paludosa* (Bresciani et al. 2004). A single intraperitonial injection of *ent*-kurenoic acid (10 mg/kg) isolated from *S. sonchifolius* to normoglycemic mice resulted in consistent blood glucose reduction persisting from 1 to 2 h observation periods (Raga et al. 2010).

Other activities: Other activities include analgesic, antifungal, anti-inflammatory activity, smooth muscle relaxant activity and vasorelaxant action. Furthermore, the compound exhibited an analgesic effect in a consistent manner and that its mechanisms involve the inhibition of cytokine production and activation of the NO–cyclic guanosine monophosphate–protein kinase G–ATP-sensitive potassium channel signaling pathway (Bresciani et al. 2004; Mizokami et al. 2012).

172. Kinsenoside

Plant source: *Anoectochilus roxburghii*, *Anoectochilus formosanus*, and so on

Anti-diabetes: Kinsenoside, a major constituent of *Anoectochilus roxburghii* (15 mg/kg), exerted antihyperglycemic and antioxidant activities in streptozotocin-diabetic rats. Histopathological observations revealed the presence of much more intact β-cells in the pancreas of kinsenoside

treated diabetic rats. Furthermore, the compound improved oral glucose tolerance in both normal and streptozotocin-diabetic rats (Zhang et al. 2007). In another study, the vascular protective effect of kinsenoside in high glucose conditions was investigated in *in vivo* and *in vitro* experiments. In *in vivo* tests, kinsenoside (50 and 100 mg/kg) efficiently lowered blood glucose and cholesterol levels and it enhanced the oxidation resistance of diabetic mice induced by streptozotocin. In the *in vitro* assay, kinsenoside (20 and 50 μg/mL) markedly inhibited changes in nitric oxide, lactic dehydrogenase, superoxide dismutase and catalase in human umbilical vein endothelial cells damaged by high glucose (35 mM) and restored vascular endothelial structure by balancing the matrix metalloproteinases, the tissue inhibitors of matrix metalloproteinases system. The vascular protective effects of kinsenoside were speculated to be attributed to oxidative stress inhibition and the reduction of NF-κB mRNA expression levels in high glucose conditions. These observations indicated that kinsenoside might be a promising agent for the treatment of diabetic vascular disease (Liu et al. 2013).

Other activities: Other reported activities include *in vitro* liver cell protection against hepato toxins, anti-inflammatory property and antioxidant effects. In an *in vivo* study, crude extracts of fresh whole plants of *Anoectochilus formosanus* showed inhibition of chronic hepatitis induced by CCl_4 in mice. Bioactivity-guided fractionation and spectroscopic analysis revealed that kinsenoside was the most active hepatoprotective compound (Wu et al. 2007).

173. Kolaviron, a bioflavonoid complex

Plant source: *Garcinia kola*

Anti-diabetes: Kolaviron, a bioflavonoid complex isolated from seeds of *G. kola*, possessed significant hypoglycemic effect in alloxan-diabetic rats. Kolaviron also inhibited rat lens aldolase activity *in vitro*. Furthermore, kolaviron showed remarkable protective effects on renal, cardiac and hepatic tissues of streptozotocin-diabetic rats (Akinmoladun et al. 2014).

Other activities: Kolaviron has strong antioxidant properties; it limits the oxidative conversion of amino acid by ROS to other damaging products. It exhibit strong antioxidant activities both *in vivo* and *in vitro* experimental models. It has been reported to prevent hepatotoxicity mediated by several toxins. Furthermore, kolaviron, isolated from *G. kola*, inhibits acetylcholinesterase activities in the hippocampus and striatum of Wistar rats (Akinmoladun et al. 2014; Ijomone and Obi 2013).

174. Kotalanol

Plant source: *Salacia oblonga*, *Salacia reticulata*

Anti-diabetes: A potent natural α-glucosidase inhibitor called kotalanol has been isolated from an anti-diabetic traditional Ayurvedic medicinal plant *S. reticulata*. Kotalanol was found to show more potent inhibitory activity against sucrase than salacinol and acarbose (Ozaki et al. 2008; Yoshikawa et al. 1998).

175. Lactucain C (triterpenes)

Plant source: *Lactuca indica*

Anti-diabetes: Lactucain C (sesquiterpene lactone) isolated from *L. indica* showed significant anti-diabetes activity (Hou et al. 2003).

176. Lactucin

Plant source: *Cichorium glandulosum*

Anti-diabetes: Lactucin isolated from the root of the Chinese medicinal plant *C. glandulosum* was reported to inhibit PTP1B with an IC_{50} value of about1 μmol/L. A patent has been filed for the same (Jiang et al. 2012b).

Other activities: Lactucin exhibited analgesic action, antimalarial activity and sedative properties (Street et al. 2013).

177. Lagerstroemin (ellagitannin)

Plant source: *Lagerstroemia speciosa*

Anti-diabetes: Lagerstroemin (an ellagitannin) stimulated glucose transport into adipocytes with a 50% effective concentration of 80 μM. In another study, in rat adipocytes, the compound increased the rate of glucose uptake and decreased the isoproterenol-induced glycerol release. In Chinese hamster ovary cells expressing human insulin receptors, it increased the Erk activity. These insulin-like actions were accompanied by the increased tyrosine-phosphorylation of the β-subunit of the insulin receptors. Tryptic digestion of the extracellular sites of the insulin receptors markedly increased the effective concentrations of insulin without changing those of lagerstroemin. Thus lagerstroemin was considered to cause its insulin-like actions by a mechanism different from that employed by insulin (Hattori et al. 2003; Hou et al. 2009).

178. Lawsone

Plant source: *Lawsonia intermis*

Anti-diabetes: Lawsone (2-hydroxy-1,4-naphthoquinone), and gallic acid previously isolated from *L. intermis* were subjected to glycation bioassay for the first time. It was found that the alcohol extract, lawsone, and gallic acid showed significant inhibition of advanced glycated end products formation (Sultana et al. 2009). Lawsone and its O-alkyl derivatives have shown hypoglycemic and lipid lowering with ability to increase glucokinase activity. Glucokinase, predominant hexokinase expressed in the liver, has very high control strength on hepatic glucose disposal (Chauhan et al. 2013).

Other activities: Lawsone and its O-alkyl derivatives have antioxidant activity (Chauhan et al. 2013).

179. Lepidine and semilepidine (alkaloids)

Plant source: *Lepidium sativum*

Anti-diabetes: Lepidine and semilepidine (imidazole alkaloids) rich total alkaloid fraction from *L. sativum* showed a potential anti-diabetic effect against alloxan-induced diabetes. It reduced oxidative stress and modulated antioxidant enzymes. The possible mechanism by which the total alkaloid fraction brings about its antihyperglycemic action may be by potentiation of pancreatic secretion of insulin from the remaining islet β-cells (Shukla et al. 2012). Studies on individual alkaloid remain to be done.

180. Leucopelargonidin (glycoside of this flavonoid), pelargonin-3-O-α-1-rhamnoside

Ficus bengalensis (bark) is an important source of glycosides of leucopelargonidin. The chemical structure of leucopelargonidin is shown in Figure 2.37.

Anti-diabetes: Glycosides of leucopelargonidin exhibited hypoglycemic and hypolipidemic activities in diabetic rats and dogs (Augusti et al. 1994; Cherian and Augusti 1993); furthermore, it increased the levels of serum insulin (Cherian and Augusti 1993).

181. Leucodelphinidin (glycoside)

Plant source: *Ficus bengalensis*

Anti-diabetes: A leucodelphinidin glycoside (flavonoid glycoside) showed hypoglycemic property in normal as well as in alloxan-diabetic rats; 5,7,3′-Trimethy ether of leucodelphinidin 3-O-α-L rhamnoside is one of the active compounds (Geetha et al. 1994). Leucodelphinidin derivative from *F. bengalensis* showed a hypolipidemic effect also in cholesterol fed rats (Mathew et al. 2012).

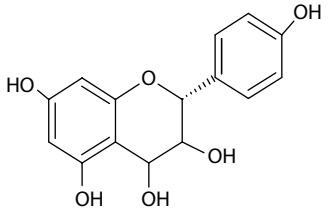


FIGURE 2.37 Structure of leucopelargonidin.

182. Licochalcone E

Plant source: *Glycyrrhiza inflata*, Daphniphyllum macropodum

Anti-diabetes: Licochalcone E is a retrochalcone isolated from the root of *G. inflata*. This compound induced 3T3-L1 preadipocyte differentiation. Furthermore, licochalcone E evidenced weak, but significant, PPAR-γ ligand-binding activity. Two weeks of licochalcone E treatment to diet-induced diabetic mice lowered blood glucose and serum triglyceride levels. Additionally, treatment with this compound resulted in marked reductions in adipocyte size and increases in the mRNA expression levels of PPAR-γ in white adipose tissue. Licochalcone E was also shown to significantly stimulate Akt signaling in epididymal white adipose tissue (Park et al. 2012).

Other activities: Licochalcone E exhibited potent anti-inflammatory effects in 12-O-tetradecanoylphorbol-13-acetate-induced mouse ear edema and lipopolysaccharide-stimulated RAW 264.7 murine macrophage models. The compound decreased the expression of pro-inflammatory cytokines and the inducible enzymes iNOS and COX-2 (Lee et al. 2013). Licochalcone E has potent antimicrobial property against *Staphylococcus aureus* (Zhou et al. 2012).

183. Lithospermans A, B, and C

Plant source: *Lithospermum erythrorhizon*

Anti-diabetes: Glycans, lithospermans A, B, and C, isolated from the water extract of *L. erythrorhizon* root, exerted marked hypoglycemic effects in normal and alloxan-induced hyperglycemic mice (Konno et al. 1985b).

184. Loganin

Plant source: *Cornus officinalis*

Anti-diabetes: Loganin (an iridoid monoterpenoid) isolated from the fruits of *C. officinalis* (5 and 10 mg/kg) showed renoprotective activity in streptozotocin-induced diabetic rats (Jiang et al. 2012b). In a recent study, loganin and its derivatives attenuated diabetic nephropathy *in vitro* in high glucose-induced mesangial cells as judged from the inhibition of expression of collagen IV, fibronectin, and IL-6 (Ma et al. 2014).

Other activities: Loganin improved learning and memory impairments induced by scopolamine in mice (Kwon et al. 2009). Furthermore, acute administration of loganin could improve spatial memory in diabetic rats (Babri et al. 2013).

185. Lophenol (phytosterol)

Plant source: *Aloe vera*

Anti-diabetes: Five phytosterols isolated from *A. vera*, namely, lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol, and 24-methylenecycloartanol exhibited anti-diabetic effects in type 2 diabetic mice. Lophenol showed marked antihyperglycemic activity in obese diabetic mice (Tanaka et al. 2006). In another detailed study, lophenol and cycloartanol, were evaluated in obese animal model of type 2 diabetes, Zucker-diabetic fatty rats. Consecutive treatment of lophenol and cycloartanol (25 μg/kg daily for 44 days) suppressed the hyperglycemia, and random blood glucose levels; the blood glucose levels after treatment for 45 days were 39.6% and 37.2% lower than the control, in lophenol and cycloartanol treatment groups respectively. Consistent with the random blood glucose level, HbA1c values of the treated rats were also lower than the diabetic control group. In the oral glucose tolerance test after 28 days of administration, the glucose intolerance was improved in phytosterols treatment groups. Additionally, the continuous administration of the compounds improved lipid profile. These observations suggest that lophenol and cycloartanol could reduce visceral fat accumulation, and would be useful for the improvement of hyperlipidemia and hyperglycemia (Misawa et al. 2008).

186. Lupanine (quinolizidine alkaloid from seed)

Plant source: *Lupinus mutabilis*, *Lupinus albus*, and so on

Anti-diabetes: Lupanine (a quinolizidine alkaloid from the seed) and its derivatives enhanced glucose-induced insulin secretion *in vitro* conditions. Multiflorine, another lupin alkaloid, and its derivatives exert hypoglycemic activity in normal as well as streptozotocin-induced diabetic mice. The most plausible action mechanism for the hypoglycemic activity of quinolizidine alkaloids is similar to that of sulfonylurea drugs (Garcia Lopez et al. 2004; Gurrola-Diaz et al. 2008).

Other activities: Lupanine from the seeds of *Lupinus albus* showed ganglioplegic activities and affinity for cholinergic receptors. It exhibited inhibitory action on nicotinic type hypertension produced by injection of acetylcholine (500 μg/kg i.v.) in the atropine-treated dog (Yovo et al. 1984).

187. Lupeol (triterpenoid)

Plant source: *Euclea undulata*, *Berberis vulgaris*, *Cassia fistul*, *Hemidesmus indicus*, *Sorbus commixta*, *Syzygium cumini*, and so on

Anti-diabetes: Lupeol and lupenone isolated from *S. commixta* inhibited PTP 1B *in vitro* and the IC_{50} value for lupeol was 5.6 μM (Nazaruk and Borzym-Kluczyk 2014).

Other activities: Lupeol has several pharmacological properties such as antiprotozoal effect, antimicrobial activity, antiinflammatory activity, antitumor, and chemopreventive properties (Gallo and Sarachine 2009).

188. Luteolin

Plant source: *Hydnocarpus wightiana*

Anti-diabetes: Luteolin (3',4',5,7-tetrahydroxyflavone) was isolated from the acetone extract of *H. wightiana*. Luteolin showed varying degrees of α-glucosidase and *N*-acetyl-β-D-glucosaminidase inhibitory activities; further it has antioxidant activity (Reddy et al. 2005). Luteolin exhibited protective effects against diabetic nephropathy in streptozotocin-induced diabetic rats. Changes in superoxide dismutase activity, the malondialdehyde content and expression of heme oxygenase-1 protein are involved in providing this protection (Wang et al. 2011).

Other activities: Luteolin has multiple biological effects such as anti-inflammation, antiallergy and anticancer. Luteolin's anticancer property is associated with the induction of apoptosis, and inhibition of cell proliferation, metastasis, and angiogenesis (Lin et al. 2008).

189. Magnolol

Plant source: Magnolol is a small polyphenolic molecule with low toxicity that is isolated from genus *Magnolia*. *Magnolia officinalis* is an important source of this compound. The chemical structure of magnolol is shown in Figure 2.38.

Anti-diabetes: Magnolol (5,5-diallyl-2,2-dihydroxybiphenyl) isolated from the cortex of *M. officinalis* retarded diabetic nephropathy in nonobese type 2 diabetic Goto–Kakizaki rats (Eunjin et al. 2007). Magnolol enhanced adipocyte differentiation and glucose uptake in 3T3-L1 cells. It is a dual agonist of PPAR-γ and retinoid X receptor-α (RXR-α); it binds to purified human PPAR-γ and activates PPAR-γ-dependent reporter gene expression as partial agonist, and it induces adipogenesis and glucose uptake in 3T3-L1 cells. In type 2 Goto–Kakizaki rats, this compound decreased fasting blood glucose and plasma insulin levels and prevented or retarded diabetic nephropathy (Wang et al. 2014). Thus, in preclinical experiments, magnolol was found to have anti-diabetic activity.

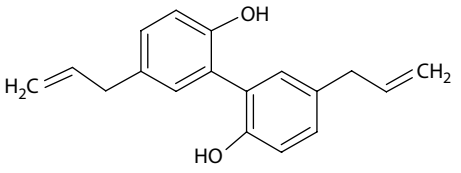


FIGURE 2.38 Structure of magnolol.

Other properties: Magnolol showed antioxidative, anti-inflammatory, antitumorigenic, antimicrobial, antineurodegenerative, and antidepressant properties. Furthermore, magnolol can effectively regulate pain control, hormonal signaling, gastrointestinal, and uterus modulation as well as provide cardiovascular and liver protective effects (Chen et al. 2011b).

190. Mahanimbine

Plant source: Mahanimbine isan important anti-DM compound isolated from *Murraya koenigii* (leaf). The chemical structure of mahanimbine is shown in Figure 2.39.

Anti-diabetes: Mahanimbine (a carbazole alkaloid from leaf) has inhibited the activities of α-amylase and, to some extent, α-glucosidase. Mahanimbin administration (50 and 100 mg/kg, i.p.) to streptozotocin-diabetic rats resulted in a marked reduction in fasting blood glucose levels and improvement in lipid profiles (Kumar et al. 2010). Furthermore, mahanimbin may increase peripheral glucose uptake and/or secretion of insulin (Nayak et al. 2010b).

Other activities: Mahanimbin showed high level of antioxidant activity. Furthermore, it showed cytotoxicity and antimicrobial activity (Handral et al. 2012).

191. Mangiferin (C-glycosyl xanthone) [C2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone]

Plant source: Mangiferin is present in *Mangifera indica*, *Anemarrhena asphodeloids*, *Salacia oblonga*, *Salacia chinensis*, and so on. The chemical structure of mangiferin is shown in Figure 2.40.

Anti-diabetes: The anti-DM principle in *A. asphodeloids* is mangiferin and its glucoside (Miura et al. 2001). Mangiferin, C-glucoside xanthone is present in the leaves and stem bark of *M. indica* (Li et al. 2010) and in many other higher plants. This compound enhances insulin sensitivity and modulates lipid metabolism. Mangiferin stimulated mitochondrial function and ATP production and showed antioxidant properties. In primary macrophages from mice, mangiferin inhibited the expression of proinflammatory cytokines, including IL-1 and TNF-α (Mirza et al. 2013). In rat myocytes, mangiferin fraction from *S. oblonga* increased GLUT4-mediated glucose uptake probably via activation of AMPK (GirGirón et al. 2009). Mangiferin decreased plasma free fatty acids through promoting its catabolism in liver by activation of AMPK (Niu et al. 2012). Furthermore, mangiferin activated the antihyperlipidemic transcription factor PPAR- α suggesting that the compound suppresses lipogenesis and stimulates lipolysis, thereby preventing HFD-induced diabetes. In KK-Ay-diabetic mice and streptozotocin-induced diabetic rats, mangiferin reduced plasma glucose and increased insulin sensitivity and glucose tolerance. Furthermore, mangiferin is an inhibitor of α-glucosidase which could reduce glucose formation from carbohydrate in

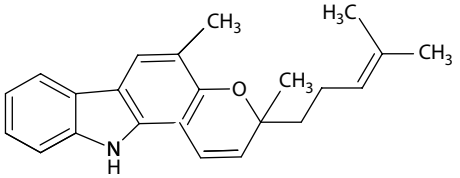


FIGURE 2.39 Structure of mahanimbine.

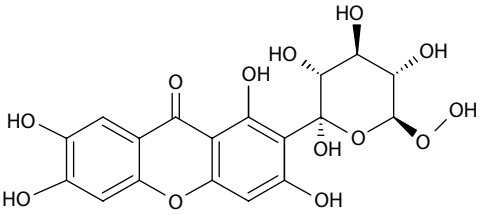


FIGURE 2.40 Structure of mangiferin.

the intestine. This compound also induced the enzymes in glycolysis (hexokinase and pyruvate kinase) and the enzymes involved in glycogen synthesis (Mirza et al. 2013). A recent study also showed the beneficial effects of mangiferin isolated from *Salacia chinensis* on biochemical and hematological parameters in streptozotocin-induced diabetic diabetes (Sellamuthu et al. 2014). Thus, mangiferin exerts its anti-DM activity through multifarious mechanisms.

Other activities: Mangiferin has potent antioxidant, cardioprotective, hypolipidemic, antihyperuricemic, anticancer, anti-inflammatory, and antiviral activities. Mangiferin can modulate molecular targets such as NF-κB signaling, and COX-2 protein expression (Mirza et al. 2013; Telang et al. 2013).

192. Marrubiin (diterpenoid)

Plant source: Marrubiin exists in high concentrations in many traditionally important Lamiaceae species.

Anti-diabetes: Marrubiin, a constituent of *Leonotis leonurus,* increased insulin levels and glucose transporter-2 gene expression in INS-1 cells. Marrubiin increased insulin secretion and HDL cholesterol level, while it normalized total cholesterol, LDL cholesterol, atherogenic index, IL-1β and IL-6 levels in an obese rat model (Mnonopi et al. 2012).

Other activities: Important pharmacological properties of marrubiin include antinociceptive activity, hypotensive effect, cardioprotective activity, gastroprotective activity, anti-inflammatory activity, antispasmodic activity, analgesic activity, anticoagulant, and antiplatelet activities, and vasorelaxant potential (Popoola et al. 2013).

193. Marsupsin (carpusin)

Plant source: *Pterocarpus marsupium* (heart-wood)

Anti-diabetes: Marsupsin (2,6-dihydroxy-2-[(4-hydroxyphenyl)methyl]-4-methoxy-1-benzofuran-3-one) decreased glucose levels in streptozotocin-induced diabetic rats and the effect was comparable to that of metformin (Manickam et al. 1997).

194. Maslinic acid (triterpene)

Plant source: *Lagerstroemia speciosa*, *Macaranga adenantha*, *Olea europaea*, and so on. The chemical structure of the maslinic acid is shown in Figure 2.41.

Anti-diabetes: Several *in vivo* and *in vitro* preclinical studies almost established the anti-diabetic properties of maslinic acid (crategolic acid). The compound (10 and 30 mg/kg, single oral administration) decreased blood glucose level at 2 and 4 h after administration in diabetic KK-A^y mice (genetic type 2 diabetes). When the compound was given daily for 4 weeks (10 mg/kg) the reduction in blood glucose was about 30% compared to the control diabetic mice; further, the treatment inhibited glycogenolysis via inhibition of glycogen phosphorylase and a dose-dependent reduction of plasma insulin levels was observed in KK-A^y mice. Besides, the treatment normalized plasma adiponectin levels. In an *invitro* assay, maslinic acid inhibited glycogen phosphorylase from rat liver with an IC_{50} value of 99 μM, being sixfold more potent than caffeine, as established inhibitor of glycogen phosphorylase. Muslinic acid binds at the allosteric activator site where the

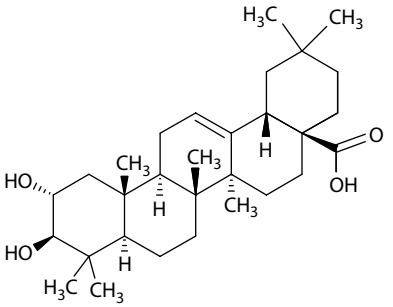


FIGURE 2.41 Structure of maslinic acid.

physiological activator AMP binds. In a mouse model of diabetes induced by adrenaline, oral administration of this compound (100 mg/kg for 7 days) resulted in marked reduction (46%) in the levels of fasting blood glucose compared to untreated control diabetic mice. In streptozotocin-induced diabetic rats, maslinic acid (80 mg/kg. p.o.) reduced postprandial blood glucose levels when co-administered with either sucrose or starch. The lowering of blood glucose by maslinic acid observed in this study was consistent with that observed in a previous study on streptozotocin-diabetic rats wherein this compound (50 mg/kg for 28 days, p.o.) showed 66% reduction in blood glucose levels (Lozano-Mena et al. 2014; Nazaruk and Borzym-Kluczyk 2014). In an *in vitro* study, the compound increased insulin receptor β phosphorylation in the hepatic cell line HepG2. In another study, when maslinic acid (50 and 100 mg/kg) was given orally to mice fed a HFD, blood glucose levels were markedly lowered. Furthermore, the treatment (100 mg/kg) improved hyperinsulinemia and adiposity (Lozano-Mena et al. 2014).

Other activities: Maslinic acid possesses a variety of pharmacological actions, including anti-tumor activity, antioxidant effect, neuroprotective activity, cardioprotective activities, and anti-parasitic property (Lozano-Mena et al. 2014). Maslinic acid only weakly inhibited CYP3A4 activity in human liver microsomes and specific CYP3A4 isoform with IC_{50} value at 46.1 and 62.3 μM, respectively (Sun et al. 2015).

195. Masoprocol (nordihydroguaiaretic acid)

Plant source: Nordihydroguaiaretic acid (masoprocol), a phenolic compound, is found in various plants and functional foods (e.g., *Larrea tridentata*).

Anti-diabetes: Masoprocal isolated from *L. tridentata* lowered blood glucose levels, without influencing the levels of insulin in 2 mouse models (C57BL/ks-db/db mice and C57BL/6J-ob/ob mice) of type 2 DM. Furthermore, masoprocal improved glucose tolerance and decreased insulin resistance (Luo et al. 1998).

Other activities: Masoprocol have known antioxidant activity, anti-inflammatory properties and lipid lowering effect. Masoprocal is a known lipoxygenase inhibitor; further it inhibited hepatitis C viral proliferation (Paracatu et al. 2015; Syed and Siddiqui 2011).

196. Meranzin

Plant source: *Limnocitrus littoralis*

Anti-diabetes: Meranzin (coumarin) isolated from the leaves of *L. littoralis* activated PPAR-γ. This observation suggests the likely anti-diabetic activity of this plant (Wang et al. 2014).

Other activities: Meranzin hydrate from natural resources exhibited antidepressive and prokinetic-like effects through the regulation of α-2-adrenoceptor (Xie et al. 2003).

197. Methylene-cycloartenol (phytosterol)

Plant source: *Aloe vera*, *Nigella sativa*, and so on

Anti-diabetes: 24-methylene-cycloartenol and cycloartanol showed marked antihyperglycemic activity in obese-diabetic mice (Tanaka et al. 2006).

198. Methylhonokiol (neolignan)

Plant source: *Magnolia officinalis* contains the neolignan, 4-O-methylhonokiol. The chemical structure of this compound is shown in Figure 2.42.

Anti-diabetes: In a recent study, the preventive effect on HFD-induced obesity and insulin resistance in mice by 4-O-methylhonokiol isolated from *M. officinalis* was compared with *M. officinalis* extract. Administration of the extract or the compound for 24 weeks with HFD slightly reduced body weight gain, body fat mass and the epididymis adipose tissue without any effect in food intake. Moreover, the compound significantly lowered HFD-induced plasma triglyceride, cholesterol levels and activity of ALT, liver weight and hepatic triglyceride level, and ameliorated hepatic steatosis. The extract reduced ALT and liver triglyceride level only. Low-dose 4-O-methylhonokiol improved HFD-induced hyperinsulinemia and insulin resistance. Furthermore, the infiltration of mast cells in adipose tissue was decreased in the compound or extract treated animals. These results suggested that 4-O-methylhonokiol might exhibit

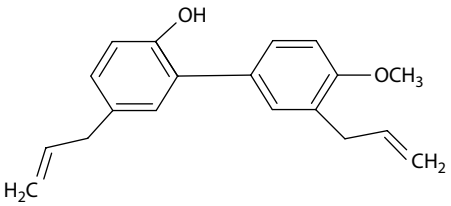


FIGURE 2.42 Structure of 4-O-methylhonokiol.

benefits for HFD-induced obesity by improvement of lipid metabolism and insulin resistance (Zhang et al. 2014). In a recent study, 4-O-methylhonokiol prevented the impairment of cardiac insulin signaling and the cardiac pathogenesis in HFD-induced obese mice. Methylhonokiol treatment significantly reduced the diet-induced impairment of insulin signaling by preferentially augmenting Akt-2 signaling. It also inhibited cardiac expression of the inflammatory factors TNF-α and plasminogen activator inhibitor-1 and increased the phosphorylation of Nrf2 as well as the expression of a Nrf2 downstream target gene heme oxygenase-1 (Zhang et al. 2015). Besides, 4-O-methylhonokiol is a PPAR-γ agonist (Hyun et al. 2015). Honokiol could serve as a regulator of various retinoid X receptor heterodimers (Kotani et al. 2012). Also, 4-O-methylhonokiol is promising candidate for the development of medicine for type 2 DM with beneficial effects on cardio-vascular problems and cancer.

Other activities: 4-O-methylhonokiol inhibits colon tumor growth via p21-mediated suppression of NF-κB activity (Oh et al. 2012). 4-O-methylhonokiol has anti-inflammatory properties through inhibition of the NF-kappaB pathway, and the authors suggested that 4-O-methylhonokiol can be used as an anti-inflammatory agent (Oh et al. 2009). In SiHa human cervical cancer cells this compound-induced apoptosis by triggering the intrinsic apoptosis pathway (Hyun et al. 2015). Furthermore, 4-O-methylhonokiol inhibited prostate tumor growth by p21-mediated suppression of NF-κB activity (Lee et al. 2013).

199. Methylhydroxychalcone

Plant source: *Cinnamomum verum*, *Cinnamomum cassia*

Anti-diabetes: Methylhydroxychalcone polymer from *Cinnamomum* sp. was found to be an effective mimetic of insulin in 3T3-LI adipocytes. This compound may be useful in the treatment of insulin resistance and in the study of the pathways leading to glucose utilization in cells (Jarvill-Taylor et al. 2001).

200. Methylswertianin (derivative of xanthone)

Plant source: Methylswertianin is present in *Swertia punicea*, *Swertia mussotii*. The chemical structure of methylswertianin is shown in Figure 2.43.

Anti-diabetes: Methylswertianin (1,8-dihydroxy-2,6-dimethoxyxanthone) was isolated from the active ethyl acetate fraction of *S. punicea*. The compound reduced fasting blood glucose in streptozotocin-induced type 2-diabetic male mice. The compound also improved oral glucose tolerance and lowered fasting serum insulin levels. Furthermore, treatment with the compound resulted in reduction in the serum levels of total cholesterol, LDL and triglyceride and increase in the levels of HDL. The compound improved insulin resistance by enhancing insulin signaling. The expression level of insulin-receptor α subunit, insulin receptor substrate-1 and phosphatidylinositol 3-kinase were also increased by methylswertianin. Besides, increased glycogen content, decreased glucokinase activities and increased glucose-6-phosphatase activities were observed in the compound-treated animals (Tian et al. 2010).

201. Mogrol and mogrosides

Plant source: *Siraitia grosvenorii;* Chemical structure of mogrol is shown in Figure 2.44.

Anti-diabetes: Recently, improved glucose tolerance, lipid utility and increased insulin sensitivity were observed on several diabetic rodent models treated with crude mogrosides isolated

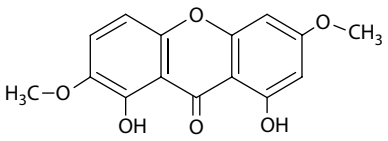


FIGURE 2.43 Structure of methylswertianin.

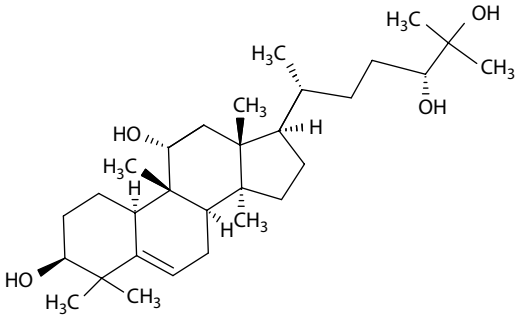


FIGURE 2.44 Structure of mogrol.

from the fruit of *S. grosvenorii*. Mogrosides lowered oxidative stress, serum glucose and lipid levels in alloxan-induced diabetic mice (Xiang-Yang et al. 2008). Crude mogrosides provided five new cucurbitane triterpenoids. The main aglycone mogrol and two cucurbitane triterpenoids were found to be potent AMPK activators in the HepG2 cell line. This result suggests that AMPK activation by the mogroside aglycones contribute at least partially to the antihyperglycemic and antilipidemic properties of *S. grosvenorii* (Chen et al. 2011a).

Alloxan-induced type 1 DM mice exhibited atrophy of pancreatic islets cells. In addition, alloxan induced a notable increase in the expression of CD8+ lymphocytes to form a dramatic decrease in CD4+/CD8+ ratio (while CD4+ was unchanged). Administration of mogroside extract to alloxan-diabetic mice for 4 weeks effectively attenuated the early clinical symptoms, biochemical abnormalities, and pathological damages in pancreatic islets. Furthermore, at low dose, mogroside extract regulated the immune imbalance observed in alloxan-induced diabetic mice by upregulating the CD4+ T-lymphocyte subsets and CD4/CD8 ratio, and altering the intracellular cytokine profiles. The expression of the proinflammatory Th1 cytokines [interferon gamma (IFN-γ) and TNF-α] in splenic lymphocytes was altered toward a beneficial Th2 pattern. Mogroside extract therapy had no effect on normal mice, except that low dosage could upregulate the IL-4 expression levels. The results revealed that the extract exhibited anti-diabetic effects presumably due to the presence of mogrosides (Xiangyang et al. 2006).

Other activities: Mogrosides inhibited lipopolysaccharide-induced inflammation and showed antioxidative effect on lipid peroxidation. Mogrosides effectively inhibited tumor growth in a two-stage carcinogenesis test, using a mouse skin tumor induced by 7,12-dimethylbenz(a)anthracene. Additionally, mogrol suppressed leukemia cell growth via inhibition of the ERK1/2 and STAT3 pathways, in particular, through the suppression of p-ERK1/2 and p-STAT3 (Liu et al. 2015).

202. Mokkolactone

Plant source: *Saussurea lappa*

Anti-diabetes: Activity guided fractionation of methanol extract of the root of *S. lappa* led to the isolation of mokkolactone and other compounds (betulinic acid, methyl ester of betulinic acid, and dehydrocostuslactone) which inhibit PTP1B (Choi et al. 2009).

Other activities: Mokkolactone is reported to have immune modulatory property (Yuuya et al. 1999).

203. Momordicine I and II

Plant source: *Momordica charntia*

Anti-diabetes: Momordicine I and II from *M. charntia* stimulated insulin secretion in MIN6 β-cells (Firdous 2014).

204. Momordin Ic (saponin)

Plant source: *Kochia scoparia*

Anti-diabetes: The methanol extract of the fruit of Japanese *Kochia scoparia* inhibited the increase in serum glucose in glucose-loaded rats. Through bioassay-guided separation, momordin Ic (scoparianoside B) and its 2′-O-β-D-glucopyranoside were isolated as the active principles from this medicinal foodstuff. These are the principle saponin constituents of this medicinal foodstuff and these saponins inhibited glucose and ethanol absorption in rats (Yoshikawa et al. 1997).

Other activities: Momordin Ic reduced carbon tetrachloride-induced hepatotoxicity in rats (Kim et al. 2005). Momordin Ic-induced HepG2 cell apoptosis through MAPK and PI3K/Akt-mediated mitochondrial pathways (Wang et al. 2013).

205. Moracin M (veraphenol)

Plant source: *Morus alba* (root bark)

Anti-diabetes: Moracin M (5-(6-Hydroxy-benzofuran-2-yl)-benzene-1,3-diol), steppogenin-4-O-β-glucoside, and mullberroside were isolated from the root of *M. alba*. All the three phenolic compounds (50 mg/kg, each) showed hypoglycemic effects in alloxan-diabetic rats (Zhang et al. 2009). Moracin C, Moracin D, moracin M and chalcomoracin, isolated from *M. alba* inhibited α-glucosidase activity (Firdous 2014).

Other activities: Moracin M from *Morus alba* is a phosphodiesterase-4 inhibitor (Chen et al. 2012).

206. Morolic and moronic acids

Plant source: *Phoradendron reichenbachianum*

Anti-diabetes: Morolic and moronic acids are the main constituents of acetone extract from *Phoradendron reichenbachianum*. Daily administered morolic and moronic acids (50 mg/kg) to noninsulin-dependent diabetic rats significantly lowered the blood glucose levels at 60% on first day and the low level was maintained until 10th day after treatment compared to untreated group. Moreover, both compounds diminished concentrations of cholesterol and triglycerides in plasma. Also, pretreatment with 50 mg/kg of each compound induced significant antihyperglycemic effect after glucose and sucrose loading (2 g/kg) compared with control group. *In vitro* studies showed that these compounds induced inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD 1) activity at 10 μM (Ramirez-Espinosa et al. 2013).

Other activities: Moronic acid is reported to have cytotoxicity and antiviral activities. Besides, moronic acid has antibacterial activity and the minimal inhibitory concentration of moronic acid was found to be between 1.5 and 3 μg/mL against some bacteria tested (Gehrke et al. 2013).

207. Morroniside and 7β-O-methylmorroniside

Plant source: *Sarracenia purpurea*, *Sarracenia alata*, *Cornus officinalis*, and so on. The chemical structure of morroniside (iridoide glycoside) is shown in Figure 2.45.

Anti-diabetes: Oral administration of morroniside (20 or 100 mg/kg, for 20 days) to streptozotocin-induced diabetic rats resulted in significant reduction in serum glucose and urinary protein levels. Moreover, the decreased levels of serum albumin and total protein in diabetic rats were significantly increased by morroniside administration at a dose of 100 mg/kg body weight/d. In addition, morroniside significantly reduced the elevated serum urea nitrogen level and showed a tendency to reduce creatinine clearance. Morroniside also significantly reduced the enhanced levels of serum glycosylated protein, and serum and renal thiobarbituric acid-reactive substances.

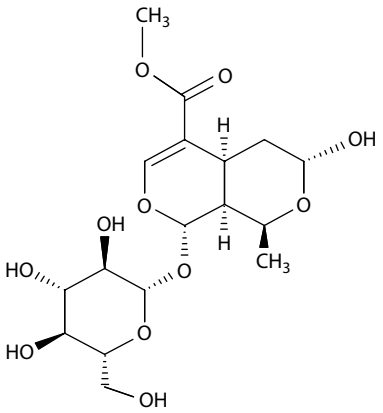


FIGURE 2.45 Structure of morroniside.

This suggests that morroniside exhibits protective effects against diabetic renal damage by inhibiting hyperglycemia and oxidative stress (Yokozawa et al. 2008). In another related study, morroniside (20 or 100 mg/kg, daily for 8 weeks, p.o.) produced significant dose-dependent reductions in serum triglyceride and renal glucose and lipid levels in type 2 diabetic db/db mice (Park et al. 2010). Besides, morroniside altered the abnormal protein expression of sterol regulatory element binding proteins (SREBP-1 and SREBP-2). In addition, the formation of ROS and lipid peroxidation were inhibited in the morroniside-treated db/db mouse group. Furthermore, 100 mg/kg morroniside downregulated the expression of NF-κB, cyclooxygenase-2 and inducible nitric oxide synthase in db/db mice (Park et al. 2010).

Another study was conducted to examine whether morroniside has an ameliorative effect on diabetes-induced alterations such as oxidative stress, inflammation, and apoptosis in the liver of type 2 diabetic db/db mice. Administration of morroniside (20 or 100 mg/kg, daily for 8 weeks, p.o.) decreased the elevated serum glucose concentration in db/db mice, and reduced the increased oxidative biomarkers including the generation of ROS and lipid peroxidation in the liver (Park et al. 2011). The db/db mice exhibited the upregulation of nicotinamide adenine dinucleotide phosphate oxidase subunits, heme oxygenase-1, NF-κB, cyclooxygenase-2, inducible nitric oxide synthase, monocyte chemotactic protein-1, and intracellular adhesion molecule-1 levels in the liver; morroniside treatment significantly reduced those expressions. Moreover, the augmented expressions of apoptosis-related proteins, Bax, and cytochrome c, were downregulated by morroniside administration. Hematoxylin–eosin staining showed that the increased hepatocellular damage in the liver of db/db mice improved on morroniside administration. Thus, the therapeutic evidence for morroniside ameliorating the development of diabetic hepatic complications via regulating oxidative stress, inflammation, and apoptosis was provided (Park et al. 2011). Morroniside and 7β-O-methylmorroniside showed significant stimulation of glucose uptake by cultured skeletal muscle cells (Eid and Haddad 2014).

Other activities: Morroniside showed neuroprotective effect against focal cerebral ischemia in rats (Wang et al. 2010). Also, 7(S)-n-butyl morroniside exhibited anti-inflammatory effect in human neutrophils (Wei et al. 2013).

208. Mulinolic acid (diterpenoid)

Plant source: *Azorella compacta*, *Mulinum crassifolium*, and so on

Anti-diabetes: Administration of mulinolic acid to streptozotocin-induced diabetic rats markedly reduced the hyperglycemia and the effect was comparable to that of chlorpropamide. Mulenic acid did not influence serum insulin levels (Fuentes et al. 2005).

209. Mullberroside A (phenolic compound)

Plant source: *Morus alba*

Anti-diabetes: Mullberroside A was isolated from the root of *M. alba*. This phenolic compound showed hypoglycemic effects in alloxan-induced diabetic rats (Zhang et al. 2009).

Other activities: Mulberroside A is known for its protective effects against melanogenesis induced by ultraviolet B irradiation, nephroprotective effects in hyperuricemic mice and neuroprotective effects. It protected against ischemic impairment in primary culture of rat cortical neurons. Furthermore, it downregulated P-glycoprotein expression and function (Li et al. 2014; Wang et al. 2014).

210. Multiflorine (alkaloid)

Plant source: *Lupinus mutabilis*

Anti-diabetes: Multiflorine, one of the lupin alkaloids, and its derivatives exert hypoglycemic activity in normal as well as streptozotocin-induced diabetic mice. The most plausible action mechanism for the hypoglycemic activity of the alkaloids is similar to that of sulfonylurea drugs (Garcia Lopez et al. 2004; Gurrola-Diaz et al. 2008). In another study, the effect of multiflorine and derivatives of spartine and lupanine on insulin secretion by pancreatic islets under *in vitro* conditions was investigated. Dioxosparteine, hydroxyl-lupanine and multiflorine at 500 μM enhanced insulin secretion from the islets incubated with 16.7 mM glucose, while thionospartine enhanced insulin secretion at 8.3 mM glucose (Gurrola-Diaz et al. 2008).

211. Myrcene

Plant source: *Cymbopogon citrates*

Anti-diabetes: The whole essential oil, geraniol and myrcene from *Cymbopogon citrates* showed insulin secretagogue action (Bharti et al. 2013). When compared to diabetic control rats, the essential oil-treated poloxamer-407-induced type 2 diabetic rats presented significant amelioration of glycaemia, insulinemia and lipid dysmetabolism, accompanied by increased GLP-1 content in cecum and remarkable reduction of oxidative markers (Wang et al. 2014).

212. Myricetin and myrciacitrin

Plant source: Myricetin (myricitrin) has been isolated from *Abelmoschus moschatus*, *Acacia leucophloea*, *Boerhaa*via *diffusa*, *Parinari excels*, *Myrcia multiflora*, *Syzygium malaccense*, and so on. It is also present in many fruits, vegetables, tea, berries and red wine. The chemical structure of myricetin is shown in Figure 2.46. Myrciacitrin is present in *Myrcia multiflora* and many other plants.

Anti-diabetes: The antihyperglycemic action of myricetin, purified from the aerial part of *A. moschatus,* was investigated in streptozotocin-induced diabetic rats. Bolus i.v. injection of myricetin decreased the plasma glucose concentrations in a dose-dependent manner in the diabetic rats. Myricetin (1.0 mg/kg) attenuated the increase of plasma glucose induced by an i.v. glucose challenge test in normal rats. A concentration-dependent stimulatory effect of myricetin (0.01–10.0 μmol/L) on glucose uptake of the soleus muscles isolated from streptozotocin-induced diabetic rats was observed. The increase of glucose utilization by myricetin was further characterized using the enhancement of glycogen synthesis in isolated hepatocytes of streptozotocin-diabetic rats. These studies suggest that myricetin has an ability to enhance

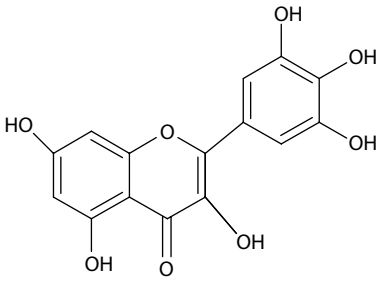


FIGURE 2.46 Structure of myricetin.

glucose utilization to lower plasma glucose in diabetic rats lacking insulin (Liu et al. 2005b). Myricetin stimulated insulin secretion and lowered blood glucose levels in diabetic rats (Ndiaye et al. 2008). It increased hepatic glycogen synthase 1 activity. Importantly, myricetin ameliorated insulin resistance; it exhibited antialdose reductase activity and antinonenzymatic glycation effect (Li and Ding 2012). Acylated flavonoid-O-glycoside derivative of myricetin is considered as one of the anti-DM principles present in the active extract of *Boerhaa*via *diffusa* (Pari and Satheesh 2004a). Flavonoids such as quercitin, and myricitrin isolated from *Myrcia multiflora,* are potent inhibitors of aldose reductase. The inhibitory activity is of the noncompetitive type (Varma et al. 1975). Although animal studies and *in vitro* studies show promising anti-DM property clinical studies are lacking.

Other activities: Other reported pharmacological actions of myricitin include anti-inflammation, antioxidative stress and antihyperlipidemia (Li and Ding 2012).

Myrciacitrins inhibited aldolase reductase and α-glucosidase. Myrciacitrin I and myrciaphenone B, were found to show potent inhibitory activities on aldose reductase and α-glucosidase (Yoshikawa et al. 1998).

213. Napthopyrone glycosides

Plant source: *Senna tora*

Anti-diabetes: The napthopyrone glycosides were isolated from the n-butanol fraction of the seed of *Senna tora* as active constituents; the napthopyrone glycosides rich butanol fraction (100 mg/kg) had blood glucose-lowering activity in normal and alloxan-induced diabetic rats in acute and prolonged treatment (Chaurasia et al. 2011).

Other activities: The napthopyrone glycosides from *Senna tora* showed antihepatotoxic activity in galactosamine damage in rats (Wong et al. 1989).

214. Napthoquinone derivative (5,8-dihydro-7-isopentyl-2,3,5,8-tetramethoxynaphthalene-1,4,6-triol)

Plant source: A napthoquinone derivative (5,8-dihydro-7-isopentyl-2,3,5,8-tetramethoxynaphthalene-1,4,6-triol) has been isolated from the root of *Steriospermam tetragonum* (Bino Kingsley et al. 2013). The chemical structure of this napthoquinone compound is shown in Figure 2.47.

Anti-diabetes: A lapachol-like compound, a derivative of napthoquinone (5,8-dihydro-7-isopentyl-2,3,5,8-tetramethoxynaphthalene-1,4,6-triol) was isolated as one of the anti-DM molecule from the active fraction of *Steriospermam tetragonum* (root). *In silico* docking studies showed binding sites in PPARs for this compound. The mechanism of action of this anti-diabetic molecule appears to be inhibition of glucose absorption from the gut as well as the activation of PPAR-γ and translocation of GLUT4 to the plasma membrane (Bino Kingsley 2014; Bino Kingsley et al. 2014b).

215. Naringenin (flavonoid)

Plant source: Naringenin is found in *Sansevieria senegambica* and in citrus fruits, tomato, and so on (Chigozie and Chidinma 2012). The chemical structure of naringenin is shown in Figure 2.48.

Anti-diabetes: Naringenin exhibited significant increase of lipogenesis in the presence and absence of insulin in primary rat preadipocytes. At the concentration range of 0.01–100 μM, naringenin inhibited 50% of epinephrine-induced lipolysis in rat adipocytes and enhanced

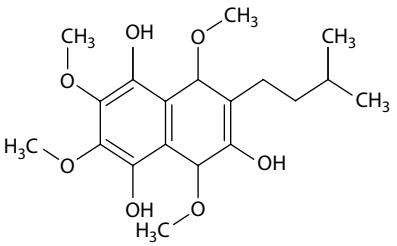


FIGURE 2.47 Structure of 5,8-dihydro-7-isopentyl-2,3,5,8-tetramethoxynaphthalene-1,4,6-triol (napthoquinone derivative).

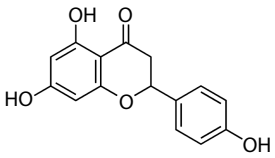


FIGURE 2.48 Structure of naringenin.

insulin's antilipolytic activity. Naringenin (100 μM) stimulated 163% glucose uptake in rat adipocytes (compared to untreated cells) and this was significantly higher than the insulin-mediated glucose uptake at similar concentration. Thus, naringenin may play an important role as an adjuvant and/or alternative to insulin therapy for the management of diabetes mellitus (Lim et al. 2007). In another study, intragastrically administered naringenin (50 mg/kg) induced a significant decrease in plasma glucose in normoglycemic and NIDDM rat models following acute and subchronic time periods. After 5 days of administration, naringenin produced significant diminished blood glucose and triglyceride levels in streptozotocin–nicotinamide-induced diabetic rats. The administration of naringenin to normal rats significantly increased the levels of triglyceride, total cholesterol and HDL. Naringenin (5 and 50 mg/kg) induced a total suppression in the increase of plasma glucose levels after administration of substrates but naringenin did not produce inhibition of α-glucosidase activity *in vitro*. However, naringenin (10 μM) was shown to inhibit 11β-HSD1 (11β-hydroxysteroid dehydrogenase type 1) activity by 39% in a cellular enzyme assay. Thus, naringenin may exert its anti-diabetic effect by extrapancreatic action and by suppressing carbohydrate absorption from intestine, thereby reducing the postprandial increase in blood glucose levels (Ortiz-Andrade et al. 2008). In a recent study, naringenin (dihydroflavonol) stimulated glucose uptake in normal and insulin-resistant primary porcine myotubes. This effect was attenuated in the presence of indinavir (GLUT4 inhibitor) and Wortmannin (PI3K and MAPK inhibitor) indicating a dependence on GLUT4 activity as well as PI3K and/or p38MAPK activity. Furthermore, naringenin-stimulated glucose uptake was dependent on AMPK activity. Besides, naringenin enhanced phosphorylation of TBC1D1 suggesting that this compound enhanced translocation of GLUT4 containing vesicles and thereby glucose uptake via a TBC1D1-dependent mechanism (Bhattacharya et al. 2014).

Other activities: Other reported pharmacological activities include hepatoprotection in streptopzotocin-induced diabetes (Kapoor and Kakkar 2014), anti-inflammatory activity and antifibrotic effects in diabetic mice (Tsai et al. 2012).

216. Naringin (naringoside)

Plant source: Naringin is commonly found in *Citrus lemon* and many other plants. The chemical structure of naringin is shown in Figure 2.49.

Anti-diabetes: The effect of the citrus flavonoid naringin on glucose and lipid regulation in C57BL/KsJ-db/db mice was investigated. Naringin significantly increased the glucokinase mRNA level, and lowered the mRNA expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in the liver. In addition, liver GLUT 2 protein expression was significantly reduced, while the expression of adipocyte GLUT4 and hepatic and adipocyte PPARγ were elevated in naringin group when compared with the control group. This flavonoid also led to a decrease in the plasma and hepatic cholesterol levels that may have been partly due to the decreased hepatic 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase and acyl CoA: cholesterol acyltransferase activities and increased fecal cholesterol excretion (Jung et al. 2006). Naringin exhibited neuroprotective effect by modulation of endogenous biomarkers in streptozotocin-induced painful diabetic neuropathy (Kandhare et al. 2012).

Other activities: Naringin inhibited some drug-metabolizing cytochrome P450 enzymes including CYP3A4 andCYP1A2 which may result in drug–drug interactions. Naringin ameliorated memory deficits in ICV-streptozotocin-induced experimental paradigm of Alzheimer's disease through attenuating mitochondrial dysfunction (Sachdeva et al. 2014).

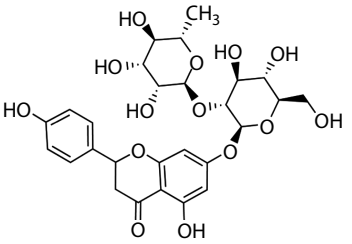


FIGURE 2.49 Structure of naringin.

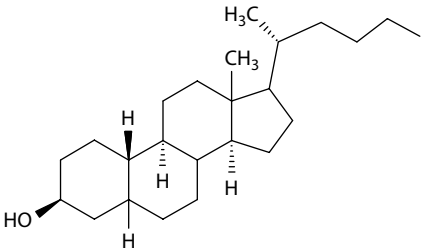


FIGURE 2.50 Structure of nymphayol.

217. 28-Nor-22(R)witha 2,6,23-trienolide (a noval steroid)

Plant source: *Elephantopus scaber* L

Anti-diabetes: 28-Nor-22(R)witha 2,6,23-trienolide showed anti-diabetic activity in streptozotocin-diabetic rats; it restored insulin levels. Stimulation of insulin release and/or β-cell mass increase could be the mechanism of action (Daisy et al. 2009a).

218. Nothofagin (dihydrochalcone)

Plant source: *Aspalathus linearis*, *Nothofagus fusca*, and so on

Anti-diabetes: Treatment with nothofagin (1-(3-β-D-glucopyranosyl-2,4,6-trihydroxyphenyl)-3-(4-hydroxyphenyl)-1-propanone found in the leaves of *Aspalathus linearis* inhibited high glucose-mediated vascular hyperpermeability, adhesion of monocytes toward human umbilical vein endothelial cells, and expression of cell adhesion molecules *in vitro*. In addition, these compounds suppressed the formation of ROS and the activation of NF-κB. *In vivo* in mice also these compounds suppressed vascular inflammation. Since vascular inflammation induced by high levels of glucose is critical in the development of diabetic complications, the authors suggest that these compounds may have significant benefits in the treatment of diabetic complications (Ku et al. 2015).

Other activities: The pharmacological properties of nothofagin include antioxidant activity, anti-inflammatory activity, antithrombotic activity, and antiendothelial cell protein C receptor shedding activity (Kwak et al. 2015).

219. Nymphayol (sterol)

Plant source: Nymphayol (25,26-dinorcholest-5-en-3b-ol) is found in *Nymphaea stellata*; the chemical structure of nymphayol is shown in Figure 2.50.

Anti-diabetes: Nymphayol [17-(hexan-2yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a] phenanthren-3-ol], a new sterol isolated from the chloroform extract of this plant flower, has been reported for its anti-diabetic activity at 20 mg/kg in streptozotocin-induced diabetic rats. Oral administration of nymphayol for 45 days significantly restored the plasma glucose levels and increased the plasma insulin levels to near normal in streptozotocin-diabetic rats. Light microscopy and immunocytochemical staining of nymphayol-treated diabetic pancreas revealed an increased number of insulin positive β-cells (Indian Patent: Ignacimuthu and Subash-Babu 2007; Subash-Babu et al. 2009). In a recent report, nymphayol treatment

improved glucose-stimulated insulin secretion by RIN-5F cells *in vitro*. Additionally, insulin sensitization and glucose uptake were increased in L6 myotubes. Nymphayol administration (5, 10 or 20 mg/kg, daily for 45 days) to streptozotocin–nicotinamide-induced type 2 diabetic rats resulted in a marked dose-dependent reduction in blood glucose levels and increase in insulin levels compared to diabetic control group. In addition, oral administration of nymphayol increased IRS1 phosphorylation and GLUT4 protein expression in liver and muscle. Nymphayol significantly restored the levels of HbA1c, hepatic glycogen and hepatic glucose-metabolizing enzyme (hexokinase, glucose-6-phosphate dehydrogenase, glucose-6-phosphatase, fructose-1, 6-bisphosphatase, glycogen synthase and glycogen phosphorylase) activity in diabetic rats. The results suggest that nymphayol may be a useful to treat DM (Subash-Babu et al. 2015).

Other activities: Nymphayol enhanced the antioxidant defense against the ROS produced under hyperglycemic conditions (Subash-Babu et al. 2009). Besides, nymphayol has multiple pharmacological activities which include antinociceptive effect, immunomodulatory property and antipyretic activity (Subash-Babu et al. 2013). Furthermore, nymphayol exhibited excellent gastroprotective effect which might be mediated by adjustment of inflammatory mediators and apoptotic markers and increasing antioxidants (Antonisamy et al. 2014).

220. Odoratin (geigerinin)

Plant source: *Chromolaena odorata*, *Cedrela odorata*, and so on

Anti-diabetes: Odoratin and (9*S*,13*R*)-12-oxo-phytodienoic acid isolated from *Chromolaena odorata* were shown to activate PPARγ receptors (Wang et al. 2014).

221. Oleanane-type triterpenoid saponins

Plant source: *Momordica cymbalaria* and *Pulsatilla koreana*

Anti-diabetes: Glucose uptake by isolated diaphragms of both streptozotocin diabetic and nondiabetic animals increased in presence of oleanane-type triterpenoid saponins isolated from the roots of *M. cymbalaria*. Insulin release was augmented by the presence of the saponins (1 mg/mL) in rat insulinoma cell line (RIN-5F) pre-exposed to adrenaline (5 μM) and nifedipine (50 μM). Pancreatic histology also indicated considerable quantitative increase in β-cells (75%) when treated with the saponin in the diabetic rats. The study suggests that the saponin of *M. cymbalaria* possesses potential anti-diabetic activity with respect to insulin secretion, which may be attributed to modulation of calcium channel, and β-cell rejuvenation (Koneri et al. 2014a). Several oleanane-type triterpenoid saponins from *Pulsatilla koreana* activated PPARs transcriptional activity significantly in a dose-dependent manner, with EC_{50} values ranging from 0.9–10.8 μM in HepG2 cells (Li et al. 2014).

Other activities: Oleanane-type triterpenoid saponins from *P. koreana* showed anti-inflammatory activity and inhibited TNFα-stimulated NF-κB activation in a dose-dependent manner, with IC_{50} values ranging from 0.75–8.30 μM in HepG2 cells (Li et al. 2014).

222. Oleanolic or oleanic acid (triterpenoid) and oleanolic acid glycosides

Plant source: Oleanolic acid is found widely in food, medicinal plants and other plants. Examples of oleanolic acid containing medicinal plants include *Berberis vulgaris*, *Eriobotrya japonica*, *Lagerstroemia speciosa*, *Ligustrum lucidum*, *Pistacia lentiscus*, *Phoradendrum reichenbachianum*, *Potentilla chinensis*, *Protium heptophyllum*, and *Sambucus adnata*. The chemical structure of oleanolic acid is shown in Figure 2.51.

Anti-diabetes: Oleanolic acid, a natural triterpenoid and an aglycone of many saponins, is a potent antioxidant. In the insulin-resistant diabetic model, oleanolic acid promoted insulin signal transduction and inhibited oxidative stress-induced hepatic insulin resistance and gluconeogenesis, in which process the phosphorylation of ERK and the protective effect on mitochondrial function may be involved. Oleanolic acid inhibited PTP 1B activity and the IC_{50} value was 3.9 μM (Nazaruk and Borzym-Kluczyk 2014). Besides, oleanolic acid showed a significant blood glucose-lowering and weight-losing effect in streptozotocin-induced diabetic animals (Wang et al. 2011). The biochemical basis of the anti-DM activity of oleanolic acid has been described (Castellano et al. 2013). It improves insulin response, preserves functionality and survival of

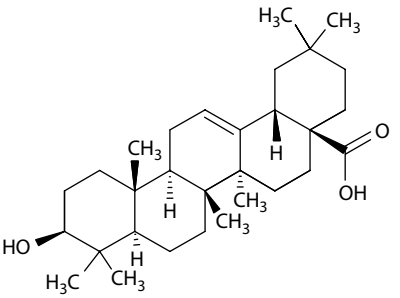


FIGURE 2.51 Structure of oleanolic acid.

β-cells, and protects against diabetes complications. Oleanolic acid may directly modulate enzymes connected to insulin biosynthesis, secretion, and signaling. However, its major contributions appear to be derived from the interaction with important transduction pathways, and many of its effects are consistently related to activation of the transcription factor Nrf2. Doing that, it induces the expression of antioxidant enzymes and phase II response genes, blocks NF-κB, and represses the polyol pathway, AGEs production, and hyperlipidemia (Castellano et al. 2013). Thus, oleanolic acis appears to be an important nutraceutic when taken regularly at proper doses to control DM.

Other activities: Oleanolic acid is known for its hepatoprotective property against toxic chemical-induced liver damage in laboratory animals. Other reported activities include anti-inflammatory and antihyperlipidemic properties (Liu 1995). However, it has been reported that repeated oral administration of oleanolic acid produces cholestatic liver injury in mice (Lu et al. 2013).

223. Oregonin (a diarylheptanoid glycoside)

Plant source: *Alnus incana* sub sp. *rugosa*

Anti-diabetes: Oregonin, a minor constituent of the alcohol extract of *Alnus incana*, blocked the differentiation and the maturation of 3T3-L1 preadipocytes (Eid and Haddad 2014).

Other activities: Oregonin reduced lipid accumulation, inflammation and ROS production in primary human macrophages, indicating that oregonin has anti-inflammatory activities (Lundqvist et al. 2015).

224. Paeoniflorin and 8-debenzoyl paeoniflorin

Plant source: *Paeonia lactiflora*, *Paeonia suffruticosa*

Anti-diabetes: Paeoniflorin and 8-debenzoylpaeoniflorin, isolated from the dried root of *Paeonia lactiflora*, produced a significant blood sugar-lowering effect in streptozotocin-treated diabetic rats and had a maximum effect at 25 min after treatment. This hypoglycemic action was also observed in normoglycemic rats. The antihyperglycemic activity of 8-debenzoylpaeoniflorin seems lower than that of paeoniflorin (1 mg/kg). Plasma insulin was not changed in paeoniflorin-treated normoglycemic rats indicating an insulin-independent action. Also, this glucoside reduced the elevation of blood sugar in glucose-challenged rats (Hsu et al. 1997). Paeoniflorin from the root of *P. lactiflora* prevented diabetic nephropathy in streptozotocin-induced diabetic rats (Jianfang et al. 2009). The protective effect of paeoniflorin and oxypaeoniflora (the two major compounds in *Paeonia suffruticosa*) on advanced glycation end products-induced mesangial cell HBZY-1 damage was studied. The study provided the evidence that paeniflorin and oxypaeniflora were able to attenuate advanced glycation end products-induced oxidative damage and inflammation in mesangial cells. Paeniflorin and oxypaeniflora might, therefore, have a beneficial effect in the treatment of diabetic complications (Zhang et al. 2013).

Other activities: Paeoniflorin suppressed rat adjuvant arthritis at least partly by inhibiting abnormal proliferation of synoviocytes and the production of IL-1, PGE2, IL-6, VEGF and GM-CSF by synoviocytes and reducing Gi and COX-2 expression in synovium (Zheng et al. 2007).

225. Palbinone (triterpene)

Plant source: *Paeonia suffruticosa*

Anti-diabetes: One of the triterpines, palbinone isolated from *Paeonia suffruticosa* stimulated glucose uptake and glycogen synthesis via activation of AMP activated protein kinase, GSK-3β, and ACC phosphorylation in insulin-resistant human HepG2 cells (Ha et al. 2009).

Other activities: Palbinone protected hepatic cells via upregulation of heme oxygenase-1. Palbinone-induced heme oxygenase-1 expression via the activation of Nrf2 in the hepatic cells (Ha et al. 2014).

226. Papaverine

Plant source: *Papaver somniferum*

Anti-diabetes: Papaverine from *P. somniferum* was found to readily dock within the binding pocket of human PTP1B (h-PTP1B) in a low energy orientation. Follow-up experimental studies showed the potent *in vitro* inhibitory effect of papaverine against recombinant h-PTP1B (IC_{50} = 1.20 μM). *In vivo*, papaverine significantly decreased fasting blood glucose level of Balb/c mice. Thus, papaverine exhibited anti-diabetic activity (Bustanji et al. 2009).

Other activities: Papaverine is a direct-acting smooth muscle relaxant used in the treatment of impotence and as a vasodilator, especially for cerebral vasodilation. The mechanism of its pharmacological actions is not clear, but it apparently can inhibit phosphodiesterases and it may have direct actions on calcium channels. This compound also exhibits antiviral activity against respiratory syncytial virus, cytomegalovirus, and HIV.

227. Pentamethylquercetin

Plant source: Pentamethylquercetin (a methylated quercetin derivative) is found in sea buckthorn (*Hippophae rhamnoids* L.) and in a variety of herbs including edible herbs in varying levels (Chen et al. 2011; Ying et al. 2013).

Anti-diabetes: Pentamethylquercetin exhibits promising anti-DM activity. Administration (p.o., daily for 10 weeks; 2.5, 5.0, and 10.0 mg/kg) of this compound to neonatally streptozotocin-induced diabetic rats resulted in a dose-dependent decrease in the levels of postprandial glucose and triglyceride levels; furthermore, the treatment prevented the onset of overt diabetes, ameliorated polydipsia symptom induced by diabetes, attenuated glucose intolerance, enhanced insulin sensitivity indices, and decreased endogenous creatinine clearance rate, urinary albumin excretion rate, and blood alanine aminotransferase levels in the diabetic rats as compared to untreated diabetic control rats (Wang et al. 2011). In another study, pentamethylquercetin exhibited beneficial effects in monosodium glutamate-induced obese mice and C2C12 myotubes by activating AMPK. This study suggests that this compound can ameliorate metabolic disorders at least in part via stimulation of AMPK activity (Shen et al. 2012). Furthermore, pentamethylquercetin upregulated adiponectin expression in differentiated 3T3-L1 cells via a mechanism that implicated PPAR-γ together with TNF-α and IL-6, suggesting this compound might be a potential candidate for the treatment of metabolic diseases. Adiponectin plays an important beneficial role in the regulation of lipid and glucose metabolism in diabetes also (Chen et al. 2011).

Other activities: Pentamethylquercetin exerted *in vivo* and *in vitro* cardioprotective effects against cardiac hypertrophy (He et al. 2012). Besides, pentamethylquercetin reduced thrombus formation by inhibiting platelet function in the collagen-epinephrine-induced acute pulmonary thrombosis in mouse (Liang et al. 2015). Furthermore, this compound reduced fat deposition via Sirt1-mediated pathways in HFD-induced male obese mice (Ying et al. 2013). Thus this compound appears to have multifarious beneficial effects.

228. Penta-O-galloyl-glucopyranose (gallotannin)

Plant source: Penta-O-galloyl-β-D-glucopyranose is found in *Lagerstroemia speciosa*, *Rhus chinensis*, and so on. The chemical structure of this compound is shown in Figure 2.52.

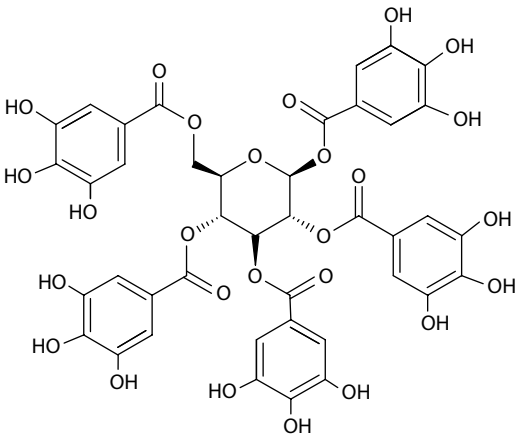


FIGURE 2.52 Structure of penta-O-galloyl glucopyranose.

Anti-diabetes: Gallotannins, penta-O-galloyl-β-D-glucopyranose (PGG) was identified as the most potent compound exhibiting insulin-like glucose transport inducing activity. PGG, an orally effective hypoglycemic molecule, binds to insulin receptors and activates insulin-mediate glucose transport. A comparison of published data with results obtained for PGG indicated that PGG has a significantly higher glucose transport stimulatory activity than lagerstroemin. Furthermore, PGG exhibited antiadipogenic properties in addition to stimulating the glucose uptake in adipocytes. The combination of glucose uptake stimulation and antiadipogenesis activity is not found in the current insulin mimetic drugs and may indicate a great therapeutic potential of PGG (Klein et al. 2007; Takagi et al. 2010; Yamada et al. 2008).

In another study, using an *in vitro* enzyme assay with human recombinant PTP1B, PGG was isolated from the roots of *Paeonia lactiflora* as an inhibitor of PTP1B, with an IC_{50} value of 4.8 μM. Additionally, PGG was shown to act as an insulin sensitizer in human hepatoma cells at a concentration of 10 μM. Thus, a potential mechanism of action is provided for PGG (Baumgartner et al. 2010). Insulin has been shown to bind to its receptors on platelets and inhibit platelet activation. A study showed that PGG mimicked inhibition of platelet activation of insulin, at least in part, by inducing phosphorylation of insulin receptors (Perveen et al. 2011). Detailed toxicity studies and follow-up clinical studies are warranted for likely medicine development.

Other activities: Several *in vitro* and some *in vivo* studies have shown that PGG exhibits multiple biological activities which implicate a great potential for PGG in the therapy and prevention of several major diseases including cancer. PGG reduced calcium oxalate crystal adhesion to renal epithelial cells by acting on the cells as well as on the crystal surface. Furthermore, PGG reduced renal crystallization and oxidative stress in a hyperoxaluric rat model (Lee et al. 2011). PGG inhibited NF-κB activation in lipopolysaccharide (LPS)-stimulated peritoneal and colonic macrophages. Mechanism of action studies has shown that PGG reduced activation of NF-κB and MAPK signaling pathways. PGG may ameliorate inflammatory diseases such as colitis (Jang et al. 2013). For anticancer activity, three published *in vivo* preclinical cancer model studies with PGG support promising efficacy to selectively inhibit malignancy without host toxicity. Potential mechanisms include antiangiogenesis, antiproliferative actions through inhibition of DNA synthesis (S-phase arrest), induction of apoptosis, anti-inflammation, and antioxidation (Zhang et al. 2009).

229. Phloroglucinol (phenolic)

Plant source: *Melothria maderaspatana* and many other plants and lower organisms.

Anti-diabetes: Phloroglucinol (0.25 mg/mL) from the methanol extract of *Melothria maderaspatana* (whole plant) inhibited 100% glucose production with or without insulin in rat liver

slices. The methanol extract of this plant (0.25 mg/mL) inhibited gluconeogenesis by 45%, and with insulin, inhibition increased to 50% (Srilatha and Ananda 2014). Phloroglucinol (25 or 75 mg/kg) administration inhibited increases in body weight caused by fructose-feeding in rats. Furthermore, the treatment increased the levels of HDL and decreased the levels of triglyceride in the fructose-fed rats. The elevated levels of blood glucose found in the fructose-fed rats were markedly reduced by the treatment. A similar pattern of effects of phloroglucinal was observed in high-fat-fed obese-diabetic rats. Furthermore, administration of phloroglucinal for 7 days decreased blood glucose levels in alloxan-induced diabetic rats also; besides this compound showed antiobesity and hypoglycemic effects in fructose-fed rats (Bansal et al. 2012). Mechanisms of actions are not clear; further studies are warranted.

Other activities: Phloroglucinol could protect the gastric mucosa against ethanol-induced injury, which is related to inhibiting the myeloperoxidase activity and increasing the catalase activity in the gastric tissues (Li et al. 2011). Studies have reported that phloroglucinol exerts a number of pharmacological activities such as antithrombotic and profibrinolytic activities, inhibitory effect on oxidative stress and inflammation, protective effect against myocardial ischemia and antispasmodic activity.

230. Piceatannol (stilbene)

Plant source: Piceatannol has been found in various plants, including grapes, passion fruit, white tea, and Japanese knotweed.

Anti-diabetes: Piceatannol (3, 3', 4, 5'-trans-trihydroxystilbene) and scirpusin B were isolated from the stem bark of *Callitemon rigidus*. These compounds inhibited α-amylase activity in isolated mouse plasma and gastrointestinal tract (Kobayashi et al. 2006). Piceatannol have a vital role in inhibiting adipogenesis. Piceatannol downregulated expression of CCAAT/enhancer-binding protein (C/EBP) and PPAR (proadipogenic transcription factors). It also inhibited phosphorylation and kinase activity of signaling pathways including IR and PI3K/Akt pathway (Kwon et al. 2012).

Other activities: Piceatannol displays a wide spectrum of biological activity. These include antitumor, antioxidant, and anti-inflammatory activities. Studies suggest that piceatannol might be a potentially useful nutritional and pharmacological biomolecule; however, more data are needed on its bioavailability, dose requirement, and toxicity in humans (Piotrowska et al. 2012).

231. Pinitol (3-O-methyl-chiroinositol)

Plant source: Pinitol (*S*,2*S*,4*S*,5*R*)-6-methoxycyclohexane-1,2,3,4,5-pentol) is found in *Abies pindrow*, *Bougainvillea spectablis*, *Caesalpinia bonbuc*, *Sutherlandia frutescens*, and so on. The chemical structure of this compound is shown in Figure 2.53.

Anti-diabetes: D-pinitol is a methyl ester of chiro-inositol (3-O-methyl-1,2,3-transhexahydroxycyclo hexanol). D-pinitol exhibits insulin-like effect. In streptozotocin-induced diabetic mice D-pinitol (100 mg/kg, i.p. or p.o.) acutely decreased hyperglycemia (by about 22% at 6 h). Chronic administration of this compound (100 mg/kg, i.p., daily for 11 days) to streptozotocin-diabetic mice maintained a reduction in plasma glucose concentration from about 14 to 10 mmol/L. In normal nondiabetic and severely insulin-resistant ob/ob mice the compound did not significantly influence plasma glucose or insulin levels during acute studies. The authors suggest that D-pinitol exerts an insulin-like effect to improve glycemic control in hypoinsulinemic streptozotocin-diabetic mice. The compound may act via a post-receptor pathway of insulin action (Bates et al. 2000). Pinitol exhibited anti-diabetes activity

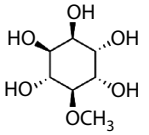


FIGURE 2.53 Structure of pinitol.

(Narayanan et al. 1987) and the mechanisms of action are stimulation of glucose-dependent insulin secretion and inhibition of α-amylase activity (Purohit and Sharma 2006). In another study, oral administration of pinitol from *B. spectabilis* to streptozotocin-diabetic rats elicited a decrease in the elevated levels of blood glucose and total cholesterol, triglyceride, free fatty acids, in serum, liver, kidney, heart, and brain (Geetham and Prince 2008).

Clinical studies on type 2 DM patients showed the beneficial effects of pinitol. In a randomized controlled clinical study, pinitol (600 mg/kg) significantly decreased mean fasting plasma glucose, insulin, fructosamine, HbA_{1c}, and the homeostatic model assessment insulin resistance index in Korean patients with type 2 DM. Besides, pinitol significantly decreased total cholesterol, LDL cholesterol, the LDL/HDL cholesterol ratio, and systolic and diastolic blood pressure and increased HDL cholesterol (Kim et al. 2005). In another clinical trial, pinitol from soybeans reduced postprandial blood glucose in patients with type 2 DM (Kang et al. 2006). In another study, in older humans, pinitol supplementation did not affect insulin-mediated glucose metabolism and muscle IR content and phosphorylation (Compbell et al. 2004).

Other activities: Among other things, it has anticancer activity. For example, pinitol significantly inhibited the proliferation of MCF-7 cells in a concentration-dependent manner, while upregulating the expression of p53, Bax and downregulating Bcl-2 and NF-κB (Rengarajan et al. 2014).

232. Piperine, pipermonaline and dehydropipermonaline (alkaloids)

Plant source: *Piper retrofractum*

Anti-diabetes: Piperidine alkaloids (piperine, pipermonaline, and dehydropipermonaline) from *P. retrofractum* attenuated HFD-induced obesity by activating AMPK and PPAR-δ, and regulated lipid metabolism, suggesting their potential antiobesity effects. Oral administration of the alkaloids (50, 100, or 300 mg/kg/day for 8 weeks) to obese mice significantly reduced HFD-induced body weight gain without altering the amount of food intake. Fat pad mass was reduced in the treatment groups, as evidenced by reduced adipocyte size. In addition, elevated serum levels of total cholesterol, LDL cholesterol, total lipid, leptin, and lipase were suppressed by the treatment. Piperidine alkaloids also protected against the development of nonalcoholic fatty liver by decreasing hepatic triglyceride accumulation (Kim et al. 2011).

Other activities: Dietary piperine, by favorably stimulating the digestive enzymes of pancreas, enhances the digestive capacity and significantly reduces the gastrointestinal food transit time. Piperine has been demonstrated in *in vitro* studies to protect against oxidative damage by inhibiting or quenching free radicals and ROS. Black pepper or piperine treatment has also been evidenced to lower lipid peroxidation *in vivo* and beneficially influence cellular thiol status, antioxidant molecules and antioxidant enzymes in a number of experimental situations of oxidative stress. The most far-reaching attribute of piperine has been its inhibitory influence on enzymatic drug biotransforming reactions in the liver. It strongly inhibits hepatic and intestinal aryl hydrocarbon hydroxylase and uridine 5'-diphospho (UDP)-glucuronyl transferase. Piperine has been documented to enhance the bioavailability of a number of therapeutic drugs as well as phytochemicals by this very property. Piperine, while it is nongenotoxic, has in fact been found to possess antimutagenic and antitumor influences (Srinivasan 2007). In mice, piperine exhibited a partially atropine-sensitive laxative effect at lower doses, whereas at higher doses it caused antisecretory and antidiarrheal activities that were partially inhibited in mice pretreated with naloxone, similar to loperamide. The presence of spasmodic (cholinergic) and antispasmodic (opioid agonist and Ca^{2+} antagonist) effects in piperine has been shown (Mehmood and Gilani 2010).

233. Polypeptide-p

Plant source: *Momordica charantia*

Anti-diabetes: The presence of molecules with insulin-like bioactivity in *M. charantia* seeds has been reported (Ng et al. 1987a). The plant insulin (polypeptide-p) may act in the absence of β-cells. It is an insulin-like hypoglycemic protein, which mimics the action of human insulin (Ng et al. 1987b). Polypeptide-p was shown to lower blood glucose levels in gerbils, langurs, and humans when injected subcutaneously (Tayyab et al. 2012). The 498-bp gene sequences

coding for the *M. charantia* polypeptide p gene have been cloned and expressed; the hypoglycemic effect of this recombinant polypeptide was shown in alloxan-induced diabetic mice (Wang et al. 2011). The p-insulin works by mimicking the action of human insulin in the body and thus may be used as plant-based insulin replacement in patients with type 1 diabetes.

234. Polyynes (e.g., cytopiloyne)

Plant source: Polyynes (polyacetylenes) are widespread in nature. The anti-DM polyynes are reported from *Bidens pilosa*. Chemical structure of cytopiloyne [2-β-D-glucopyranose-1-hydroxy trideca-5,7,9,11-tetrayne] is shown in Figure 2.54 (Yang et al. 2014).

Anti-diabetes: Three active polyynes [2-β-D-glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne (cytopiloyne), 3-β-D-glucopyranosyl-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne, and 2-β-D- glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne] were isolated from the butanol extract of *B. pilosa*. These compounds showed similar effects on Th cell differentiation as the *B. pilosa* butanol fraction. Moreover, cytopiloyne showed greater activity than the other two compounds in terms of enhancement of differentiation of Th0 to Th2 and inhibition of differentiation to Th1 (Chang et al. 2004; Chiang et al. 2007). In another study, the nonobese mice received i.p. or intramuscular injection of the most active cytopiloyne at 25 g/kg, three times per week. Remarkably, 12- to 30-week-old mice treated with cytopiloyne showed normal levels of blood glucose (200 mg/dL) and insulin (1–2 ng/mL), whereas untreated control 12-week-old nonobese-diabetic mice started to develop type 1 DM, and 70% of these mice aged 23 weeks and overdeveloped type 1 DM. Consistent with type 1 DM incidence, cytopiloyne delayed and reduced the invasion of CD4+ T-cells into the pancreatic islets (Chang et al. 2007). First, [^{3}H] thymidine incorporation assay showed that cytopiloyne inhibited ConA/IL-2- and CD3 antibody-mediated T-cell proliferation, implying that cytopiloyne could inhibit T-cell activation. Second, *in vitro* study showed that cytopiloyne inhibited the differentiation of CD4+ T-cells into Th1 cells and promoted differentiation of Th0 cells into Th2 cells (Chiang et al. 2007). The *in vitro* data are consistent with the *in vivo* results, indicating that cytopiloyne reduced Th1 differentiation and increased Th2 differentiation as shown by intracellular cytokine staining and fluorescence-activated cell sorting (FACS) analysis. Cytopiloyne also enhanced the expression of GATA binding protein-3 (GATA-3), a master gene for Th2 cell differentiation, but not the expression of T-bet, a master gene for Th1 cell differentiation, further supporting its role in skewing Th differentiation. In line with the skewing of Th differentiation, the level of serum IFN-γ and IgG2c decreased, while that of serum IL-4 and serum IgE increased compared to the negative controls. Third, cytopiloyne partially depleted CD4+ rather than CD8+ T-cells in nonobese diabetic (NOD) mice (Chang et al. 2007). Coculture assays showed that the depletion of CD4+ T-cells was mediated through the induction of Fas ligand expression on pancreatic islet cells by cytopiloyne, leading to apoptosis of infiltrating CD4+ T-cells in the pancreas via the Fas and Fas ligand pathway. However, cytopiloyne did not induce the expression of TNF-α in pancreatic islet cells and, thus, had no effect on CD8+ T-cells (Chang et al. 2007). Cytopiloyne is an immunomodulatory compound rather than an immunosuppressive compound. The mechanism of action of cytopiloyne in type 1 DM includes inhibition of T-cell proliferation, skewing of Th cell differentiation and partial depletion of Th cells, and protection of β-cells of pancreatic islets (Yang 2014).

3-β-D-glucopyranosyl-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne and 2-β-D-glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne are two of the three compounds discussed above. The mixture

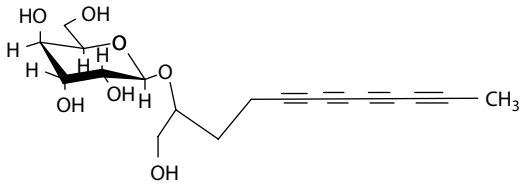


FIGURE 2.54 Structure of cytopiloyne (a polyyne).

of these compounds in a 2:3 ratio significantly reduced blood glucose level and food intake on the second day when administered at doses of 250 mg/kg twice a day to C5BL/Ks-db/db diabetic mice. When evaluated at 500 mg/kg, a more substantial decrease in blood glucose level as well as the stronger anorexia was noticed. This study suggests that these two compounds are anti-DM ingredients of *B. pilosa* (Ubillas et al. 2000). The anti-diabetic effect of both polyynes was partially caused by the hunger suppressing effect. However, the anoxic effect of the ethanol extract of *B. pilosa* was not observed in the study described below. In this study (Hsu et al. 2009) water extracts of *B. pilosa* were tested in diabetic db/db mice. Like oral anti-diabetic glimepiride, which stimulates insulin release, one single dose of the water extract reduced blood glucose levels from 20.8 to 8.0 mmol/L (374 to 144 mg/dL).

Cytopiloyne reduced postmeal blood glucose levels, increased blood insulin, improved glucose tolerance, suppressed HbA1c level, and protected pancreatic islets in db/db mice. Nevertheless, cytopiloyne never managed to decrease blood glucose in streptozocin-diabetic mice whose β-cells were already almost completely destroyed. In addition, cytopiloyne dose-dependently promoted insulin secretion and expression in β-cells as well as calcium influx, diacylglycerol, and activation of protein kinase Cα. Taken together, the mechanistic studies suggest that cytopiloyne acts via regulation of β-cell functions (insulin production and β-cell preservation) involving the calcium/diacylglycerol/PKCα cascade. Intriguingly, about 36 polyynes have been found in *B. pilosa* so far.

235. Pongamol

Plant source: Pongamol is found in *Pongamia pinnata*. The chemical structure of this compound is shown in Figure 2.55.

Anti-diabetes: Pongamol isolated from *P. pinnata* fruit showed anti-diabetic property in both streptozotocin-induced diabetic rats and type 2 DM mice. Pongamol (50 mg/kg, single dose) lowered blood glucose levels by 20%, 6 h after oral administration in streptozotocin-induced diabetic rats. The compound (100 mg/kg for 7 days) also significantly lowered blood glucose levels in type 2 DM db/db mice; the reduction was 35% compared to diabetic control mice. Pongamol and karanjin from *P. pinnata* inhibited significantly the activity of PTP1B in an *in vitro* system (Tamrakar et al. 2008). The effect of pongamol on glucose uptake and GLUT4 translocation in skeletal muscle cells was studied. In myotubes treatment with pongamol significantly promoted both glucose transport and GLUT4 translocation to the cell surface in a concentration-dependent manner, without changing the total amount of GLUT4 protein and GLUT4 mRNA; additive effects were seen with insulin. Cycloheximide treatment inhibited the effect of pongamol on GLUT4 translocation suggesting the requirement of new protein synthesis. The pongamol-induced increase in GLUT4 translocation was completely abolished by Wortmannin, and pongamol significantly potentiated insulin-mediated phosphorylation of Akt (Ser-473). The authors conclude that pongamol-induced increase in glucose uptake in L6 myotubes is the result of an increased translocation of GLUT4 to plasma membrane, driven by a PI3K/Akt-dependent mechanism (Tamrakar et al. 2011).

236. Prunin (naringenin 7-O-β-D-glucoside)

Plant source: *Prunus davidiana*, *Bixa orellana*, *Dracocephalum rupestre*, and so on

Anti-diabetes: Prunin (naringenin 7-O-β-D-glucoside) improved hyperglycemia and hyperlipidemia in streptozotocin-induced diabetic rats (Choi et al. 1991).

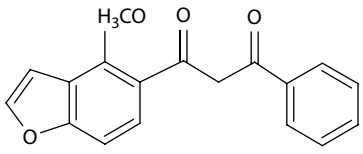


FIGURE 2.55 Structure of pongamol.

Other activities: Naringenin-7-O-glucoside, isolated from *Dracocephalum rupestre*, could protect from cardiomyocyte apoptosis and induce endogenous antioxidant enzymes against doxorubicin toxicity (Han et al. 2012).

237. Pseudolaric acid B

Plant source: *Pseudolarix amabilis*

Anti-diabetes: Pseudolaric acid B isolated from the root of *Pseudolarix* and its analogs are shown to have PPAR-γ agonist activity (Wang et al. 2014).

Other activities: Pseudolaric acid B has anticancer activity. It has a significant inhibitory effect and an additive inhibitory effect in combination with adriamycin on the growth of gastric cancer *in vivo*, which reverses the multidrug resistance of gastric neoplasm to chemotherapy drugs by downregulating the cyclooxygenase-2/protein kinase C-α/P-glycoprotein/multidrug resistance 1 (Cox-2/PKC-α/P-gp/mdr1) signaling pathway (Sun and Li 2014).

238. Psidials B and C

Plant source: *Psidium guajava*

Anti-diabetes: Sesquiterpenoid-based meroterpenoids, psidials B and C isolated from the leaves of *Psidium guajava*, showed PTP1B inhibitory activity at 10 μmol/L (Jiang et al. 2012).

239. Psoralen and isopsoralen

Plant source: *Psoralea corylifolia*

Anti-diabetes: Psoralen and isopsoralen (coumarins) showed preventive effects against hydrogen peroxide-induced β-cell death *in vitro*. Oral administration of psoralen and isopsoralen containing *P. corylifolia* seed extract resulted in a significant improvement of hyperglycemia in streptozotocin-induced diabetic mice. The extract treatment improved glucose tolerance and increased serum insulin levels. The extract also showed antioxidant activity (Seo et al. 2014).

Other activities: Psoralen and isopsoralen exhibited *in vitro* inhibitory actions on monoamine oxidase activities in rat brain mitochondria (Kong et al. 2001). In rat and human preclinical studies, psoralen and isopsoralen inhibited drug-metabolizing enzyme, CYP1A2, in a reversible and concentration-dependent manner (Zhuang et al. 2013). The compounds showed anticancer activities also. Psoralen and isopsoralen induced apoptosis or necrosis of osteosarcoma (Lu et al. 2014).

240. Pterosin A

Plant source: Pterosin A is found in *Hypolepis punctata* (a fern) and many other ferns. The International Union of Pure and Applied Chemistry (IUPAC) name is (2*S*)-6-(2-hydroxyethyl)-2-(hydroxymethyl)-2,5,7-trimethyl-3H-inden-1-one. The chemical structure of this compound is shown in Figure 2.56.

Anti-diabetes: Pterosin A (10–100 mg/kg, p.o., daily for 4 weeks) effectively improved hyperglycemia and glucose intolerance in streptozotocin-HDF-fed and db/db diabetic mouse. In db/db mice and in dexamethasone–insulin-resistant mice, pterosin A treatment reversed the increased serum insulin and insulin resistance. Furthermore, pterosin A significantly reversed the reduced muscle GLUT4 translocation and the increased liver PEPCK expression in diabetic mice. The compound also reversed the decreased phosphorylation of AMPK and Akt in muscles of diabetic mice. Pterosin A enhanced glucose uptake and AMPK phosphorylation in cultured human muscle cells. In cultured liver cells the compound inhibited inducer-enhanced PEPCK expression, triggered the phosphorylations of AMPK, acetyl CoA carboxylase, and glycogen synthase kinase-3, and increased the intracellular glycogen level (Hsu et al. 2013). In

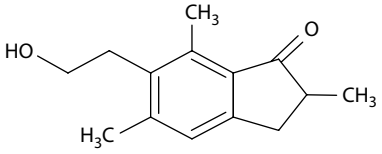


FIGURE 2.56 Structure of pterosin A.

a recent study pterosin A and its analogs were isolated from four ferns from Taiwan. Although the analogs exhibited the same effects in glucose uptake assays, pterosin A prevented β-cell death and reduced ROS production also (Chen et al. 2015).

Other activities: *In vitro* activities include smooth muscle relaxant activity, anticancer property, and leishmanicidal activity (Hsu et al. 2013).

241. Pterostilbene (3',5'-dimethoxy-resveratrol)

Plant source: Pterostilbene (trans-3,5-dimethoxy-4-hydroxystilbene) is a natural dietary compound and the primary antioxidant component of blueberries. It is also present in *Pterocarpus marsupium* (heartwood). The chemical structure of pterostilbene is shown in Figure 2.57.

Anti-diabetes: Pterostilbene was found *in vitro* to be a PPAR-α agonist, which can lower both plasma cholesterol and glucose. Feeding hypercholesterolemic hamsters a diet containing 25 ppm pterostilbene resulted in a 29% lower plasma LDL cholesterol, 7% higher HDL cholesterol, 14% lower glucose, and a lower LDL/HDL ratio, compared to controls (Rimando et al. 2005). Pterostilbene treatment increased antioxidant activity and normalized lipid peroxidation in streptozotocin-nicotinamide-induced type 2 diabetic rats (Satheesh and Pari 2006). Besides, Pterostilbene was found to be effective in ameliorating dyslipidemia in streptozotocin–nicotinamide-induced type 2 diabetic rats. Oral administration of pterostilbene (40 mg/kg, daily for 6 weeks) significantly reduced serum VLDL and LDL cholesterol and increased serum HDL cholesterol in the diabetic rats. Triglycerides, phospholipids, free fatty acids, and total cholesterol were reduced (Satheesh and Pari 2008).

In another study, administration of pterostilbene significantly reduced pathological changes seen in the liver and kidney of diabetic rats. Pterostilbene (40 mg/kg) significantly decreased plasma glucose and increased insulin levels in normal and streptozotocin–nicotinamide-induced type 2 diabetic rats. Administration of this compound also resulted in a significant reduction of glycosylated hemoglobin in the diabetic rats (Pari and Satheesh 2006). Pterostilbene promoted cytoprotective macroautophagy in vascular endothelial cells. The compound promoted autophagy via a rapid elevation in intracellular calcium concentration and subsequent AMPKα1 activation, which in turn inhibited mammalian target of rapamycin, a potent inhibitor of autophagy (Zhang et al. 2013). These effects may suggest the beneficial effects of this compound in DM and its complications.

Other activities: Multiple studies have demonstrated the antioxidant activity of pterostilbene in both *in vitro* and *in vivo* models illustrating both preventative and therapeutic benefits. The antioxidant activity and lipid-lowering effect of pterostilbene has been implicated in anticarcinogenesis, modulation of neurological disease, anti-inflammation, attenuation of vascular disease, and amelioration of diabetes (McCormack and McFadden 2013). As a potent chemo-preventative, antioxidant, and anti-inflammatory agent, pterostilbene has the potential to ameliorate the effects of aging when used by healthy individuals at the optimum dose. Pterostilbene may be effective in correcting the dyslipidemia that leads to atherosclerosis and coronary heart disease.

242. Puerarin

Plant source: Puerarin, one of several known isoflavones, is found in a number of plants such as the root of *Pueraria lobata*. The chemical structure of puerarin is shown in Figure 2.58.

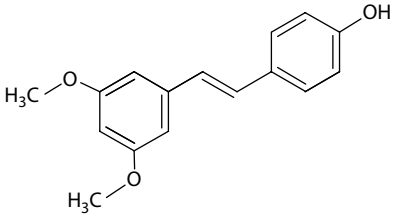


FIGURE 2.57 Structure of pterostilbene.

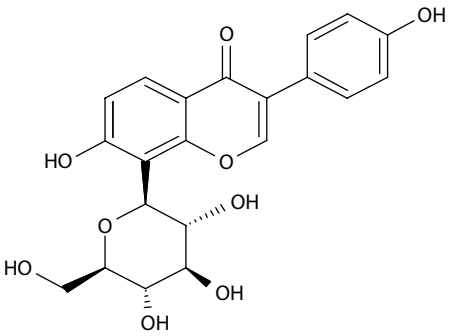


FIGURE 2.58 Structure of puerarin.

Anti-diabetes: Puerarin, isolated from *P. lobata* root, showed antihyperglycemic activity in streptozotocin-diabetic mice. Serum insulin level was increased by the treatment. Histopathological examination of the pancreas revealed that the compound alleviated streptozotocin-induced lesions in the pancreas. Furthermore, the levels of IRS-1 and insulin-like growth factor-1 (IGF-1) in the pancreas were increased. Endogenous mRNA levels of skeletal muscle insulin receptor and PPAR-γ were increased in the treated animals. Besides, the compound improved the dyslipidia in the diabetic mice (Wu et al. 2013). Puerarin (80 mg/kg) provided protection from diabetic nephropathy in streptozotocin-induced diabetic rats (Li et al. 2009). Furthermore, the compound ameliorated retinal microvascular dysfunction in retinal pigment epithelial cells in both C57BL/6 mice and streptozotocin-diabetic rats (Hao et al. 2010).

Another *in vitro* study suggests that the hypoglycemic effects of puerarin can be attributed to the upregulation of PPAR-γ and its downstream target genes, GLUT4 and adiponectin expression (Lee et al. 2010). Puerarin treatment significantly enhanced differentiation of 3T3-L1 preadipocytes accompanying increased lipid accumulation and glucose-6-phosphate dehydrogenase (G6PDH) activity. Puerarin upregulated mRNA expression of PPAR-γ and its target genes, an adipocyte-specific aP2 and GLUT4. Puerarin also caused a significant increase in mRNA level of adiponectin, an important insulin-sensitizing adipocytokine that is downregulated in insulin-resistant and diabetic states. In addition, treatment with puerarin was found to upregulate mRNA levels of G6PDH, glutathione reductase, and catalase (Lee et al. 2010).

Other activities: Puerarin is endowed with a wide spectrum of pharmacological properties such as vasodilation, cardioprotection, neuroprotection, antioxidant, anticancer, anti-inflammation, alleviating pain, promoting bone formation, inhibiting alcohol intake, and attenuating insulin resistance. However, the direct molecular mechanisms and targets remain unclear (Zhou et al. 2014).

243. Quercetin and quercetin glycosides

Plant source: Quercetin is reported from many plants. Examples include *Bougainvillea spectabilis*, *Citrullus lanatus*, *Myrcia multiflora*, *Dillenia indica*, *Leandra lacunose*, *Myrcia multiflora*, *Melothria mederaspatana*, *Cinnamomum* sp, *Opuntia ficus-indica*, *Phyllanthus emblica*, and *Phyllanthus fraternus*. Quercetin glycosides are also present in many plants; examples include *B. spectabilis*, *Eucommia ulmoides*, and *Phaseolus vulgaris*. Quercetin and its glycosides are also found in many edible fruits, vegetables, leaves and grains. The chemical structure of quercetin is shown in Figure 2.59.

Anti-diabetes: Quercertin (flavonoid) helps regeneration of β-cells and increases insulin release in streptosotozin-diabetic rats. Quercetin protected rats from streptozotocin-induced oxidative stress and β-cell damage (Hii and Howell 1985; Coskun et al. 2005). Furthermore, it enhances glucose uptake by isolated β-cells (Vessal et al. 2003). Quercetin from *M. mederaspatana* at 0.25 and 0.5 mg/mL caused 65% and 89% inhibition of glucose production in rat liver slices. Addition of insulin did not increase the inhibition (Srilatha and Ananda 2014).

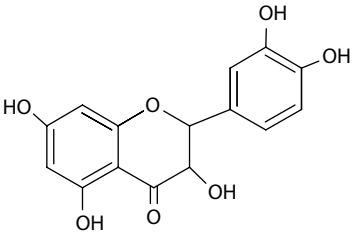


FIGURE 2.59 Structure of quercetin.

Insulin release was enhanced by approximately 44–70fold when isolated rat islets were exposed to quercetin (0.01–0.1 mmol/l). Quercetin (0.1 mmol/l) inhibited $^{45}Ca^{2+}$ efflux in the presence and absence of extracellular $^{45}Ca^{2+}$. In the presence of 20 mmol/L glucose both the short-term (5 min) and steady-state (30 min) $^{45}Ca^{2+}$ uptake were significantly increased by quercetin (Hii and Howell 1985). The authors suggest that these compounds may, at least in part, exert their effects on insulin release via changes in Ca^{2+} metabolism (Hii and Howell 1985). Interestingly, in a recent study, quercetin-induced insulin secretion by direct activation of L-type calcium channels in pancreatic β-cells in culture (Bardy et al. 2013).

Although quercetin had no effect on plasma glucose levels of normal rats, it dose-dependently decreased the plasma glucose levels of streptozotocin-induced diabetic rats. The treatment also decreased plasma levels of cholesterol and triglyceride whereas it increased liver glucokinase activity. In normal rats quercetin did not influence the glucose tolerance, but it increased the levels of cholesterol and triglyceride in the plasma and decreased liver glucokinase activity. The number of pancreatic islets increased in both normal and diabetic groups treated with the drug. Thus, quercetin, a flavonoid with antioxidant activity, brings about regeneration of pancreatic islets and probably increases insulin release in diabetic rats (Vessal et al. 2003).

Quercetin 3-O-α-L-arabinopyranosyl–(1 α 2)β-D-glucopyranoside (flavonoid) isolated from *Eucommia ulmoides* has glycation inhibitory activity (Kim et al. 2004). Quercetin-3-O-β-D-glucuronide isolated from the leaves of *Cyclocarya paliurus* was active against PTP1B (Jiang et al. 2012). Quercetin and quercetin glycosides from *E. almoidea* inhibited AGEs formation. Quercetin from *Myrcia multiflora* inhibited aldose reductase. In addition, quercetin effectively blocked polyol accumulation in intact rat lenses incubated in a medium containing high concentration of sugars (Varma et al. 1975). Quercetin glycosides from *Bauhinia forficata* were reported to inhibit intact microsomal glucose-6-phosphatase and activate insulin signaling pathways (Estrada et al. 2005).

Other activities: Quercetin decreased oxidative stress, NF-κB activation, and iNOS overexpression in the liver of streptozotocin-induced diabetic rats (Dias et al. 2005). Quercetin has been reported to be effective in inflammation, arteriosclerosis, bleeding, allergy and swellings. It is also known to be associated with reduced risk of certain types of cancers. It is believed to protect against several degenerative diseases by preventing lipid peroxidation (Joshi et al. 2011).

Limitations: The major problem associated with the use of quercetin is the very low *in vivo* bioavailability. However, the degree and method of quercetin's absorption *in vivo* has yet to be absolutely determined. It is thought that the predominant glucoside form is converted to the aglycone, which is then converted to one of several quercetin metabolites. Therefore, *in vitro* studies may not fully reflect *in vivo* effects (Joshi et al. 2011).

244. Quinides (4-Caffeoyl-1,5-quinide or 4-Caffeoylquinic-1,5-lactone)

Plant source: *Coffea arabica* (roasting can convert chlorogenic acid into quinides).

Anti-diabetes: Quinides are known to enhance insulin action in animal models (Chang et al. 2013).

Other activities: 4-Caffeoyl-1,5-quinide in roasted coffee inhibited [^{3}H] naloxone binding and reversed antinociceptive effects of morphine in mice (de Paulis et al. 2004).

245. Quinquefolans A, B and C (glycans)

Plant source: *Panax quinquefolium*

Anti-diabetes: Quinquefolans A, B, and C, displayed significant hypoglycemic activity in normal mice and in mice with alloxan-induced hyperglycemia at a dose of 10, 100, and 10 mg/kg of quinquefolans A, B, and C, respectively (Oshima et al. 1987).

246. Radicamines A and B (pyrrolidine alkaloids)

Plant source: *Lobelia chinensis*

Anti-diabetes: Two new pyrrolidine alkaloids radicamines A and B isolated from *L. chinensis* exhibited promising α-glucosidase inhibitory activity *in vitro* (Shibano et al. 2001).

247. Rebaudioside A

Rebaudioside A is found in *Stevia rebaudiana*. It is a natural sweetener.

Anti-diabetes: Under *in vitro* conditions, in presence of glucose, rebaudioside A stimulated insulin secretion from isolated mouse islets in a dose-dependent manner. This effect of rebaudioside was dependent on the presence of extracellular calcium. Thus, this compound possesses insulinotropic property (Abudula et al. 2004). The insulinotropic effect of rebaudioside A was mediated via inhibition of ATP-sensitive K^+ channels and requires the presence of high glucose. The inhibition of ATP-sensitive K^+ channels is probably induced by changes in the ATP/ADP ratio. The study indicates that rebaudioside A may offer a distinct therapeutic advantage over sulfonylureas because of less risk of causing hypoglycemia (Abudula et al. 2008).

Other activities: Rebaudioside A exhibited antilipid peroxidative, antihyperlipidemic, and antioxidant properties in diabetic rats (Saravanan and Ramachandran 2013).

248. Regeol A

Plant source: *Salacia chinensis*

Anti-diabetes: Regeol A and triptocalline A from *S. chinensis* showed an inhibitory effect on rat lens aldose reductase (Morikawa et al. 2003).

Other activities: Regeol B is shown to have antitumor effects (Chinese patent no.: CN104231029 A).

249. Resveratrol (a stilbene compound)

Plant source: Resveratrol (*trans*-3,5,4′-trihydroxystilbene) is a compound found largely in the fruit skins of red grapes (*Vitis vinifera*), *Arachis hypogaea* (seed), and many other plants including many berries. The chemical structure of resveratrol is shown in Figure 2.60.

Anti-diabetes: The anti-diabetic action of resveratrol has been extensively studied in animal models and in diabetic humans. Resveratrol, among others, improved glucose homeostasis, decreased insulin resistance, protected pancreatic β-cells, improved insulin secretion, and ameliorated metabolic disorders. Evidence suggests that resveratol exerts its action through multiple mechanisms: the compound activated AMPK and the downstream molecules in db/db mice. It also prevented β-cell death, to considerable extent, in streptozotocin-treated mice. Besides, the compound enhanced glucose-mediated insulin secretion by β-cells. Moreover, antioxidant and anti-inflammatory effects of resveratrol were shown to be also involved in its action in diabetic animals (Chang et al. 2013; Szkudelski and Szkudelska 2015).

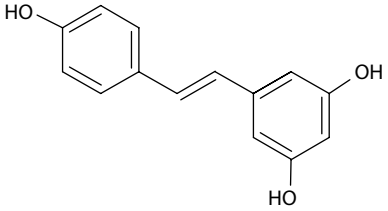


FIGURE 2.60 Structure of resveratrol.

Preliminary clinical trials show that resveratrol is also effective in type 2 diabetic patients. In a clinical trial, resveratrol (10 mg/day for 4 weeks) improved insulin sensitivity in humans, which might be due to a resveratrol-induced decrease in oxidative stress that leads to more efficient insulin signaling via the Akt pathway (Brasnyo et al. 2011). Resveratrol may, among others, improve glycemic control and decrease insulin resistance. Effects induced by resveratrol are strongly related to the capability of this compound to increase expression/activity of AMPK and SIRT-1 or sirtuin 1 in various tissues of diabetic subjects. These results show that resveratrol holds great potential to treat diabetes and would be useful to support conventional therapy (Szkudelski and Szkudelska 2015). However, in one study, high dose resveratrol supplementation in obese men did not influence endogenous glucose production and metabolic markers (Poulsen et al. 2013). At any rate, current data suggest that resveratrol could improve specific metabolic variables in individuals with type 2 diabetes, but more research is needed to assess its effect in individuals at risk for diabetes, including obese subjects with impaired glucose tolerance (Szkudelski and Szkudelska 2015).

Other activities: In preclinical studies, resveratrol has been shown to possess numerous biological functions. These include hepatoprotection, anticancer activity, anti-inflammatory property and immunomodulation. Animal experiments have shown that resveratrol has a protective effect at low doses against cardiovascular injury, gastric lesions, ischemic stroke, Alzheimer's disease and osteoporoses, but an adverse or no beneficial effect was observed in these medical conditions at high doses. In cell proliferation assays, under *in vitro* conditions, resveratrol stimulated growth of a variety of cell types including cancer cells whereas high concentrations inhibited cancer cell proliferation (Calabrese et al. 2010).

250. Rhododendric acid A

Plant source: *Rhoroedendron brachycarpum*

Anti-diabetes: Bioassay-guided fractionation on the leaves of *R. brachycarpum* yielded seven PTP1B inhibitory triterpenoids, including a new potent triterpene, rhododendric acid A (Choi et al. 2012).

251. Roseoside

Plant source: *Bauhinia variegata*, *Vinca rosea*, and so on

Anti-diabetes: The ethanol extract of *B. variegata* and its major constituent, roseoside, have demonstrated enhanced insulin release from the β-cell lines INS-1 (Frankish et al. 2010).

Other activities: Roseoside exhibited inhibitory activity on leukotriene release from mouse bone marrow-derived cultured mast cells. The (6*S*) isomers of roseoside were about twice as active as (6*R*) isomers (Yajima et al. 2009).

252. Rosmarinic acid

Plant source: Rosmarinic acid (rosemary acid; rosmarinate) is found in a variety of plants (e.g., *Perilla frutescens*).

Anti-diabetes: Rosmarinic acid rich fraction from *P. frutescens* inhibited α-glucosidase activity and glucose transport activity under *in vitro* and *in vivo* in rats (Higashino et al. 2011). Furthermore, this compound inhibited aldose reductase (IC_{50}: 2.77 μM) (Paek et al. 2013).

Other activities: Rosmarinic acid exhibits anti-inflammatory, antioxidative activity and antiviral properties. Other reported activities include sensitization of cell death through suppression of TNF-α-induced NF-κB activation and ROS generation in human leukemia U937 cells (Moon et al. 2010), and induction of melanogenesis through protein kinase A activation signaling (Lee et al. 2007).

253. Rutin (flavonoid)

Plant source: Rutin (rutoside; quercetin 3-rutinoside) is one of the abundant flavonoid natural products; it occurs in many plants. *Cinnamomum* sp, *Opuntia ficus-indica*, and *Phyllanthus fraternus* are examples. The chemical structure of rutin is shown in Figure 2.61.

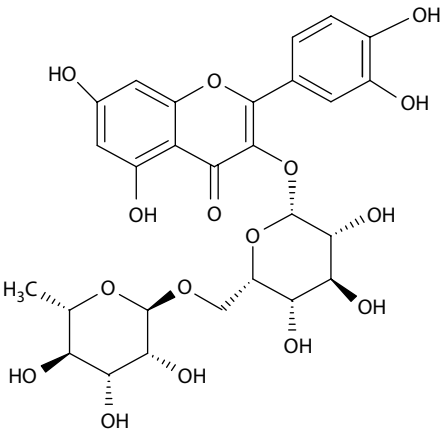


FIGURE 2.61 Structure of rutin.

Anti-diabetes: *In vitro* and *in vivo* studies have shown the multifarious beneficial actions of rutin in diabetes mellitus (DM) through its properties such as antioxidant, anti-inflammatory, and protection of various organs (Haptemariam and Lentini 2015). Oral administration of rutin (100 mg/kg) to streptozotocin diabetic rats for a period of 45 days resulted in a decrease of plasma glucose and an increase in insulin levels along with the restoration of glycogen content and the activities of carbohydrate metabolic enzymes in rutin-treated diabetic rats. The histopathological study of the pancreas revealed the protective role of rutin. There was an expansion of the islets and decreased fatty infiltrate of the islets in rutin-treated diabetic rats. In normal rats, rutin did not show any significant change in these parameters (Prince and Kamalakkannan 2006). In a recent study, administration of rutin (50 and 100 mg/kg, p.o., daily for 3 weeks) improved body weight, reduced plasma glucose, glycosylated hemoglobin, TNF-α, and IL-6, and restored the depleted liver antioxidant status and serum lipid profile in HFD + streptozotocin-induced type 2 diabetic rats. Rutin treatment also improved histoarchitecture of β-cells and reversed hypertrophy of hepatocytes (Niture et al. 2014). Thus, the anti-DM properties of rutin were established based on animal experiments. Controlled clinical trials including long-term dose response studies are warranted.

Other activities: Rutin is believed to exhibit several pharmacological properties including antioxidation, anti-inflammation, antiadipogenic, and neuroprotective actions. There are more than 130 registered therapeutic medicinal formulations that contain rutin as an ingredient (Chua 2013).

254. Salacinol

Plant source: *Salacina reticulata*

Anti-diabetes: A most potent α-glucosidase inhibitor named salacinol has been isolated from an anti-diabetic traditional medicinal plant, *S. reticulata*, through bioassay-guided separation (Yoshikawa et al. 2002). Salacinol bound to α-glucosidase with a similar binding mode as casuarine. Salacinol glycoside also inhibits α-glucosidase (Nakamura et al. 2010; Ozaki et al. 2008). Salacinol from *Salacxina oblonga* has been found to have inhibitory effects against the enzyme activities of maltase, isomaltase and sucrose. It has also been found that the inhibitory effect against sucrase is more potent than the α-glucosidase inhibitors acarbose and voglibiose that are used in the treatment of diabetes (Matsuda et al. 2005).

255. Salasol A (triterpene)

Plant source: *Salacia chinensis*

Anti-diabetes: A new acylated eudesmane-type sesquiterpene, salasol A was isolated from *S. chinensis*. This compound showed an inhibitory effect on rat lens aldose reductase (Kishi et al. 2003; Morikawa et al. 2003).

Other activities: Salasol A exhibited *in vitro* antituberculosis activity, with an minimum inhibitory concentration (MIC) value of 15.0 μg/mL against *Mycobacterium tuberculosis* $H_{37}Rv$ (Chou et al. 2008).

256. Salicortin (β-D-glucopyranoside)

Plant source: Salicortin, an ester of salicyl alcohol glucoside and an abundant component of most species of *Salix* and *Populus* genera (e.g., *Populus balsamifera*)

Anti-diabetes: Salicortin was identified as the inhibitor of adipogenesis. A treatment study was then carried out in the diet-induced obesity (DIO) model where mice were allowed to become obese and insulin resistant before the onset of treatment with the plant's crude extract and the corresponding dose of salicortin (12.5 mg/kg). Both the crude extract and salicortin reduced body weight, glycemia, insulinemia, liver triglycerides, and leptin/adiponectin ratio. However, the profile of activities of the crude extract differed somewhat from that of salicortin. Salicortin's action on body weight gain was immediate and maintained throughout the treatment period whereas the crude extract caused a small initial drop and only began decreasing weight gain significantly after several weeks. The crude extract of *P. balsamifera* had a sustained effect on blood glucose whereas salicortin's effects were initially equivalent but waned with time. Salicortin can explain part of the plant's effects, notably on body weight loss but its effect on glucose and lipid homeostasis appears to be weaker and more transient (Eid and Haddad 2014). This suggests that there are better anti-DM compounds in this extract or compounds act synergistically to give better results.

Salicortin was identified, through bioassay (inhibition of adipogenesis in 3T3-L1 adipocytes)-guided fractionation, as the active component responsible for the activity of *P. balsamifera* extract. When mice were subjected to HFD for 16 weeks with salicortin (12.5 mg/kg) introduced in the HFD for the last 8 of the 16 weeks, salicortin effectively reduced whole body and retroperitoneal fat pad weights, as well as hepatic triglyceride accumulation. Glycemia, insulinemia, leptin, and adiponectin levels were also improved. Salicortin (slightly) also modulated key components in signaling pathways involved with glucose regulation and lipid oxidation in the liver, muscle, and adipose tissue (Harbilas et al. 2013).

Other activities: Salicortin suppressed lipopolysaccharide-stimulated inflammatory responses via blockade of NF-κB and C-Jun N-terminal kinase (JNK) activation in RAW 264.7 macrophages (Kwon et al. 2014).

257. S-allyl L-cystine sulfoxide (L-Alliin)

Plant source: *Allium sativum*

Anti-diabetes: S-Allyl L-cystine sulfoxide showed hypoglycemic activity in streptozotin-induced diabetic rats. This compound is considered as an insulin secretagogue in diabetic rats (Augusti and Sheela 1996; Kumari and Augusti 2002).

Other activities: S-Allyl-L-cysteine sulfoxide is an antiatherosclerotic compound with antioxidant and anti-inflammatory activities. It is cytotoxic to several mammalian cancer cell lines and can protect against tumor formation induced by various exogenous chemical carcinogens. Furthermore, S-allyl-L-cysteine sulfoxide inhibited tumor necrosis factor-α-monocyte adhesion and intercellular cell adhesion molecule-1 expression in human umbilical vein endothelial cells (Hui et al. 2010).

258. Sanggenon C and G

Plant source: *Morus* sp.

Anti-diabetes: Bioassay-guided fractionation of *Morus* root bark resulted in the isolation of sanggenon C, sanggenon G, mulberrofuran C, and kuwanon L as PTP1B inhibitors. Sanggenon C and sanggenon G inhibited PTP1B with IC_{50} values of about 2 μM (Chi et al. 2006).

Other activities: Sanggenon G has antitumor activity. It inhibited X-linked inhibitor of apoptosis protein (Seiter et al. 2014). Sanggenon C inhibited tumor cell viability via induction of cell cycle arrest and cell death, which is associated with its ability to inhibit the proteasome function (Huang et al. 2011).

259. Saurufuran A

Plant source: *Saururus chinensis*

Anti-diabetes: Saurufuran A, a new furanoditerpene, isolated from the roots *S. chinensis*, exhibited agonist effect on PPARγ expressed in mouse National Institute of Health/3TC fibroblast cells (NIH/3T3) cells assessed as receptor activation after 16 h by luciferase based reporter gene assay (EC_{50}: 16 μM) (Wang et al. 2014).

260. Schiarisanrin A and B

Plant source: *Schisandra arisanensis*

Anti-diabetes: Schiarisanrin A and B isolated from *S. arisanensis* showed a dose-dependent protective effect against cytokine-mediated β-cell death (Hsu et al. 2012).

261. Schweinfurthiin (steroid)

Plant source: *Anthocleista schweinfurthii*

Anti-diabetes: A new steroid schweinfurthiin from *A. schweinfurthii* was found to be a highly promising α-glucosidase inhibitor (Mbouangouere et al. 2007).

262. Scirpusin B

Plant source: *Callistemon rigidus* (stem bark); *Passiflora edulis* (seed), and so on

Anti-diabetes: Scirpusin B (phenolic compound) inhibits α-amylase and controls postprandial blood glucose levels (Kobayashi et al. 2006).

Other activities: Scirpusin B has vasorelaxing activity; scirpusin B could increase coronary flow via production of NO and vasodilating prostanoids (Sano et al. 2011).

263. Scoparic acid D, a diterpenoid

Plant source: *Scoparia dulcis*

Anti-diabetes: The antihyperglycemic effect of scoparic acid D, a diterpenoid isolated from the ethanol extract of *S. dulcis* in streptozotocin-diabetic rats, was evaluated. Scoparic acid D treatment resulted in decreased levels of glucose as compared with diabetic control rats. The improvement in blood glucose levels of the compound-treated rats was associated with a significant increase in plasma insulin levels. Furthermore, the effect of the scoparic acid was tested on streptozotocin-treated rat insulinoma cell lines (RINm5F cells) and isolated islets *in vitro*. Scoparic acid D evoked twofold stimulation of insulin secretion from isolated islets, indicating its insulin secretagogue activity (Latha et al. 2009). Docking studies showed greater affinity of scoparic acid D toward the active site of human α-glucosidase with a docking score of 8.1675, which is better than that of existing inhibitors (Saikia et al. 2012).

264. Scopoletin (7-hydroxy-6-methoxycoumarin)

Plant source: Scopoletin is found in plants such as *Aegle marmelos* (leaves), *Canarium patentinervium*, and *Magnolia fargesii*. Scopoletin is also known as gelseminic acid, chrysatropic acid, scopoletin, and methylesculetin.

Anti-diabetic: Scopoletin (7-hydroxy-6-methoxy coumarin), isolated from the leaves of *A. marmelos*, when administered to levo-thyroxine-induced hyperthyroid rats, decreased the levels of serum thyroid hormones, glucose and liver glucose-6-phosphatase activity. It also inhibited hepatic lipid per oxidation (Panda and Kar 2006). Besides, scopoletin is known to inhibit aldose reductase activity. When galactose-fed rats were orally dosed with scopoletin (10 or 50 mg/kg, daily for 2 weeks), the progression of the cataracts that were induced by dietary galactose was delayed. Scopoletin also prevented galactose-induced changes in lens morphology, such as lens fiber swelling and membrane rupture. Scopoletin's protective effect against sugar cataracts was mediated by inhibiting both aldose reductase activity and oxidative stress (Kim et al. 2013).

Other activities: Scopoletin is known to have anti-inflammatory, anticholinesterase, and antioxidant properties (Mogana et al. 2013).

265. Scrophuside

Plant source: *Scrophularia ningpoensis*

Anti-diabetes: A new phenylpropanoid glycoside, designated scrophuside was obtained from the roots of *S. ningpoensis*. Scrophuside showed marked α-glucosidase inhibitory activity (Hua et al. 2013; Firdous 2014).

266. Scropolioside-D (iridoid glycoside)

Plant source: *Scrophularia deserti*, *Scrophularia ilwensis*, and so on

Anti-diabetes: Scropolioside-D (10 mg/kg), isolated from *S. deserti* aerial parts, reduced blood glucose levels in alloxan-induced diabetic rats (Ahmed et al. 2003).

267. Secoisolariciresinol diglucoside (phytoestrogen)

Plant source: *Linum usitatissimum*

Anti-diabetes: Secoisolariciresinol diglucoside isolated from *L. usitatissimum* delayed the development of type 2 DM in Zucker rats (Prasad 2001).

268. Semilicoisoflavone B

Plant source: *Glycyrrhiza uralensis*

Anti-diabetes: The inhibitory effects of 10 components from the root of *G. uralensis* on aldose reductase and sorbitol formation in rat lenses with high levels of glucose were investigated. Of the compounds tested, semilicoisoflavone B (5,7,8′-trihydroxy-2′,2′-dimethyl-2′H,4H-3,6′-bichromen-4-one) showed the most potent inhibition, with the IC_{50} values of 1.8 and 10.6 μM for rat lens aldose reductase and human recombinant aldose reductase, respectively. It showed noncompetitive inhibition against rat lens aldose reductase. Furthermore, semilicoisoflavone B inhibited sorbitol formation of rat lens incubated with a high concentration of glucose, indicating that this compound may be effective for preventing osmotic stress in hyperglycemia (Lee et al. 2010).

269. Senegasaponins

Plant source: *Polygala senega*

Anti-diabetes: E and Z-senegasaponins C and E and Z-senegins II, III, and IV were found to exhibit hypoglycemic activity in the oral D-glucose tolerance test. (E) and (Z)-Senegins II also showed an inhibitory effect on alcohol absorption in rats (Yoshikawa et al. 1996c).

Other activities: Senegasaponins (senegin II, senegin III, senegin IV senegasaponin a, and senegasaponin b) from *P. senega* were discovered as selective antiproliferative substances against human umbilical vein endothelial cells (HUVECs). These senegasaponins showed antiproliferative activity against HUVECs with IC_{50} values in the range 0.6–6.2 μM (Arai et al. 2011).

270. Shamimin (flavonoid glycoside)

Plant source: *Bombax ceiba*

Anti-diabetes: Shamimin, a C-flavonal glucoside from *B. ceiba* leaves, showed significant hypoglycemic activity at 500 mg/kg in Sprague-Dawley rats (Saleem et al. 1999).

Other activities: It showed potencey as a hypotensive agent at doses of 1–25 mg/kg in rats (Saleem et al. 1999).

271. Shikonin (naphthoquinone derivative)

Plant source: *Lithospermum erythrorhizon*

Anti-diabetes: Shikonin, a naphthoquinone isolated from *L. erythrorhizon*, when administered i.p. (10 mg/kg) once daily for 4 days, improved plasma glucose levels in diabetic Goto–Kakizaki rats. Furthermore, it increased glucose uptake in skeletal muscle cells (Oberg et al. 2011). Shikonin increased glucose uptake in L-6 skeletal muscle myotubes without phosphorylating Akt indicating that in these cells its effect is mediated via a pathway distinct from that used for insulin-stimulated uptake. The compound increased intracellular levels of calcium in these cells and this increase was necessary for shikonin-stimulated glucose uptake. Furthermore, the compound stimulated the translocation of GLUT4 from intracellular vesicles to the cell surface in L-6 myocytes. The authors conclude that shikonin increases glucose uptake in muscle cells via an insulin-independent pathway dependant on intracellular free calcium (Oberg et al. 2011).

Shikonin inhibited adipogenic differentiation via suppression of the ERK signaling pathway during the early stages of adipogenesis in 3T3-L1 cells (Gwon et al. 2013).

Other activities: Shikonin is endowed with various biological activities including inhibition of human immunodeficiency virus (HIV) type 1, wound healing property and antimicrobial activity. Anti-HIV and anti-inflammatory activities of shikonin may be related to its interference with chemokine receptor expression and function (Chen et al. 2003). Several studies suggest the promising anticancer property of this compound. For example, a recent study has shown that shikonin selectively induced apoptosis in human prostate cancer cells through the endoplasmic reticulum stress and mitochondrial apoptotic pathway (Gara et al. 2015).

272. Shogaol (6-Shogaol)

Plant source: *Zingiber officinale*

Anti-diabetes: 6-Shogaol and 6-gingerol, the pungents of ginger, inhibited the TNF-α-mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes (Wang et al. 2014). A recent study has shown that 6-shogaol inhibited the expression of two master regulators of adipogenesis, PPAR-γ and C/EBPα, and also stimulated lipolysis in mature 3T3-L1 adipocytes. It is 6-shogaol, not 6-gingerol, that is the major compound present in ginger responsible for its reported antiadipogenic properties. This is the first study to investigate the antiobesity effect of 6-shogaol *in vitro*, and provides a new perspective on future development of ginger-based antiobesity strategies (Suk et al. 2015).

Other activities: Other known properties include anti-inflammatory and anticancer properties: 6-Shogaol inhibited breast cancer cell invasion by reducing matrix metalloproteinase-9 expression via blockade of NF-κB activation (Ling et al. 2010). Also, 6-Shogaol suppressed lipopolysaccharide-induced up-expression of iNOS and COX-2 in murine macrophages (Pan et al. 2008).

273. Silymarin (composed of silybin, silydianin, and silychristin)

Silymarin is a mixture of silybin, silydianin and silychristin from *Silybum marianum*. Silybin is the major component in silymarin. The chemical structure of silybin B is shown in Figure 2.62.

Anti-diabetes: It has been reported that silymarin has a favorable impact on glycemic and lipidemic control in type 2 DM with cirrhosis and that it could reduce fat-induced insulin resistance (McCarty 2005). Silymarin prevented the progression of diabetic nephropathy in streptozotocin-diabetic rats (Vessal et al. 2010). It has been reported that silymarin can rescue β-cell function in alloxan treated rats. Isosilybin A, a phenolic mixture from the seeds of *S. marianum,* activated PPAR-γ (Chang et al. 2013; Wang et al. 2014). Beneficial effects of silymarin (200 mg/day) on fasting blood glucose, postprandial glucose, and HbA1c levels have been observed in type 2 DM patients maintained on glibenclamide. In another study on humans, oral intake of silymarin (600 mg/day for 4 months) decreased blood glucose, HbA1c, and glucosuria in insulin-treated diabetic patients with alcoholic liver cirrhosis (Ghorbani 2013).

Other activities: Silymarin is a well-known hepatoprotective agent. Reported activities include antioxidant and anti-inflammatory (Ghorbani 2013).

274. β-Sitosterol (phytosterol), β-sitosterol glycoside, and γ-sitosterol

Plant source: These compounds are widely distributed in plants. These are present in foodstuffs such as cashew fruit, rice bran, wheat germ, pea nut, soybean, and pumpkin seeds. Examples

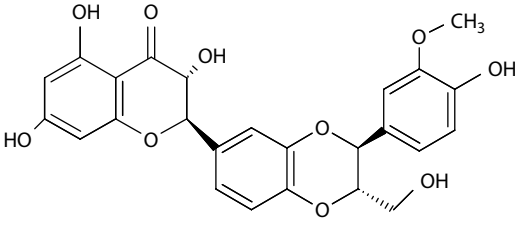


FIGURE 2.62 Structure of silybin B.

of plants containing β-sitosterol include *Azadirachta indica*, *Abroma augusta*, *Acacia leucophloea*, *Aloe vera*, *Bougainvillea spectabilis*, *Bambusa arundinacea*, *Bauhinia variegata*, *Balanites roxburghii*, *Caesalpinia bonbuc*, *Centaurea seridis*, *Clerodendron phlomidis*, *Coccinia indica*, *Dillenia indica*, *Ficus carica*, *Ipomoea digitata*, *Lippia nodiflora*, *Lycium barbarum*, *Mirabilis jalapa*, *Mucuna pruriens*, *Musa sapientum*, *Nigella sativa*, *Potentilla chinensis*, *Sereroa repens*, *Solanum virginianum* (syn: *S. surattense*), *Swertia chiragita*, *Syzygium malaccense*, *Tectona grandis*, *Premna latifolia*, *Prunus amygdalus*, and *Hippophae rhamnoides* (sea buckthorn). β-Sitosterol glycoside is also reported in many plants. Examples are *Centaurea seridis*, *Musa sapientum*, *Premna latifolia*, and *Prunus amygdalus*. γ-Sitosterol is present in many plants. Examples include *Abelmoschus manihot* (Jain et al. 2009), *Acacia nilotica* (Sundarraj et al. 2012), *Girardinia heterophylla* (Tripathi et al. 2013), and *Lippia nodiflora*. The chemical structure of β-sitosterol is shown in Figure 2.63.

Anti-diabetes: The effect of β-sitosterol 3-β-glucoside (antihyperglycemic principle isolated from the aerial part of *Centaurea seridis* var. maritima) and its aglycone on plasma insulin and glucose levels in normo- and hyperglycemic rats were investigated. Oral treatment with the glycoside or with the β-sitosterol increased the fasting plasma insulin levels and decreased fasting glycemia. In addition, these compounds improved the oral glucose tolerance with an increase in glucose-induced insulin secretion. But, when these products were administered orally, the effect of glycoside, either on fasting insulinemia or on glucose-induced insulin secretion, lasted longer than that of aglycone. It is suggested that β-sitosterol 3-β-D-glucoside acts by increasing insulin levels, and that this effect is due to their aglycone, β-sitosterol (Ivorra et al. 1998). In a follow-up study, β-sitosterol did not change insulin and glucose levels in rats with severe diabetes. However, it stimulated insulin release from isolated rat islets in the presence of a non-stimulatory glucose concentration, but did not increase the insulin releasing capacity of glucose (16 mmol/L). These data suggest that the compound exerts its action on intact pancreatic β-cells by stimulating insulin secretion (Ivorra et al. 1990).

In another study, treatment with β-sitosterol isolated from *S. surattense* (*S. xanthocarpum*) (10, 15 and 20 mg/kg, p. o.) for 21 days resulted in a dose-dependent decrease in glycated hemoglobin, serum glucose, and nitric oxide with concomitant increase in serum insulin levels in streptozotocin-induced diabetic rats. Furthermore, the treatment increased pancreatic antioxidant levels with a concomitant decrease in thiobarbituric acid reactive substances. β-Sitosterol helps in the regeneration of β-cells and insulin release (Gupta et al. 2011).

Besides, oral administration of γ-sitosterol (20 mg/kg for 21 days) isolated from *L. nodiflora* to streptozotocin-induced diabetic rats resulted in a significant decrease in blood glucose and glycosylated hemoglobin with an increase in plasma insulin level and body weight. Furthermore, the treatment showed antihyperlipidemic activity as evidenced from marked decrease in serum total cholesterol, triglycerides, and LDL levels coupled with elevation of HDL levels. In isolated

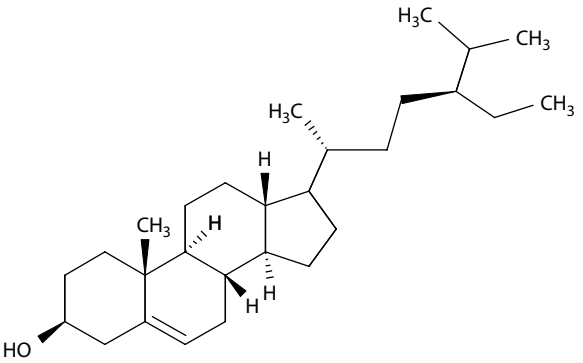


FIGURE 2.63 Structure of β-sitosterol.

rat islets, γ-sitosterol increased insulin secretion in response to glucose. Immunohistochemical study of the pancreas confirmed the biochemical findings (Balamurugan et al. 2011).

Other activities: β-Sitosterol has been associated with cardiovascular protection, exerting its effect mainly through increasing the antioxidant defense system and effectively lowering the serum cholesterol levels in humans. It has anti-inflammatory effect also (Loizou et al. 2010).

275. S-methyl cysteine sulfoxide (S-methyl L-cystine-S-oxide)

Plant source: S-methyl cysteine sulfoxide is found in *Allium cepa* and several cultivars of cabbage.

Anti-diabetes: S-methyl cysteine sulfoxide isolated from *A. cepa* (200 mg/kg, daily for 45 days) exhibited both anti-diabetes and hypolipidemic effects in alloxan-induced diabetic rats (Kumar et al. 1995). Besides, S-methyl cysteine sulfoxide from onions showed antioxidant and anti-DM properties in alloxan-diabetic rats (Kumari and Augusti 2002).

Other activities: Antioxidant activity

276. Spartine derivatives (quinolizidine alkaloids)

Plant source: *Lupinus mutabilis*

Anti-diabetes: Derivatives of spartine and lupanine (ketonic derivative of sparteine) on insulin secretion by pancreatic islets under *in vitro* conditions was investigated. Dioxosparteine, hydroxyl-lupanine, and multiflorine at 500 μM enhanced insulin secretion from the islets incubated with 16.7 mM glucose, while thionospartine enhanced insulin secretion at 8.3 mM glucose (Gurrola-Diaz et al. 2008).

Other activities: Lupanine (ketonic derivative of sparteine) is more efficient than sparteine for antagonizing secondary reflex hypertension in carotid occlusion and hypotension resulting from the stimulation of the pneumogastric nerve in both cats and dogs. Furthermore, lupanine is much less toxic in one single injection in both mice and guinea pigs (Yovo et al. 1984).

277. Stevioside (glycoside)

Plant source: Stevioside is found in *Stevia rebandina*. The chemical structure of stevioside is shown in Figure 2.64.

Anti-diabetes: Stevioside isolated from *S. rebaudiana* showed anti-DM in rats. The sweet compound, stevioside, has promising anti-diabetes activity. Under *in vitro* conditions, stevioside and steviol enhanced insulin secretion from mouse islets in the presence of glucose

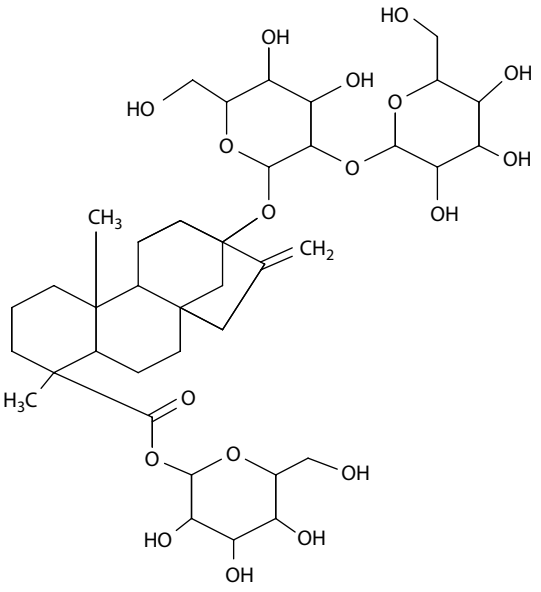


FIGURE 2.64 Structure of stevioside.

(Jeppesen et al. 2000). In the intravenous (i.v.) glucose tolerance test stevioside significantly suppressed the increase in glucose in the type 2 Goto–Kakizaki rats. Furthermore, in the glucose tolerance test, the compound suppressed the levels of glucagon also. In the normal rats, stevioside enhanced insulin levels above baseline values during the glucose tolerance test, without altering the blood glucose response and the glucagon levels. Thus, stevioside showed antihyperglycemic and insulinotrophic actions (Jeppesen et al. 2002). The effect of this compound on skeletal muscle glucose transport was studied in both insulin-sensitive lean and insulin-resistant obese. Acute oral stevioside administration increased whole-body insulin sensitivity. Furthermore, low concentrations of stevioside improved *in vitr*o insulin action in skeletal muscle glucose transport in both lean and obese rat skeletal muscle (Lailerd et al. 2004). Stevioside (0.5 mg/kg) lowered blood glucose levels in streptozotocin-induced diabetic rats, with a peak at 90 min. Stevioside administration twice daily also demonstrated dose-dependent effects both in streptozotocin and alloxan-diabetic rats. Stevioside dose-dependently decreased protein as well as mRNA levels of phosphoenol pyruvate carboxylase after 15 days of treatment (Chen et al. 2005). The authors conclude that stevioside is able to decrease blood glucose levels by enhancing not only insulin secretion, but also insulin utilization in insulin-deficient rats.

Other activities: Stevioside possesses pharmacodynamic effects such as anti-infective and a beneficial influence on the cardiovascular system. In stevioside-pretreated rats, the amount of verapamil needed to produce the decrease in heart rate was significantly lower compared to the control (Vasovic et al. 2014).

278. Stigmasterol (Stigmasterin)

Plant source: Stigmasterol is found in many plants such as *Gymnema sylvestre*, *Musa sapientum*, *Premna latifolia*, and *Pseuderanthemum palatiferum*.

Anti-diabetes: Stigmasterol and sitosterol-3-O-β-D-glucopyranoside, isolated from *P. palatiferum* (0.25 and 0.50 mg/kg, for 21 days) decreased FBG levels at the two doses studied with a concomitant increase in serum insulin in diabetic rats. Stigmasterol at the dose of 0.50 mg/kg showed the highest hypoglycemic effect. These compounds also improved the biochemical data and hematology parameters such as total cholesterol, triglycerides, HDL, LDL, blood urea nitrogen, creatinine, red blood cells, platelet, and white blood cells (Nualkaew et al. 2015). Administration of stigmasterol isolated from *Butea monosperma* to mice for 20 days reduced serum triiodothyronine, thyroxin, and glucose levels with a significant increase in insulin, indicating its thyroid inhibiting and hypoglycemic properties (Panda et al. 2009).

Other activities: Other reported activities include antioxidant, anti-inflammatory, antiosteoarthritic, antihypercholestrolemic, antitumor, and central nervous system effects (Kaur et al. 2011). Stigmasterol has been found to compete with cholesterol for intestinal absorption and thus lower the concentration of cholesterol. Furthermore, this compound is reported to inhibit cholesterol biosynthesis in human Caco-2 and HL-60 cell lines (Kaur et al. 2011).

279. Swerchirin (1:8 dihydroxy 3:5 dimethoxy xanthone)

Plant source: *Swertia chirayita*, *Swertia mussotii*, *Swertia longifolia*, and so on

Anti-diabetes: Swerchirin (50 mg/kg, p.o., single dose) administration resulted in lowering of blood glucose levels in healthy rats and in streptozotocin-induced moderately diabetic, but not in severe diabetic, rats (Saxena et al. 1991). Swerchirin lowered blood glucose level by stimulating insulin release from islets of Langerhans. Single oral administration of swerchirin (50 mg/kg) to fed rats induced about 60% fall in blood glucose by 7 h post-treatment. This was associated with marked depletion of aldehyde-fuchsin stained β-granules and immunostained insulin in the pancreatic islets. *In vitro*, glucose uptake and glycogen synthesis by muscle (diaphragm) was significantly enhanced by the serum of swerchirin-treated rats. At 100, 10, and 1 μM final concentration, swerchirin greatly enhanced glucose (16.7 mM)-stimulated insulin release from isolated islets (Saxena et al. 1993).

Other activities: Swerchirin, one of the xanthones in *Swertia* spp., has many pharmacological properties, such as antihepatotoxic, antimalarial, and radioprotective effects. Swerchin protected mice from paracetamol-induced hepatotoxicity (Hajimehdipoor et al. 2006).

280. Swertiamarin (swertiamarine)

Plant source: *Enicostemma littorale*. The chemical structure of swertiamarin is shown in Figure 2.65.

Anti-diabetes: Swertiamarin, a glycoside, was found to be a major component in the hot water extract of *E. littorale*, while it was almost absent in cold extract. Swertiamarin isolated from *E. littorale* alleviated insulin resistance in type 2 diabetes. Swertiamarin (50 mg/kg) exhibited a hypolipidemic and insulin sensitizing effect in experimentally induced type 2 DM in rats. Administration of swertiamarin (50 mg/kg) for 40 days resulted in tight regulation of serum glucose, insulin, and lipid profile in the diabetic rats. The mode of action was by restoring G6Pase and HMG-CoA reductase activities to normal levels and restoring normal transcriptional levels of PEPCK, glycokinase, GLUT2, PPAR-γ, leptin, adiponectin, lipoprotein lipase, SREBP-1c, and GLUT4 genes. This suggests that the treatment increased insulin sensitivity and regulated carbohydrate and fat metabolism. Thus, swertiamarin has a role in regulating the PPARγ-mediated regulation of candidate genes involved in metabolism in peripheral tissues *in vivo* (Patel et al. 2013). An *in vitro* study indicated that anti-diabetic activities of swertiamarin are due to an active metabolite, gentianine, that upregulates PPAR-γ gene expression in 3T3-L1 cells (Vaidya et al. 2013). Gentianine is an active metabolite of swertiamarin that possesses a pharmacophoric moiety. The anti-diabetic effect of swertiamarin is due to gentianine. Swertiamarin treatment had no significant effect on adipogenesis, or the mRNA expression of PPAR-γ and GLUT4; however, there was a significant increase in the mRNA expression of adiponectin. On the other hand, treatment with gentianine significantly increased adipogenesis, which was associated with a significant increase in the mRNA expression of PPAR-γ, GLUT4, and adiponectin. These findings suggest that the anti-diabetic effect of swertiamarin is, to a large extent, due to gentianine, an active metabolite of swertiamarin (Vaidya et al. 2013).

Other activities: Other reported activities include antioxidant activity, hepatoprotection, and anti-inflammation. Swertiamarin ameliorated inflammation and osteoclastogenesis in IL-1β-induced rat fibroblast-like synoviocytes (Saravanan et al. 2014).

281. Syringic acid

Plant source: *Conyza dioscorides*, *Dendrobium nobile*, *Mangifera indica*, and so on

Anti-diabetes: Syringic acid (4-Hydroxy-3,5-dimethoxybenzoic acid) extracted from *D. nobile* provided protection from D-gal-induced damage to rat lenses by consistently maintaining lens transparency and delaying lens turbidity development. Syringic acid prevented diabetic cataract in rat lenses by inhibiting aldose reductase activity and gene expression, which has potential to be developed into a novel drug for therapeutic management of diabetic cataracts (Wei et al. 2012). Oral administration of syringic acid (50 mg/kg, for 30 days) positively modulated the glycemic status in alloxan-induced diabetic rats. The levels of plasma glucose were decreased with significant increase of plasma insulin and C-peptide level. The altered levels of plasma and tissue glycoprotein components were restored to near normal. No significant changes were noticed in normal rats treated with syringic acid (Muthukumaran et al. 2013).

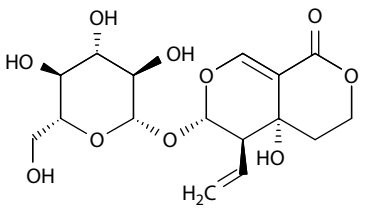


FIGURE 2.65 Structure of swertiamarin.

Other activities: Syringic acid exhibited a hepatoprotective effect against carbon tetrachloride-induced liver injury (Itoh et al. 2010).

282. Syringin

Syringin is found in plants such as *Acanthopanax senticosus*, *Eleutherococcus senticosus*, *Ilex rotunda*, *Musa paradisiaca*, and *Jasminum mesnyi*. The chemical structure of syringin is shown in Figure 2.66.

Anti-diabetes: Syringin (a compound isolated from *Acanthopanax senticosus*) injection to streptozotocin-diabetic rats resulted in an increase in plasma glucose utilization accompanying with the increase of plasma insulin and C-peptide levels in the anesthetized diabetic rats (Niu et al. 2008). In another study, administration of syringin (50 mg/kg/day for 30 days) to streptozotocin-induced diabetic rats resulted in restoration to near normal levels of blood glucose, insulin, hemoglobin, HbA1c, total protein, urea, uric acid, and creatinine (Krishnan et al. 2014). Syringin has an ability to raise the release of acetylcholine from nerve terminals that stimulates muscarinic M3 receptors in pancreatic cells and augments insulin release (Liu et al. 2008).

Other activities: Other reported pharmacological actions include antioxidant activity, protection against neuronal cell damage, anti-inflammatory effect, inhibition of apoptosis, antinociceptive action and antiallergic effect (Mahavedarao et al. 2015).

283. 3-β-Taraxerol

Plant source: *Mangifera indica*, *Erythrophleum fordii*, and so on

Anti-diabetes: 3-β-Taraxerol, isolated from leaves of *M. indica*, exhibited insulin-stimulated glucose uptake through translocation and activation of the GLUT4 in an insulin receptor tyrosine kinase (IRTK) and PI3K-dependent fashion in 3T3-L1 adipocytes. Furthermore, 3-β-taraxerol activated protein kinase B (Akt) and stimulated glycogen synthesis (Sangeetha et al. 2010).

Other activities: Other reported activities include anti-*Trypanosoma brucei* activity *in vitro* and inhibition of iNOS-mediated NO production in LPS-induced mouse microglial cells (Tsao et al. 2008).

284. Tecomine (alkaloid)

Plant source: *Tecoma stans*

Anti-diabetes: The hypoglycemic properties of tecomine were reported on fasting blood sugar, glucose tolerance, depancreatized and alloxan-diabetic rabbits (Hammouda and Amer 1966). However, in a subsequent *in vivo* study, it decreased blood cholesterol levels without much effect on glycemia. However, tecomine increased glucose uptake by normal rat white adipocytes *in vitro* (Costantino et al. 2003). The low stability of tecomine has been reported. The results of a stability study indicate that the degradation of the alkaloid is dependent on the pH of its solution and that antioxidants are beneficial in delaying its deterioration (Hammouda and Khalafallah 1971).

Other activities: Other reported activity includes antimicrobial activity (Al-Azzawi et al. 2012).

285. Tectorigenin (flavonoid)

Plant source: *Pueraria thunbergiana* (flower)

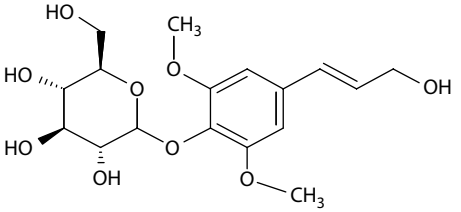


FIGURE 2.66 Structure of syringin.

Anti-diabetes: Tectorigenin is a potent hypoglycemic and hypolipidemic agent. I.p. administration of tectorigenin (5 mg/kg) for 7 days to streptozotocin-induced rats significantly reduced the blood glucose, total cholesterol, LDL, and VLDL cholesterol and triglyceride levels when compared with those of control group (Lee et al. 2000). In addition, tectorigenin showed *in vitro* antioxidant effects. In an *in vitro* study, tectorigenin effectively inhibited the ability of palmitic acid to induce the production of ROS and collapse of mitochondrial membrane potential. Moreover, tectorigenin presented strong inhibition effect on ROS-associated inflammation, as TNF-α and IL-6 production in endothelial cells was greatly reduced with suppression of I kappa B kinase-β (IKKβ)/NF-κB phosphorylation and JNK activation. Tectorigenin also could inhibit inflammation-stimulated IRS-1 serine phosphorylation and restore the impaired insulin PI3K signaling, leading to a decrease in NO production. These results demonstrated its positive regulation of insulin action in the endothelium (Wang et al. 2013).

Other activities: Tectorigenin is known to have anti-inflammatory and antioxidant properties. It protected the Vero cell line from injury by hydrogen peroxide (Lee et al. 2000).

286. Terocarpans

Plant source: Pterocarpans are found in *Erythrina abyssinica*, *Phaseolus vulgaris*, and many other plants of Fabaceae; pterocarpans are derivatives of isoflavanoids (members of the class of benzofurochromene with a 6a,11a-dihydro-6*H*-[1]benzofuro[3,2-*c*]chromene skeleton and its substituted derivatives).

Anti-diabetes: Several pterocarpans isolated from the stem bark of *E. abyssinica* exhibited PTP1B inhibitory activity (Jiang et al. 2012).

Other activities: Pterocarpans showed antifungal and many other biological properties.

287. Thymoquinone (thymoquinon) or 2-isopropyl-5-methylbenzoquinone

Plant source: Thymoquinone (2-isopropyl-5-methylbenzo-1,4-quinone) is present in plants such as *Nigella sativa* and *Monarda fistulosa*. The chemical structure of thymoquinone is shown in Figure 2.67.

Anti-diabetes: Several studies using experimental diabetic animals have established the anti-DM property of thymoquinone isolated from the seeds of *N. sativa*. Thymoquinone showed anti-DM (anti-β-cell damage), antioxidative, and neuroprotective activities in streptozotocin–nicotinamide-induced diabetic rats (Sankaranarayanan and Pari 2011). The anti-DM properties of thymoquinone have been reviewed as well (AbuKhader 2012). In one study, daily administration of thymoquinone (50 mg/kg, for 30 days) to diabetic rats and hamsters reduced fasting blood glucose levels and blood glycated hemoglobulin levels. In agreement with this, in another study, thymoquinone (80 mg/kg for 45 days) produced a consistent dose-dependent decrease in blood glucose levels in diabetic rats; the treatment reduced the activities of gluconeogenic enzymes in liver. In another related study, administration of thymoquinone (3 mg/kg. i.p., for 3 days) decreased serum and pancreatic nitrite levels, which reflect NO production. NO is involved in the immune system-mediated destruction of pancreatic β-cells during the development of type 1 DM. Regarding the anti-DM mechanisms, thymoquinone restores the

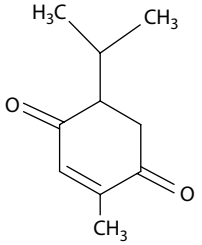


FIGURE 2.67 Structure of thymoquinone.

activity of enzymes involved in glucose metabolism such as glucose-6-phosphatase and fructose-1,6-bisphospatase of gluconeogenesis. Thymoquinone has a protective effect on β-cells of the pancreas against damaging effects of oxidative stress and NO leading to enhanced insulin production and secretion.

Other activities: Antioxidant activity and free radical scavenging properties of thymoquinone are known. Furthermore, thymoquinone showed protective effects against sodium fluoride-induced hepatotoxicity and oxidative stress in rats (Abdel-Wahab 2013). Anticancer and analgesic properties of this compound have been reported.

288. Tiliroside (potengriffioside A or tribuloside)

Plant source: *Trans*-tiliroside is a principal phytochemical in *Potentilla chinensis*. It is also found in plants such as *Potentilla discolor* and *Rosa canina*.

Anti-diabetes: *Trans*-tiliroside (potengriffioside A) revealed antihyperglycemic, antihyperlipidemic activities in alloxan-induced and streptozotocin-induced diabetic (Qiao et al. 2011). The level of fasting serum glucose levels, triglycerides, and total cholesterol in alloxan-induced diabetic mice were significantly decreased after daily oral administration of trans-tiliroside (0.4, 0.8, and 1.6 mg/kg, for 15 days). Blood glucose level was significant decreased in streptozotocin-induced diabetic rats by trans-tiliroside (1.2 and 0.3 mg/kg for 10 weeks). The content of total cholesterol, LDL cholesterol, and triglyceride levels were decreased and HDL cholesterol content was increased in the treated diabetic rats. Moreover, *trans*-tiliroside revealed antioxidant activity. Histological morphology examination showed that the *trans*-tiliroside restored the damage of pancreas tissues in rats with diabetes mellitus (Qiao et al. 2011). Potengriffioside A exhibited inhibitory effects on the activity of glycogen phosphorylase *in vitro*. The inhibition on glycogen phosphorylase may be one molecular mechanism through which the extract ameliorated hyperglycemia (Yang et al. 2009). Trans-tiliroside (0.1–10 mg/kg, daily for 2 weeks) potently inhibited the gain of body weight, especially visceral fat weight in mice, and significantly reduced blood glucose levels after glucose loading (1 g/kg, i.p.) in mice. Furthermore, a single oral administration of *trans*-tiliroside at a dose of 10 mg/kg increased the expression of PPAR-α mRNA of liver tissue in mice (Ninomiya et al. 2007).

Other activities: *Trans*-tiliroside exhibited anti-inflammatory and free radical scavenging activity (Sala et al. 2003). Tiliroside (1, 5, or 10 mg/kg) induced a dose-dependent long-lasting decrease in blood pressure in conscious hypertensive rats that was accompanied by an increased heart rate (Silva et al. 2013).

289. Tingenone and tingenine B

Plant source: *Salacia chinensis*

Anti-diabetes: Tingenone and tingenine B from this plant showed an inhibitory effect on rat lens aldose reductase (Morikawa et al. 2003).

Other activity: Tingenone showed very high toxicity (IC_{50}: 8.233 μM) against Vero cells (Thembela 2010). This compound is likely to have *in vivo* toxicity.

290. Timosaponin A III, psedoprototimosaponin A III, and prototimosaponin A III

Plant source: *Anemarrhema asphodeloides*

Anti-diabetes: Timosaponin A III, psedoprototimosaponin A III, and prototimosaponin A III have anti-diabetes activity. These steroidal saponins (50 mg/kg, i.p.) showed hypoglycemic activity in alloxan-induced diabetic mice. It lowered gluconeogenesis and glycogenolysis in liver (Lee et al. 2010).

Other activities: Timosaponin AIII isolated from *A. asphodeloides* ameliorated learning and memory deficits in scopolamine-treated mice (Lee et al. 2009). Treatment with the compound counteracted the increase in TNF-α and IL-1β-induced by scopolamine administration. It also inhibited the activation of NF-κB signaling in BV-2 microglia and in SK-N-SH neuroblastoma cells induced with TNF-α or scopolamine (Lee et al. 2009).

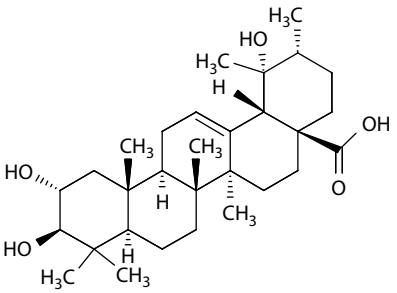


FIGURE 2.68 Structure of tormentic acid.

291. Tormentic acid (a triterpenoid saponin)

    Plant source: *Potentilla discolor*, *Poterium ancisroides*, *Eriobotrya japonica*; the chemical structure of tormentic acid is shown in Figure 2.68.

    Anti-diabetes: Tormentic acid in the presence of 1.66 mM glucose initiated insulin secretion by isolated rat islets of Langerhans in a dose-dependent fashion at concentrations ranging from 0.05 to 0.5 mM. However, the compound has no effect on the insulin-releasing capacity of 16.6 mM glucose. These results suggest that the hypoglycemic effect of tormentic acid is due to a direct effect of the compound *in vitro* (Ivorra et al. 1989). Tormentic acid exhibited inhibitory effects on glycogen phosphorylase. The inhibition on glycogen phosphorylase may be one molecular mechanism through which the extract ameliorated hyperglycemia (Yang et al. 2009). The effect of tormentic acid on diabetes and dyslipidemia was studied in high-fat-fed mice. HFD increased glucose, triglyceride, insulin, and leptin levels, whereas tormentic acid administration for 4 weeks to the high-fat-fed mice effectively prevented these phenomena and ameliorated insulin resistance. Tormentic acid reduced visceral fat mass and hepatic triacylglycerol contents; moreover, it significantly decreased both the area of adipocytes and ballooning degeneration of hepatocytes. The compound caused increased skeletal muscular AMPK phosphorylation and Akt phosphorylation and GLUT4 proteins, but reduced the hepatic expressions of PEPCK and glucose-6-phosphatase (G6 Pase) genes. Tormentic acid enhanced skeletal muscular Akt phosphorylation and increased insulin sensitivity. It also enhanced phospho-AMPK in the liver. Therefore, it is possible that the activation of AMPK by the compound results in decreasing hepatic glucose production while increasing skeletal muscular GLUT4 contents, thus contributing to attenuating the diabetic state. Moreover, tormentic acid exhibited an antihyperlipidemic effect by downregulations of the hepatic SREBP-1c and apolipoprotein C-III and an increased PPAR-α expression, thus resulting in decreases in blood triglycerides. These findings demonstrated that tormentic acid was effective for the treatment of diabetes and hyperlipidemia in HFD-fed mice (Wu et al. 2014).

    Other activities: Tormentic acid has anti-inflammatory activity. It inhibited LPS-induced iNOS, COX-2, and TNF-α expression through inactivation of the NF-κB pathway in RAW 264.7 macrophages (An et al. 2011). Tormentic acid inhibited proliferation and induced apoptosis in vascular smooth muscle cells *in vitro.*

292. Trichosan A (glycan)

    Plant source: *Trichosanthes kirilowii*

    Anti-diabetes: Bioactivity guided fractionation identified five glycans (trichosans A, B, C, D, and E). These fractions showed hypoglycemic activity in normal mice, but only one glycan (trichosan A) exhibited blood glucose-lowering effect in alloxan-induced diabetic mice (Hikino et al. 1989).

293. Trigonelline (alkaloid)

    Plant source: Trigonelline is found in the anti-DM plant, *Trigonelia foenum-graecum* (seed). The chemical structure of trigonelline is shown in Figure 2.69.

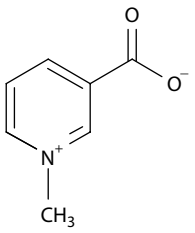


FIGURE 2.69 Structure of trigonelline.

Anti-diabetes: The seed water extract containing trigonelia reduced glucose levels in glucose tolerance test in alloxan-diabetic rabbits (Mowla et al. 2009). Trigonelline increased serum insulin levels, increased sensitivity of tissues to insulin action, and stimulated activity of enzymes of glucose utilization (Puri et al. 2011). It acts by positively influencing β-cell regeneration, insulin secretion, activities of enzymes related to glucose metabolism, ROS, axonal extension, and neuron excitability (Zhou et al. 2012). Further studies including detailed toxicity evaluation and follow-up clinical trials are required.

Other activities: Trigonelline has hypolipidemic, neuroprotective, antimigraine, sedative, memory-improving, antibacterial, antiviral, and antitumor activities; it has been shown to reduce diabetic auditory neuropathy and platelet aggregation (Zhou et al. 2012).

294. Trilobatin (polyphenol)

Plant source: *Lithocarpus polystachyus*

Anti-diabetes: The sweet compound from *L. polystachyus*, trilobatin, inhibited α-glucosidase strongly and α-amylase mildly (Dong et al. 2012). A comparative study showed that α-glucosidase activity was inhibited remarkably by the trilobatin, and the inhibition was noncompetitive and did not exhibit a significant difference when compared to acarbose. Its inhibition rate against α-amylase, however, was lower than that of acarbose despite of having a stronger 2, 2'-diphenyl-1'-picryl-hydrazil (DPPH)-free radical scavenging effect than rutin (Zhang et al. 2011).

Other activities: Trilobatin exhibited antioxidant and anti-inflammatory properties. Trilobatin attenuated the LPS-mediated inflammatory response by suppressing the NF-κB signaling pathway (Fan et al. 2015).

295. Triptocalline A

Plant source: *Salacia chinensis*, *Tripterygium wilfordii*, and so on

Anti-diabetes: Triptocalline A from *S. chinensis* showed an inhibitory effect on rat lens aldose reductase (Morikawa et al. 2003).

296. Ursolic acid

Plant source: Ursolic acid is present widely in food, medicinal plants, and other plants. Examples of medicinal plants include *Campsis grandiflora*, *Campsis grandifolia*, *Cornus officinalis*, *Eriobotrya japonica*, *Phoradendron reichenbachianum*, *Rhododendron brachycarpum*, *Syzygium malacense*, *Hedyotis biflora*, *Hintonia latiflora*, *Leandra lacunose*, *Ocimum gratissimum*, *Ocimum sanctum*, *Potentilla chinensis*, *Protium heptophyllum*, and *Symplocos paniculata*. The chemical structure of ursolic acid is shown in Figure 2.70.

Anti-diabetes: Ursolic acid is a powerful inhibitor of PTP1B activity *in vitro*. Ursolic acid from *Phoradendron reichenbachianum* inhibited PTP1B and the IC_{50} value was 2.3 μM (Nazaruk and Borzym-Kluczyk 2014; Ramirez-Espinosa et al. 2011). Furthermore, ursolic acid was found to stimulate glucose uptake in L6 myotubes and facilitate glucose transporter isoform 4 translocation in CHO/hIR cells via enhancing IR phosphorylation (Jiang et al. 2012). Recently, the effect of *in vivo* treatment with ursolic acid on glycemia in hyperglycemic rats and its mechanism of action on muscle were studied. Ursolic acid presented a potent antihyperglycemic effect, increased insulin vesicle translocation, insulin secretion and augmented glycogen

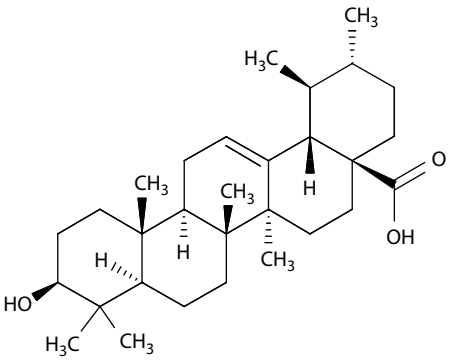


FIGURE 2.70 Structure of ursolic acid.

content. Also, ursolic acid stimulated the glucose uptake through insulin signaling related to the GLUT4 translocation to the plasma membrane as well as GLUT4 synthesis. Besides, the modulation of calcium, phospholipase C, protein kinase C, and PKCaM II is mandatory for the full stimulatory effect of ursolic acid on glucose uptake. Ursolic acid did not change the serum LDH and serum calcium balance (Castro et al. 2015). In another study, the anti-DM activity of ursolic acid acetate isolated from *Coleus vettiveroides* was evaluated in streptozotocin-induced diabetic rats. Administration of the compound (50 mg/kg) to diabetic rats for 15 days resulted in significant reduction in blood glucose levels from day 7 onward and the loss of body weight was also controlled compared to diabetic control rats. The treatment also reversed the changes caused by streptozotocin-DM in the relevant serum biochemical parameters and liver glycogen content (Gopalakrishnan and Dhanapal 2015).

Other properties: Reported pharmacological properties include antitumor, hepatoprotective, anti-inflammatory (oral and topical), antiulcer, antimicrobial, antiviral, and antihyperlipidemic activity (Liu 1995).

297. Valonic acid dilactone (hydrolysable tannin)

Plant source: *Punica granatum*

Anti-diabetes: An anti-diabetes principle (valonic acid dilactone) has been isolated from methanol extract of fruit rinds of *P. granatum*; valonic acid dilactone (25 or 50 mg/kg, p.o.) showed promising dose-dependent anti-diabetic activity (Jain et al. 2012). In an alloxan-induced diabetes model, valonic acid dilactone (10, 25, and 50 mg/kg, p.o.) has shown significant and dose-dependent anti-diabetic activity by maintaining the blood glucose levels within the normal limits. Furthermore, valonic acid dilactone treatment resulted in very minimal acinar damage and adequate number of pancreatic islets in the alloxan-induced diabetic rats. Besides, the active compound inhibited the activities of α-amylase, aldose reductase, and PTP1B, which mimicked insulin action to some extent. Thus, valonic acid dilactone was found to act through several mechanisms, which include inhibition of aldose reductase, α-amylase, and PTP1B (Jain et al. 2012).

298. Vanillin (4-Hydroxy-3-methoxybenzaldehyde)

Plant source: Vanillin is found in vanilla beans (*Vanilla planifolia*) and other plants such as *Gastrodia elata*; it is used as a flavoring agent.

Anti-diabetes: Vanillin from *G. elata* reduced insulin resistance. Vanillin and the water extract containing vanillin and 4-hydroxybenzaldehyde as active principles decreased body fat and improved insulin resistance in diet-induced obese rats (Park et al. 2011).

Other activities: Vanillin, an anticlastogen, has been demonstrated to inhibit gene mutations in both bacterial and mammalian cells. Besides, vanillin showed protective effect against radiation-induced chromosomal damage (Keshava et al. 1998).

299. Verbascoside (acteoside)

Plant source: *Eremophila alternifolia* and *Eremophila longifolia* and many other plants in Lamiaceae in particular

Anti-diabetes: Verbacoside (caffeoyl phenylethanoid glycoside) is a potent lens aldose reductase inhibitor (Ghisalberti 2005).

Other activities: Verbascodide showed anti-inflammatory and antimicrobial properties (Pardo et al. 1993).

300. Vescalagin (ellagitannin)

Plant source: Vescalagin is found in *Syzygium samarangense* (vescalagin and castalagin are two diastereoisomers).

Anti-diabetes: Vescalagin (an ellagitannin) isolated from *S. samarangense* fruit enhanced glucose uptake in insulin-resistant FL83B cells. In a follow-up study, vescalin showed hypotriglyceridemic and hypoglycemic effects in high-fructose-diet-induced diabetic rats. Fasting blood glucose, C-peptide, fructose amine, triglyceride, and free fatty acid contents decreased in vescalin treated (4 week-treatment, daily, 30 mg/kg) high-fructose-diet-fed rats (Shen and Chang 2013). In a related study, vescalagin improved oral glucose tolerance, reduced cardiovascular risk index, AGEs, and tumor necrosis factor-α while increasing C-peptide and D-lactate contents significantly in rats orally administered methylglyoxal. The unbalance of glucose metabolism in humans may cause the excessive formation of methylglyoxal, which can react with various biomolecules to form the precursor of AGEs. Thus, vescalagin prevented methylglyoxal-induced inflammation and carbohydrate metabolic disorder in rats (Chang et al. 2013).

Other activities: Vescalagin specifically inhibits Top2α *in vitro* and in cells at pharmacological concentrations (Auzanneau et al. 2011). Furthermore, this compound is known to have anti-inflammatory and antiherpetic activity.

301. Vicine (a glycal alkaloid)

Plant source: *Momordica charantia*

Anti-diabetes: The glycol alkaloid vicine (a pyrimidene nucleoside) isolated from the seeds of *M. charantia* is shown to induce hypoglycemia in nondiabetic fasting rats (Joseph and Jini 2013).

302. Vincamine (alkaloid)

Plant source: *Vinca minor*, *Catharanthus roseus*

Anti-diabetes: Vincamine, an alkaloid found in the leaves of *V. minor*, is reported to have hypoglycemic property (De and Saha 1975; Farahanikia et al. 2011).

Other properties: Other properties include pronounced cerebrovasodilatory and neuroprotective activity (Farahanikia et al. 2011). Vincamine has modulatory effects on brain circulation and neuronal homeostasis, and exhibits antihypoxic and neuroprotective potencies (Vas and Gulyas 2005).

303. Vitexin (flavonoid glycoside)

Plant source: *Microctis folium*, *Vitex lucens*, *Vitex agnus-castus*, and so on

Anti-diabetes: Vitexin (apigenin 8-C-glucoside) from *M. folium* inhibited α-glucosidase activity (Gaikwad et al. 2014).

2.3 Isolation of Anti-Diabetic Phytochemicals

Different methods are to be employed for the isolation of active principles depending on the chemical nature of the compounds, their solubility in different solvents, and stability. In general, plant extracts are subjected to various chromatographic techniques such as paper chromatography, thin-layer chromatography, high-performance thin-layer chromatography (TLC), gas liquid chromatography (GLC), and high-performance liquid chromatography (HPLC) for the separation of various phytoconstituents.

For large-scale separations, preparatory chromatographic techniques such as preparative TLC, column chromatography coupled with automated fraction collection and preparative HPLC are used. Structures of separated molecules are elucidated using spectral data (ultraviolet and visible spectroscopy, infrared spectroscopy, mass spectroscopy, nuclear magnetic resonance spectroscopy, etc.) and other properties of the compounds. Details of these techniques can be found elsewhere and not considered in this book.

However, certain specific points relevant to the isolation of active principles from plant materials are the following: It should be remembered that certain bioactive molecules could be destroyed and metabolites with activity could be formed during the isolation procedure. During isolation certain compounds may be changed or broken down by enzymatic actions. This could be prevented by cold extraction procedures or hot water extraction, if the compound is heat stable. Some of the phytochemicals are destroyed by heat. Another point to be considered is the solvent to be used for extraction; different solvents including highly nonpolar to polar solvents are to be used. Some of the bioactive compounds are soluble in highly nonpolar solvents. The conventional methods used by phytochemists to defat the dried plant material with petroleum ether extraction may lead to loss of the active compounds in certain cases. This has to be overcome with initial extraction with solvents like hexane or petroleum ether and testing the bioactivity of extracts. Development of suitable dosage forms or drug delivery systems for sticky, insoluble extracts and fractions is a hindrance. Traditional medicinal plant should be tested first for bioactivity in *in vivo* systems using the crude homogenate or crude traditional preparation of the plant part as used in traditional medicine. If active, it is always better and proper to follow activity guided isolation following phytotherapeutic approach rather than a phytochemical approach. In the phytochemical approach, first phytochemicals are separated without caring for biological activity and then isolated compounds are tested for bioactivity. In this approach, there is a possibility of losing active compounds in the isolation process. Furthermore, testing each compound for biological activity is a laborious task.

2.4 Proven Anti-DM Plants without Identified Active Principles

Although considerable phytochemical studies were carried out on most of the promising anti-DM plants, activity guided isolation of active principles were not carried out even in the case of many of the promising anti-DM plants where pharmacological studies using plant extracts have proved their anti-DM activities beyond any doubt. Some of these plants are *Abroma augusta*, *Acacia catechu*, *Ajuga iva*, *Alstonia scholars*, *Annona muricata*, *Asparagus racemosus*, *Bauhinia variegata*, *Brassica juncea*, *Cassia auriculata*, *Cassia fistula*, *Cassia kleinii*, *Cassia occidentalis*, *Coccinia indica*, *Clerodendron phlomidis*, *Coriandrum sativum*, *Cucumis sativus*, *Cyamopsis tetragonoloba*, *Ficus racemosa*, *Fraxinus excelsior*, *Gongronema latifolium*, *Helicteres isora*, *Hemionitus arifolia*, *Lepidium sativum*, *Olea europaea*, *Opuntia streptacantha*, *Phyllanthus amarus*, *Prunus amygdalus*, *Semecarpus anacardium*, *Tamarindus indica*, *Tephrosia purpuria*, and *Ziziphus jujube* (Subramoniam 2016). In most of the cases, phytochemical studies were not done in tune with anti-diabetic (pharmacological) studies. Anti-DM studies were carried out, to a large extent, using crude preparations of plant parts, extracts and active fractions. It should be noted that almost all of the plants with anti-DM properties exhibit pharmacological properties other than anti-DM activities also. Some of the phytochemicals are isolated from these plants in connection with other pharmacological studies. In some cases, phytochemical studies on these plants were carried out following a phytochemical approach rather than a phytotherapeutic or phytopharmacological approach. Activity-guided isolation of anti-DM principles from these plants is urgently needed.

2.5 Conclusions

A perusal of phytochemicals reported in anti-DM plants shows that some of the anti-DM compounds are occurring in many plants. Examples of these compounds include quercetin, ursolic acid, ferulic acid, β-sitosterol, oleanolic acid, chlorogenic acid, α- and β-amyrin, and myricitin. Another interesting point is many of these compounds have more than one pharmacological activity and target molecule.

Crude preparations of plant parts including extracts and active fractions may contain, possibly, molecules with diverse bioactivities. It is also possible to have pro-DM and anti-DM molecules in the same preparation. For example, caffeine (present in coffee) intake was associated with an acute reduction of insulin sensitivity in short-term metabolic studies in humans. This effect reflects decreased glucose storage, probably due to increased epinephrine release (Gomes et al. 2013). Diterpenes, in particular, cafestol and kahweol in coffee, have been reported to increase the serum total cholesterol levels and to be associated with higher rates of coronary heart disease in coffee drinkers from Norway (Bisht and Sisodia 2010). Chlorogenic acid, a major component of coffee, is being recognized as an important anti-diabetic compound. When a mixture of compounds is used as in the case of crude extracts, synergistic, additive, inhibitory or stimulatory effects may occur (see Chapter 4).

As expected for a complex metabolic disease, there are many molecular targets for therapeutic agents in DM. Diverse phytochemicals belonging to various chemical classes show varying levels of anti-DM activities in *in vitro* and *in vivo* studies. More than 300 active anti-DM molecules are presented in this chapter. However, active principles remain to be identified from many established traditional anti-DM plants. There is a need to identify the active principles and their properties in each case.

3

Mechanism of Action of Anti-Diabetes Mellitus Plants

3.1 Introduction

Various levels of scientific studies involving *in vivo* animal experiments and *in vitro* assays were carried out on more than a thousand anti-diabetes mellitus (anti-DM) medicinal plants regarding their anti-DM properties. However, mechanisms of action studies were attempted only on a limited number of the plant species. As given in Table 3.1, although varying degrees of mechanisms of action studies were done on more than 399 plants, in most cases the studies are still incomplete and complete studies were done only on some plants. The mechanisms of action are diverse and there are several target molecules for the anti-DM phytochemicals to act in the complex disease, DM. Studies reveal that many plant species act through multiple pathway to control DM. Anti-DM molecules present in the crude extracts of anti-DM plants exert additive effects or synergistic effects in many cases; however, molecules that antagonize or block the anti-DM action of active principles has also been reported in the same plant in a few cases. Many of the mechanism of action pathways are interconnected and study results could, possibly, be erroneously interpreted for direct and indirect effects. For example, hepatic glucose production can be lowered by the direct inhibition of the activities of one or more key enzymes involved in glucose production by the phytochemicals; it can also be lowered indirectly by enhanced insulin levels and/or improvement in insulin action. Insulin indirectly influences the enzymes involved in glucose metabolism through signal transduction pathways. Furthermore, the activation of adenosine monophosphate-activated protein kinase (AMPK) can also lead to decrease in hepatic glucose production.

3.2 Major Mechanism of Action of Anti-DM Molecules and Extracts

The important known mechanisms of actions of anti-DM plants (crude preparation, extracts, active fractions, and/or active compounds) include (1) stimulation of insulin secretion and/or regeneration of the β-cells, (2) sensitization of insulin action (decreasing insulin resistance), (3) insulin-like action (partial or complete), (4) activation of AMPK, (5) increasing the levels of glucagon-like peptide-1 (GLP-1), (6) activation of peroxisome proliferators–activated receptor-gamma (PPAR-γ), (7) inhibition of carbohydrate digestion in the intestine, (8) inhibition of glucose absorption from the intestine, (9) inhibition of glucose reabsorption in the kidney, and (10) inhibition of aldose reductase activity (Figure 3.1). Modulation of specific immune reactions by plant products could lead to delay or prevention of the development of diabetes, type 1 DM in particular, in genetically susceptible individuals. In addition to these, other mechanisms of action have also been observed in some anti-DM plants. Furthermore, there could be mechanisms of action not known currently to the scientific world.

3.2.1 Stimulation of Insulin Secretion and/or Regeneration of the β-Cells

Numerous anti-DM plants stimulate insulin secretion, induce regeneration of β-cells, and/or increase size and number of β-cells. Interestingly, a few plant extracts (active molecules) induced the differentiation of precursor cells into β-cells. These herbal drugs may be useful to rectify insulin deficiency in type 2 DM and may help to retard type 1 DM development. Conophylline, a vinca alkaloid, from leaves of *Tabernaemontana divaricata* (L.) Roemer & Schultes, induced the differentiation of pancreatic precursor

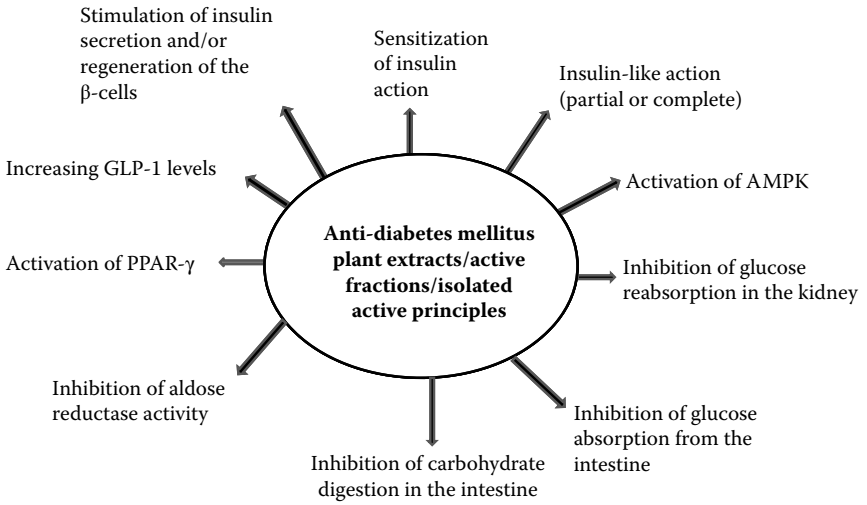


FIGURE 3.1 Different major mechanisms of actions of anti-diabetes mellitus plants. AMPK, adenosine monophosphate–activated protein kinase; GLP-1, glucagon-like peptide 1; PPAR-γ, peroxisome proliferator–activated receptor- γ.

TABLE 3.1

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
1.	*Abelmoschus moschatus* Medik., Malvaceae	Myricetin from aerial parts; extract of aerial parts	Enhanced glucose uptake and utilization *in vitro* and in diabetic rats lacking insulin; reduced insulin resistance by enhancements in IRS-1-associated PI3K step in fructose chow-fed rats (Liu et al. 2010)
2.	*Abies balsamea* (L.) Mill., Pinaceae	Ethanol extract of inner bark	Enhanced phosphorylation of Akt and AMPK *in vitro*; improved muscle and adipose tissue glucose uptake and reduced hepatic glucose production (Eid and Haddad 2014)
3.	*Abies pindrow* Royle, Pinacea	Ethanol extract	Showed insulin secretagogue activity in INS-1 cells at 10 μg/mL level (Hussain et al. 2004)
4.	*Abroma augusta* L. f., Sterculiaceae	Water extract of fresh leaves	Reduced absorption of glucose in fasted rats (Islam et al. 2012)
5.	*Abutilon indicum* (L.) Sweet, Malvaceae	Water extract of whole plant	Inhibited glucose absorption and stimulated insulin secretion in rodents (Krisanapun et al. 2009)
6.	*Acalypha indica* L., Euphorbiaceae	Ethanol extract	Regeneration of β-cells in streptozotocin-nicotinamide-type 2 diabetic rats (Raghuram Reddy et al. 2012)
7.	*Acalypha wilkesiana* Mull., Euphorbiaceae	Methanol extracts of root	Regeneration of β-cells in diabetic rats (Odoh et al. 2013)
8.	*Acanthopanax koreanum* Nakai, Araliaceae	A diterpene from root	Inhibition of PTP1B (Jiang et al. 2013)
9.	*Acanthopanax senticosus* Rupr. & Maxim, Araliaceae	Syringin	Release of acetylcholine from nerve terminals that stimulates mascarinic M3 receptors in pancreatic cells and augments the insulin release (Liu et al. 2008)
10.	*Acer saccharum* Marshall, Sapindaceae	Leaf extract (active principle, acertannin)	Inhibition of α-glucosidase activity in both *in vivo* and *in vitro* (Honma et al. 2010)
11.	*Achillea santolina* L., Asteraceae	Water extract	Enhanced β-cell proliferation *in vitro* (Kasabri et al. 2012a)
12.	*Acosmium panamense* Benth., Fabaceae	Butanol extract of stem bark	Marked inhibition of α-glucosidase activity (Andrade-Cetto et al. 2008b)
13.	*Aegiceras corniculatum* (L.) Blanco, Myrsinaceae	Falcarindiol	Inhibited PTP1B at a low concentration (Jiang et al. 2013)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
14.	*Aegle marmelos* (L.) Correa, Rutaceae	Water and ethanol extracts of leaves	Improved functional state of β-cells and improved regeneration in streptozotocin-diabetic rats (Maity et al. 2009) (detailed mechanism of action is not known)
15.	*Agave tequilana* Gto., Asparagaceae	Fructons	Induced production of GLP-1 and its precursor mRNA in the different colonic segments (Urias-Silvas et al. 2007)
16.	*Agrimonia eupatoria* L., Rosaceae	Water extract	Stimulation of insulin secretion (glucose independent) from BRIN-BD11 pacreatic β-cell line (Gray and Flatt 1988)
17.	*Agrimonia pilosa* Ledeb., Rosaceae	Water extract	Inhibition of α-amylase activity *in vitro*; reversal of free fatty acid-induced insulin resistance in C2C12 myotubes; Stimulation of synthesis of Akt protein and mRNA in myotubes (Sang-Mi et al. 2013)
18.	*Alisma orientale* (Sam.) Juzepcz., Alismataceae	Alisol F and Alisol B (triterpenes) and alcohol extract of rhizome	Inhibited α-glucosidase activity *in vitro*; increased glucose uptake in 3T3-L1 adipocyte (Li and Qu 2012)
19.	*Alisma plantago-aquatica* L., Alismataceae	Ethanol extract of root	Activation of PPAR-γ (Rau et al. 2006)
20.	*Allium porrum* L., Lilliaceae	Ethanol extract of bulb	α-amylase inhibitory activity and reduction in glucose absorption from intestine (Belemkar et al. 2013; Nickavar and Yousefian 2009)
21.	*Allium sativum* L., Alliaceae	Allicin (diallyl thiosulfinate), and garlic juice	Increased the levels of insulin (?) (WHO 1999)
22.	*Alnus incana* sub sp. *rugosa* (Du Roi) R.T. Clausen, Betulaceae	Oregonin (a diarylheptanoid glycoside)	Stimulation of glucose transport and AMPK in cultured myocytes; blockage of differentiation and the maturation of 3T3-L1 preadipocytes (Eid and Haddad 2014)
23.	*Aloe vera* (L.) Burm. f., Aloaceae	Polysaccharides	Increased insulin levels (Sahu et al. 2013) (the mechanism of action of major anti-DM compounds of this plant is not known)
24.	*Alstonia macrophylla* Wall & G. Don, Apocynaceae	Picraline type alkaloids from leaves and their derivatives	Inhibited the activity of Na (+)-glucose cotransporter in the kidney (Arai et al. 2010)
25.	*Amaranthus spinosus* L., Amaranthaceae	Methanol extract of leaves	Inhibition α-amylase activity (Ashokkumar et al. 2011)
26.	*Amomum villosum* var. xanthioides (Wall. ex Baker) T.L.Wu & S.J.Chen., Zingiberaceae	Aqueous-ethanol extract of seeds	Suppression of NF-κB activation; potentiation of insulin-stimulated glucose uptake (Kang and Kim 2004)
27.	*Amorpha fruticosa* L., Fabaceae	Amorfrutins from fruit	Activation of PPAR-γ (Wang et al. 2014; Weidner et al. 2012)
28.	*Amorphophallus konjac* K.Koch., Araceae	An oligosaccharide fraction from root	Increased insulin secretion and protection of β-cells from free radical (?) mediated damage (Lu et al. 2002)
29.	*Anabasis articulata* Forssk. Moq., Chenopodiaceae	The saponin fraction of ethanol extract of aerial parts	Increased blood insulin and α-fetoprotein levels and decreased the levels of TNF-α and fructose amine (Metwally et al. 2012)
30.	*Anacardium occidentale* L., Anacardiaceae	Hydroethanol extracts of seed and anacardic acid	Stimulation of glucose uptake into C2C12 myotubes; activation of AMPK in the myotubes (Tedong et al. 2010)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
31.	*Andrographis paniculata* (Burm. f.) Nees, Acanthaceae	Alcohol extract of whole plant and andrographolide	Mediation of β-endorphin (Yu et al. 2008). Improvement of β-cells in streptozotocin-diabetic rats (Nugroho et al. 2014)
32.	*Anemarrhena asphodeloides* Bunge, Lilliaceae	Water extract of rhizome, and mangiferin; ethanol extract of rhizome; water extract of the rhizome	Reducing insulin resistance in fatty diabetic mice and activation of AMPK (Han et al. 2015); stimulation of insulin secretion from isolated islet of rats (Hoa et al. 2004); stimulation of GLP-1 secretion (Kim et al. 2013)
33.	*Angelica sinensis* (Oliv.) Diels, Apiaceae	Purified polysaccharide from the root	Reduction in insulin resistance-related IL-6 and TNF-α in serum in streptozotocin-induced diabetic mice; improvement in blood insulin levels (Wang et al. 2015)
34.	*Anisopus mannii* N.E.Br., Apocynaceae	Saponin fraction from methanol extract of leaves	Induction of insulin secretion via K+ ATP-dependent channels (Zaruwa et al. 2013)
35.	*Annona muricata* L. Annonaceae	Water extract of leaf; methanol extract of leaf	Protection of pancreatic β-cell integrity in streptozotocin diabetic rats (Adewole and Caxton-Martins 2006); regeneration of β-cell in streptozotocin-destructed islets (Adeyemi et al. 2007)
36.	*Anthocleista schweinfurthii* Gilg., Gentianaceae	Bauerenone, bauerenol and schweinfurthiin (steroids)	α-Glucosidase inhibitors (Mbouangouere et al. 2007)
37.	*Apium graveolens* L., Apiaceae	Chloroform extract of whole plant	Anti-glycation activity *in vitro* in RIN-5F cells; stimulation of insulin production by protecting pancreatic β-cells (Gutierrez et al. 2014)
38.	*Aquilaria sinensis* (Lour.) Gilg, Thymalaeaceae	95% Ethanol extract of leaves; methanol and water extracts	Activation of AMPK; improvement in insulin resistance; methanol and water extracts stimulated glucose uptake in adipocytes (Pranakhon et al. 2011)
39.	*Aralia elata* (Miq.) Seem, Araliaceae	Water extract of root and elatoside E	Inhibition of α-glucosidase (Yoshikawa et al. 1995; Xi et al. 2009)
40.	*Areca catechu* L., Arecaceae	Ethanol extract of nut	Inhibition of α-glucosidase (Amudhan et al. 2012)
41.	*Artemisia amygdalina* Decne, Asteraceae	The hydroethanolic and methanol extracts	Regeneration/ protection of β-cells in streptozotocin-diabetic rats (Ghazanfar et al. 2014)
42.	*Artemisia capillaries* Thunb, Asteraceae	Extract	Protection of β-cells by suppressing NF-κB activation (Kim et al. 2007a)
43.	*Artemisia dracunculus* L., Asteraceae	6-Demethoxycapillarisin and 2,4-dihydroxy-4-methoxy dihydrochalcone (poly phenolic compounds); standardized ethanol extract	Both compounds decreased phosphoenolpyruvate carboxykinase mRNA expression; 6-demethoxycapillarisin activated PI3K pathway where as the other compound activated AMPK pathway (Govorko et al. 2007; Wang et al. 2008a); increased insulin sensitivity via restoration of Akt phosphorylation and attenuated the FFA-induced upregulation of protein tyrosine phosphatase 1B (Obanda et al. 2012)
44.	*Artemisia minor* Jacq. ex Besser, Compositae	1,4-Benzodioxane lignin and caffeic acid from aerial parts	PTP1B inhibition (Jiang et al. 2013)
45.	*Artemisia santonicum* L., Asteraceae	Ethanol extract of aerial part	Insulin secretagogue activity in INS-1 cells *in vitro* (Hussain et al. 2004)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
46.	*Artemisia sphaerocephala* Krasch, Asteraceae	Gum from the seed powder	Reduced insulin resistance and liver fat accumulation in high fat diet and low dose streptozotocin-induced type 2 diabetic rats (Xing et al. 2009)
47.	*Aspalathus linearis* (Burm.f.) R. Dahlgren, Fabaceae	Aspalathin from leaf; leaf tea extract	Stimulated glucose uptake by L6 myotubes; increased insulin secretion from cultured RIN-5F β-cells (Kawano et al. 2009); stimulation of glucose uptake in C2C12 myocytes; α-glucosidase inhibitory activity (Ku et al. 2015)
48.	*Asparagus adscendens* Buch. Ham. ex Roxb., Liliaceae	Water extract	Stimulation of both the secretion and action of insulin in colonel pancreatic β-cell line; it inhibited starch digestion also (Mathews et al. 2006)
49.	*Asparagus racemosus* Willd., Liliaceae	Ethanol extract of root	Stimulated insulin secretion in isolated perfused rat pancreas, rat islets and clonal β-cells (Hannan et al. 2007); inhibited the absorption of glucose during *in situ* gut perfusion with glucose; enhanced glucose transport and insulin action in 3T3-L1 adipocytes (Hannan et al. 2012)
50.	*Astilbe grandis* Stapf ex E.H.Wilson	Triterpenes from rhizome	Inhibition of tyrosine phosphatase 1B (Jiang et al. 2013)
51.	*Astragalus membranaceus* Bunge, Fabaceae	Ethanol extract and isolates formononetin and calycosin	Activation of PPAR-α and PPAR-γ (Shen et al. 2006a)
52.	*Azadirachta indica* A. Juss., Meliaceae	Chloroform extract of leaf; water extract of leaf	Regeneration of β-cells and increase in plasma insulin; inhibition of intestinal α-glucosidase activity (Bhat et al. 2011a, 2011b); abrogation of inhibitory effect of serotonin and epinephrine on insulin secretion mediated by glucose (Chattopadhyay 1999)
53.	*Azorella compacta* Phil, Ambelliferae	Azorellanol	Elevation of blood insulin level (Fuentes et al. 2005)
54.	*Baccharis articulata* (Lam.) Pers., Asteraceae	Ethanol extract of leaf	Insulin secretagogue effects (Kappel et al. 2012)
55.	*Bacopa monnieri* (L.) Wettst., Scrophulariaceae	Bacosine, a triterpene from whole plant	Increased glucose utilization in the diaphragm of diabetic rats *in vitro* (Ghosh et al. 2011)
56.	*Bauhinia forficata* Link, Fabaceae	Kaempferitrin, a major constituent of leaf and leaf extract	Activation of the insulin signaling pathway and stimulation of secretion of adiponectin in 3T3-L1 adipocytes (Tzeng et al. 2009); inhibition of of α-glucosidase (Ferreres et al. 2012)
57.	*Bauhinia multinervia* (Kunth) DC, Caesalpeniaceae	Flavonoid glycosides: quercetin 3-O-α-(2″-galloyl) rhamnoside and kaempferol 3-O-α-(2″-galloyl) rhamnoside from leaf	Inhibition of intact microsomal glucose-6-phosphatase (Estrada et al. 2005)
58.	*Bauhinia variegata* L., Caesalpeniaceae	Ethanol extract of leaf and its major constituent, roseoside	Enhanced insulin release from the β-cell lines INS-1 (Frankish et al. 2010)
59.	*Belamcanda chinensis* (L.) DC, Irdaceae	Extract of leaf	Stimulates insulin secretion (Wu et al. 2011)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
60.	*Berberis aristata* DC., Berberidaceae	Berberine	Improved insulin action by activating AMPK (Arif et al. 2014); berberine mimicked insulin action by increasing glucose uptake by 3T3-L1 adipocytes and L6 myocytes in an insulin independent manner; inhibited PTP1B activity and increased phosphorylation of IR, IRS1, and Akt in 3T3 L1 adipocytes (Chen et al. 2010); increased GLP-1 secretion in streptozotocin-diabetic rats, which is dependent on PKC or AMPK (Yu et al. 2010)
61.	*Berberis brevissima* Jafri, Berberidaceae	Berberine and 8-oxo-berberine	(As above)
62.	*Berberis parkeriana* C.K.Schneid., Berberidaceae	Berberine and 8-oxo-berberine	(As above)
63.	*Berberis vulgaris* L., Berberidaceae	Berberine (high concentration in root), 8-oxo-berberine	(As above)
64.	*Bergenia ciliata* (Haw.) Sternb., Saxifragaceae	(−)-3-O-Galloylepicatechin and (−)-3-O-galloylcatechin	Inhibition of rat intestinal α-glucosidase and porcine pancreatic α-amylase (Bhandari et al. 2008)
65.	*Bergenia himalaica* Boriss., Saxifragaceae	Ethanol extract of aerial parts; bergenicin	Insulin secretagogue activity in INS-1 cells (Hussain et al. 2004); Bergenicin, enhanced glucose-stimulated insulin secretion in isolated pancreatic islets (Siddiqui et al. 2014)
66.	*Beta vulgaris* L., Amaranthaceae	Extract of leaf or root	Regeneration of the β-cells in streptozoation diabetic rats (Bolkent et al. 2000)
67.	*Bidens pilosa* L., Asteraceae	Butanol fraction from whole plant, and cytopiloyne and other polyynes isolated from it	Prevented type 1 DM development in mice by immune modulation (inhibition of T cell differentiation, downregulation of Th1, up regulation of Th2 cells, reduced invasion of CD4+ T cells into β-cells) mediated protection of β-cells (Yang 2014); protected against islet atrophy and increased insulin levels; suppressed hunger in type 2 DM and thus showed anti-type 2 DM activity (Yang 2014)
68.	*Bixa orellana* L., Bixaceae	Bixin and norbixin (anti-DM activity is dependent on species, etc); hot water extract and isoscutellarein from the extract	Regulated mRNA expression involved in adipogenesis and enhanced insulin sensitivity in 3T3-L1 adipocytes through PPAR-γ activation (Wang et al. 2014); inhibited lens aldose reductase activity (Terashima et al. 1991)
69.	*Blighia sapida* Koenig, Sapindaceae	Hypoglycin A from unripe fruit and hypoglycin B from seeds (unusual amino acids) [toxins]	The injection of hypoglycin A forms a metabolite called methylene cyclopropane acetyl CoA, which inhibits several enzymes that are essential for metabolism of lipids, gluconeogenesis, etc. This toxin induces hypoglycemia, depletion of glucose reserves, and inability of cells to regenerate glucose (Atolani et al. 2009)
70.	*Boerhaavia diffusa* L., Nyctaginaceae	Extracts of leaves (methanol, water, and chloroform)	Rejuvenation of pancreatic beta-cells or through extra pancreatic action (?) (Nalamolu et al. 2004); Inhibition of α-glucosidase enzyme (Gulati et al. 2012)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
71.	*Bougainvillea spectabilis* Willd., Nyctaginaceae	D-Pinitol; water and ethanol extract of leaf	It may act via a post receptor pathway of insulin action affecting glucose uptake (Geetham and Prince 2008); regeneration of β-cells in the extract treated diabetic mice (Bhat et al. 2011a) and α-amylase & intestinal glucosidase inhibitory activity (Bhat et al. 2011b)
72.	*Boswellia serrata* Roxb. ex Colebr., Burseraceae	Boswellic acid from gum resin	Inhibition of aldose reductase in rat lens and inhibition of advanced glycation end products formation in diabetic rats (Rao et al. 2013)
73.	*Brachylaena discolor* D.C., Asteraceae	Plant extract	Stimulated glucose utilization in 3T3-L1 adipose cells, C2C12 muscle cells, and Change liver cells (van deVenter et al. 2008)
74.	*Brassica nigra* (L.) Koch, Brassicaceae	Water extract of seed	Release of insulin from pancreas and change of glucose metabolizing enzyme activities to normal levels in streptozotocin diabetic rats (Anand et al. 2009)
75.	*Brassica oleracea* L., var. botrytis, Brassicaceae	Methanol extract of cauliflower	Potent inhibitory activities against PTP1B (Jung et al. 2014)
76.	*Broussonetia papyrifera* L., Moraceae	Flavonoids from root	Inhibitory activities against PTP1B (Jiang et al. 2012)
77.	*Brucea javanica* (L.) Merr, Simaroubaceae	Ethyl acetate fraction of ethanol extract	Inhibition of glycogen phosphorylase-α *in vitro* (Ablat et al. 2014)
78.	*Bruguiera gymnorrhiza* (L.) Lam. Rhizophoraceae	Gymnorrhizol (macyrocylic polydisulfide) from seed	Inhibitory activity against protein tyrosine phosphatase 1B (Jiang et al. 2012)
79.	*Buddleja officinalis* Maxim., Longaniaceae	Extract of flower	Dipeptidyl peptidase IV (DPP-IV) inhibitory activity (Lei 2008) and inhibition of aldose reductase *in vitro* (Matsuda et al. 1995)
80.	*Caesalpinia bonbuc* (L.) Roxb., Caesalpiniaceae/ Febaceae	Seed fractions	Insulin secretagogue action on isolated islets (Chakrabarthi et al. 2005)
81.	*Caesalpinia sappan* L., Caesalpiniaceae	Brazilin	Increased basal glucose transport in 3T3-L1 fibroblasts and adipocytes; decreased the PKC activity in 3T3-L1 fibroblasts and adipocytes (Kim et al. 1995); inhibited adipocyte differentiation (Liang et al. 2013)
82.	*Camellia sinensis* (Linn.) Kuntze, Theaceae	Black tea (water extract of leaf) containing epigallocatechin gallate; catechin	*In vitro* insulin-enhancing activity (Anderson and Polansky 2002); catechin promoted adipocyte differentiation in human bone marrow mesenchymal stem cells through PPAR-γ activation (Wang et al. 2014)
83.	*Campsis grandifolia* (Thunb.) K. Schum, Bignoniaceae	Pentacyclic triterpenoid such as ursolic acid	Showed insulin-mimetic and insulin-sensitizing activities (Jung et al. 2007)
84.	*Cannabis sativa* L., Cannabaceae	Delta-9-tetrahydrocannabinol from leaf	Activated PPAR-γ *in vitro* (Wang et al. 2014)
85.	*Cassia alata* L., syn. *Senna alata* (L.) Roxb., Caesalpiniaceae	Ethyl acetate and n-butanol fractions of leaf	Inhibition of α-glucosidase activity (Varghese et al. 2013)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
86.	*Cassia sophera* L., Cesalpinaceae	Water extract of the plant	Stimulation of insulin secretion from isolated pancreatic islets; this effect is not dependent on ATP-sensitive potassiun (K-ATP) channels of β-cells (Sharma et al. 2013)
87.	*Catharanthus roseus* (L.) G. Don f., Apocyanaceae	Whole plant methanol extract	Regeneration of β-cells of pancreas in alloxan diabetic rats (Ahmed et al. 2010)
88.	*Cecropia obtusifolia* Bertol., Cereopiaceae	Isoorientin and chlorogenic acid (3-caffeoylquinic acid) were identified as the major constituents in the active water and butanol extracts of leaf (these are known anti-DM compounds)	*In vitro* assays of α-glucosidase activity showed an IC_{50} of 14 μg/mL for the butanol extract which was lower than that of acarbose (128 μg/mL) (Andrade-Cetto et al. 2008b) (mechanism of action of chlorogenic acid is given elsewhere in this table)
89.	*Cecropia peltata* L., Cecropiaceae	Chlorogenic acid and isoorientin from leaf	Blocking the hepatic glucose output, especially in the fasting state (Andrade-Cetto et al. 2010); chlorogenic acid decreases glucose absorption from intestine; it activates AMPK
90.	*Celastrus vulcanicola* J.D. Smith, Celastraceae	Friedelane-type triterpenes from root bark; astragaloside IV	Mediated phosphorylation of IR in the absence of insulin (Nazaruk and Borzym-Kluczyk 2015); in 3T3-L1 adipocytes astragaloside IV stimulated glucose uptake and antagonized TNF-induced insulin resistance (Nazaruk and Borzym-Kluczyk 2015)
91.	*Centaurea corcubionensis* Lainz, Compositae	Extracts of leaves and flowers	Stimulation of insulin release from rat islets of Langerhans (Chucla et al. 1998)
92.	*Centaurea iberica* Spreng., Compositae	Ethanol extract	Insulin secretagogue activity in INS-1 cells (Hussain et al. 2004)
93.	*Centaurea seridis* L., Compositae	β-Sitosterol-3-beta-D-glucoside	The compound exerted its action on intact pancreatic β-cells by stimulating insulin secretion (Ivorra et al. 1990)
94.	*Centella asiatica* (L.) Urban, Apiaceae	Ethanol extract of whole plant; centellsapogenol A	Inhibition of of both intestinal disaccharidase and α-amylase; inhibition of carbohydrate absorption and glucose-fiber binding (Kabir et al. 2014); inhibition of aldolase reductase activity (Matsuda et al. 2001)
95.	*Chaenomeles sinensis* (Thouin) Koehne, Rosaceae	Ethyl acetate fraction of fruit	Inhibition of α-glucosidase, α-amylase and lipase activities (Sancheti et al. 2013)
96.	*Chelidonium majus* L., Papaveraceae	Berberine, an isoquinoline alkaloid	(Xia et al. 2011) (see under *Berberis aristata*)
97.	*Chiliadenus iphionoides* (Boiss. & Blanche) Brullo, Asteraceae	Ethanol extract; water extract	Increased insulin secretion in β-cells as well as glucose uptake in adipocytes and skeletal myotubes, *in vitro* (Gorelick et al. 2011); inhibition of α-amylase and α-glucosidase activities *in vitro* (Kasabri et al. 2011)
98.	*Chromolaena odorata* (L.) R.M. King &H. Rob., Asteraceae	(9S,13R)-12-Oxo-phytodienoic acid and odoratin	Activation of PPAR-γ receptors (Wang et al. 2014)
99.	*Cichorium glandulosum* Boiss. & A. Huet, Compositae	Lactucin from root	Inhibition of PTP1B activity (Jiang et al. 2012)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
100.	*Cichorium intybus* L., Asteracease	Tannins from whole plant	Enhanced glucose uptake and inhibited adipogenesis in 3T3-L1 adipocytes through PTP1B inhibition (Muthusamy et al. 2008)
101.	*Cinnamomum burmannii* (Nees & Th. Nees) Nees ex Blume, Lauraceae	Water extract of bark; water-soluble polyphenol type A polymers	Increased GLUT1 mRNA levels sevenfold after 16 h treatment in mouse adipocytes and regulated multiple genes involved in insullin signalling in adipocytes (Cao et al. 2010); increased insulin-dependent *in vitro* glucose metabolism roughly 20-fold (Anderson et al. 2004)
102.	*Cinnamomum cassia* (Nees & T. Nees) J. Presl. and *Cinnamomum verum* J.S. Presl.	Extract of inner bark and cinnamtannin B1; methylhydroxychalcone polymer; polyphenol type A polymers	Inhibition of pancreatic α-amylase and α-glucosidase; Stimulation of cellular glucose uptake by translocation of GLUT4; stimulation of glucose metabolism and glycogen synthesis; inhibition of gluconeogenesis by influencing key regulatory enzymes; and stimulation of insulin release and potentiating insulin signaling (*in vitro* studies) (Bandara et al. 2012); mimetic of insulin action in 3T3-LI adipocytes (Jarvill-Taylor et al. 2001); increase insulin-dependent *in vitro* glucose metabolism (Anderson et al. 2004).
103.	*Citrullus colocynthis* (L.) Schrd, Cucurbitaceae	Different extracts of seed	Insulinotropic effect (Nmila et al. 2000)
104.	*Citrullus lanatus* (Thunb.) Matsumara & Makai, Cucurbitaceae	Methanol extract of leaves	Inhibition of α-amylase and α-glucosidase; Inhibition of non-enzymatic glycosylation of hemoglobin (Aruna et al. 2014)
105.	*Citrus aurantium* L., Rutaceae	Alcohol extract of fruit peel and hexane fraction	Stimulaton of NCI-H716 cells to secrete GLP-1 (Choi et al. 2012)
106.	*Citrus lemon* (L.) Burm.f., Rutaceae	Hesperidin and naringin (flavonoids); lemon juice	Hesperidin and naringin both significantly increased the glucokinase mRNA level, while naringin also lowered the mRNA expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in the liver; in addition, the hepatic GLUT2 protein expression was reduced, while the expression of adipocyte GLUT4 and hepatic and adipocyte PPAR-γ were elevated in the hesperidin and naringin groups when compared with the control C57BL/KsJ-db/db mice (Jung et al. 2006b); increased blood insulin levels in alloxan diabetic rats (Riaz et al. 2013)
107.	*Clausena anisata* (Willd) Hook., Rutaceae	Methanol extract of root	*In vitro* inhibition of hepatic glucose-6-phosphatase and α-amylase (Leshweni et al. 2012)
108.	*Clausena lansium* (Lour.) Skeels, Rutaceae	Clausenacoumarine from leaf; methanol extract of stem bark, and imperatorin and chalepin	Antagonized the elevation of blood glucose caused by adrenaline in normal mice (Shen et al. 1989); stimulation of insulin secreation (Adebajo et al. 2008)
109.	*Clematis pickeringii* A.Gray, Ranunculaceae	Stem ethanol extract	Activated the expression of PPAR-α and PPAR-γ proteins in HepG2 cells (El-Abhar and Schaalan 2014)
110.	*Cleome droserifolia* (Forssk.) Del, Cleomaceae	Ethanol extract of leaf	Protection of β-cells from oxidative stress-mediated damage (Nagy and Mohamed 2014)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
111.	*Clitoria ternatea* L., Fabaceae, butterfly pea	Ethanol extract of aerial parts	Regeneration of β-cells (Verma et al. 2013)
112.	*Coccinia indica* Wight & Arn., Cucurbitaceae	Ethanol extract of leaf, fruit and so on	Ingredients present in leaf and fruit may act like insulin, correcting the elevated enzymes glucose-6-phosphatase (G-6-P), lactic dehydrogenase (LDH) in glycolytic pathway and restore the lipoprotein lipase (LPL) activity in lypolytic pathway with the control of hyperglycemia in diabetes (Ghosh and Roy 2013; Kamble et al. 1998)
113.	*Coffea arabica* L., Rubiaceae	Chlorogenic acid	(See above for chlorogenic acid)
114.	*Coix lacryma-jobi* var. ma-yuen (Rom. Caill.) Stapf ex Hook. f., Poaceae	Seed water extract; hydroxy unsaturated fatty acids	Reduced the expression of neuropeptide Y and leptin receptor levels in the hypothalamus of high-fat-fed rats (Kim et al. 2007b); acted as PPAR-γ ligands (Wang et al. 2014)
115.	*Combretum lanceolatum* Pohl ex Eichler, Combretaceae	Ethanol extract of flower and quercetin from flower	Activation of AMPK (Dechandt et al. 2013)
116.	*Commelina communis* L., Commelinaceae	Water extract of whole plant	Inhibition of α-glucosidase activity (Youn et al. 2004)
117.	*Commiphora mukul* (Hook. ex Stocks) Engl., Burseraceae	Commipheric acid from the gum of the tree	Activation of PPAR-γ and PPAR-α (Wang et al. 2014)
118.	*Coptis chinensis* Franch, Ranunculaceae	Berberine; protoberberine-type alkaloids	Berberine has multiple mechanisms of actions (Ma et al. 2010) (see under *Berberis aristata* DC); inhibited rat lens aldose reductase activity (Jung et al. 2008)
119.	*Coptis deltoides* C.Y. Cheng et Hsiao, Ranunculaceae	Berberine from root	(See under *Berberis aristata* DC) (Chen and Xie 1986)
120.	*Coptis japonica* (Thunb.) Makino, Ranunculaceae	Isoquinoline alkaloids from root	Inhibited rat lens aldose reductase activity (Lee 2002)
121.	*Coriandrum sativum* L., Apiaceae	Water extract of coriander seeds (chlorogenic acid, β-sitosterol, quercetin, rutin, and so on have been reported from seeds)	Insulin-releasing and insulin-like activity (Gray and Flatt 1999)
122.	*Cornus alternifolia* L.f., Cornaceae	Kaempferol-3-O-β-D-glucopyranoside from leaf	Activated liver PPAR-γ and X receptor (Wang et al. 2014)
123.	*Cornus kousa* F. Buerger ex Miquel, Cornaceae	Leaf extract	Increased PPAR-γ ligand-binding activity, enhanced adipogenesis and expression of GLUT4 and adiponectin in 3T3-L1 cells (Kim et al. 2011)
124.	*Cornus officinalis* Sieb., Cornaceae	Ursolic acid from fruit, and so on	Inhibited protein tyrosine phosphatase 1B (Nazaruk and Borzym-Kluczyk 2015)
125.	*Costus pictus* D. Don., Costaceae	Leaf methanol extract; insulin-like protein	Increased insulin levels *in vivo* and increased glucose mediated insulin secretion *in vitro* (Al-Romaiyan et al. 2010; Jothivel et al. 2007); a novel protein showed oral hypoglycemic activity (Joshi et al. 2013)
126.	*Croton klozchianus* L., Euphorbiaceae	Extracts of aerial parts	Increase in insulin secretion from MIN6 cells (Govindarajan et al. 2008)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
127.	*Cucurbita ficifolia* Bouche, Cucurbitaceae	Water extract of edible fruit; the extract and D-chiro-inositol from fruit	Stimulation of insulin synthesis and secretion (Xia and Wang 2006a, 2006b); increased the levels of insulin and insulin mRNA expression in RINm5F cells (Xia and Wang 2006b)
128.	*Cuminum cyminum* L., Apiaceae	Cuminaldehyde from seed	Inhibition of aldose reductase and α-glucosidase isolated from rat (Lee 2005)
129.	*Curcuma longa* L., Zingeberaceae	Curcumin, demethoxycurcumin, sesquiterpenoids, bisdemethoxycurcumin, and arturmerone; curcumin; turmeric volatile oil and ar-turmerone	Exhibited PPAR-γ ligand-binding activity (Arun and Nalini 2002; Kuroda et al. 2005; Nishiyama et al. 2005); curcumin inhibited PTP1B and improved insulin and leptin sensitivity in the liver of rats (Li et al. 2010); inhibition of α-glucosidase and α-amylase activities (Lekshmi et al. 2012)
130.	*Cyamopsis tetragonoloba* (L.) Taub., Fabaceae	Methanol extract of bean (quercetin, gallic acid, genistein, ellagic acid, kaemferol, and chlorogenic acid are reported in cluster been)	Protection of β-cells of pancreatic tissues in diabetic rats (Gandhi et al. 2014)
131.	*Cyclocarya paliurus* (Batal.) Ijinskaja, Cyclocaryaceae	Leaf extract; quercetin-3-O-β-D-glucuronide and cyclonoside A from leaf	Inhibited α-glucosidase activity *in vitro* (Kurihara et al. 2003); inhibited PTP1B activity (Jiang et al. 2012)
132.	*Cymbopogon citratus* (DC.) Stapf, Poaceae	Essential oil from leaf and its components geraniol and myrcene; citral	Insulin secretagogue action *in vitro* and *in vivo* (Bharti et al. 2013); exhibited PPAR-γ agonist action (Wang et al. 2014)
133.	*Dasylirion* spp, Nolinaceae	Fructons	Promoted the production of GLP-1 in the lower parts of the gut (Urias-Silvas et al. 2007)
134.	*Daucus carota* L., Apiaceae	Falcarinol (polyacetylene)	Falcarinol enhanced phosphorylation of TBC1D1 suggesting that this compound enhanced translocation of GLUT4 containing vesicles via a TBC1D1-dependent mechanism (Bhattacharya et al. 2014)
135.	*Dendrobium moniliforme* (L.) Sw., Orchidaceae	A phenanthraquinone-type metabolite	Inhibited protein tyrosine phosphatase 1B activity (Jiang et al. 2012)
136.	*Dendrobium nobile* Lindl, Orchidaceae	Syringic acid	Inhibition of aldose reductase activity and gene expression (Wei et al. 2012)
137.	*Desmodium gangeticum* (L.) DC, Fabaceae	Extract of aerial part	Increase in insulin secretion from MIN6 cells (Govindarajan et al. 2007)
138.	*Dioscorea bulbifera* L., Dioscoriaceae	Water extract of tubers; ethyl acetate extract of bulb and diosgenin (a phytosterol)	Activation of β-cells and/or regenerated β-cells (Ahmed et al. 2009); inhibition of α-amylase and α-glucosidase (Ghosh et al. 2014a)
139.	*Dodonaea viscosa* (L.) Jacq., Sapindaceae	Water extract and polar fraction of ethanol extract of aerial parts	Inhibition of PTP-1B activity and binding to PPAR-γ *in vitro*; stimulation of glucose uptake by skeletal muscles (Veerapur et al. 2010a, 2010b)
140.	*Echinacea purpurea* (L.) Moench, Asteraceae	Ethanol extract; alkamides from hexane extract of flower; 2-isomeric dodeca 2E,4E,8Z,10E/Z-tetraenoic acid 2-methylbutylamides	Activation of PPAR-γ and increased insulin-stimulated glucose uptake; increase in the expression of PPAR-γ and CCAAT/enhancer-binding protein α (C/EBPα) in adipocytes (Shin et al. 2014); activation of PPAR-γ (Wang et al. 2014); activation of PPAR-γ and stimulation of glucose uptake in adipocytes (Kotowska et al. 2014)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
141.	*Eclipta alba* (L.) Hassk., Asteraceae	Ethanol extract of whole plant; eclalbasaponin VI (echinocystic acid glycoside)	Inhibition of α-glucosidase and aldose reductase (Jaiswal et al. 2012); inhibition of α-glucosidase activity (Kumar et al. 2012)
142.	*Elaeis guineensis* Jacq., Arecaceae	Tocotrienols from palm oil	Improveed insulin sensitivity through activating PPAR-γ (Wang et al. 2014)
143.	*Elephantopus scaber* L., Asteraceae	Ethyl acetate extract of root and methanol extract of leaf; deoxyelephantopin	Regeneration of β-cells of pancreas in streptozotocin diabetic rats (Daisy et al. 2011); a selective partial agonist against of PPAR-γ (Wang et al. 2014)
144.	*Eleutherine palmifolia (L.) Merr*., Iridaceae	Water and ethanol extracts of bulbs	Inhibition of α-glucosidase activity (Febrinda et al. 2014)
145.	*Eleutherococcus senticosus* (Rupr. & Maxim) Maxim., Araliaceae	Eleutheroside E; syringin	Protected pancreatic α- and β-cells from diabetic damage; Improved hepatic glucose metabolism in obese type 2 diabetic mice; increased the insulin-provoked glucose uptake in C2C12 myotubes (Ahn et al. 2013); augmented insulin release indirectly (Liu et al. 2008)
146.	*Enicostemma littorale* Blume, Gentianacea	Water extract of the herb; compound SGL-1 (uncharacterized isolate)	Potentiating of glucose-mediated insulin release and increase in insulin sensitivity (Maroo et al. 2003; Murali et al. 2002); stimulated islet neogenesis in cell culture conditions (Gupta et al. 2010)
147.	*Ephedra distachya* L., Ephedraceae	Ephedrine	Islet regeneration in streptozotocin diabetic mice (Xiu et al. 2001)
148.	*Epimedium brevicornum* Maxim, Berberidaceae	Icarin; water extract of leaf and baohuoside I (a flavonol from the leaves)	Modulating transforming growth factor β1 and type IV collagen expression in diabetic rats (Qi et al. 2011); strong inhibition against α-glucosidase activity (Phan et al. 2013)
149.	*Eremophila alternifolia* R. Br., and *Eremophila longifolia* (R.Br.) F.Muell., Myoporaceae	Phenylethanoid verbascoside (acteoside)	Lens aldose reductase inhibitor (Ghisalberti 2005)
150.	*Erigeron annuus* (L.) Pers, Compositae	Erigeroflavanone from the flower	Inhibited AGE formation and rat lens aldose reductase activity (Yoo et al. 2008)
151.	*Erigeron breviscapus* (Vaniot) Hand., Asteraceae	Breviscapine (a flavonoid)	Attenuated renal injury in the diabetic rats; Mechanism: suppression of increased oxidative stress and PKC activities as well as overexpression of TGFβ1 in renal tissue (Xu et al. 2013)
152.	*Eruca sativa* Mill., Brassicaceae	Ethanol extracts of leaves	Inhibited activities of α-amylase, α-glucosidase and β-galactosidase (Hetta et al. 2014)
153.	*Ervatamia microphylla* (Pit.) Kerr (botanical name: *Tabernaemontana bufalina* Lour.), Apocynaceae	Canophylline, an alkaloid from leaf	Effective in stimulating the differentiation of progenitor cells into β-cells (Chang et al. 2013a)
154.	*Eryngium creticum* Lam., Umbelliferae	Water extract	Potentiated insulin secretion from the β-cells (Kasabri et al. 2012a)
155.	*Erythrina abyssinica* DC, Fabaceae	Prenylated flavanones and terocarpan derivatives from stem bark	Exhibited PTP1B inhibitory activity (Jiang et al. 2012)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
156.	*Eucalyptus globulus* Labill, Myrtaceae	Water extract of leaf	Enhanced 2-deoxy-glucose transport, glucose oxidation and incorporation of glucose into glycogen in abdominal muscle of mice; enhancement of insulin secretion from the clonal pancreatic β-cell line (Gray and Flatt 1998); reduction in carbohydrate absorption from the intestine and reduction in oxidative stress *in vivo* (Dey and Mitra 2013)
157.	*Euclea undulata* Thunb, Ebenaceae	Acetone extract of root bark; epicatechin, betulin (triterpene), and lupeol	Stimulated glucose uptake (162.2%) by Chang liver cells at 50 μg/mL; the extract inhibited the activities of α-glucosidase and α-amylase (Deutschlander et al. 2009); *in vitro* assays on cultured C2C12 myocytes revealed that epicatechin (166.3%) and betulin (21.4%) were active in lowering glucose levels; epicatechin and lupeol inhibited α-glucosidase activity (Deutschlander et al. 2011)
158.	*Eucommia ulmoides* Oliv., Eucommiaceae	Water extract of leaves	Stimulated glucose uptake in L6 rat muscle cells; stimulated the activity of phosphatidylinositol 3-kinase and its downstream effectors, PKB and atypical form of PKC (Hong et al. 2008)
159.	*Euonymus alatus* (Thunb.) Siebold, Celastraceae	Ethyl acetate fraction of methanol extract; kaempferol and quercetin	Stimulation of insulin release, improvement in glucose uptake and suppression of oxidative-stress (Fang et al. 2008a, 2008b); improved glucose uptake of 3T3-L1 cells (Wang et al. 2014)
160.	*Euphorbia helioscopia* L., Euphorbiaceae	Ethanol extract	Insulin secretagogue activity in INS-1 cells at 10 μg/mL level (Hussain et al. 2004)
161.	*Ficus amplissima* Smith, Moraceae	Methanol extract of the plant bark	Regenerative effect on the β-cells of streptozotocin diabetic rats (Karuppusamy and Thangaraj 2013)
162.	*Ficus bengalensis* L., Moraceae	Glucoside of leucopelargonidin; a leucocyanidin derivative from this plant	Serum insulin raising effects in moderately diabetic rats (Cherian and Augusti 1993); insulin sparing action (Kumar and Augusti 1994)
163.	*Ficus exasperata* Vahl., Moraceae	Water extract of leaf	Inhibition of α-amylase and α-glucosidase *in vitro* (Kazeem et al. 2013a)
164.	*Ficus lutea* Vahl, Moraceae	Acetone extract of leaf	α-Amylase and α-glucosidase inhibitory activity *in vitro*; EC_{50} value for α-amylase inhibition was 9.4 μg/mL (Olaokun et al. 2013); in the pancreatic insulin secretory assay it showed promising secretory activity; significantly increased glucose uptake in the primary muscle cells, fat cells, C2C12 muscle and H-4-II-E liver cells (Olaokun et al. 2014)
165.	*Fraxinus excelsior* L., Oleaceae	Water extract of seeds	Caused a potent inhibition of renal glucose reabsorption (Eddouks and Maghrani 2004)
166.	*Gastrodia elata* Blume, Orchidaceae	Ethanol extract of the herb	Ameliorated endothelial dysfunction by downregulation of endothelin-1 and adhesion molecules in the aorta; induced markedly phosphorylation of AMPK in the liver, muscle, and fat (Kho et al. 2014)
167.	*Ginkgo biloba* L., Ginkgoaceae	EGb761 (a standardized and well-defined product extract of *G. biloba* leaves)	Protected the β-cells against HFD-induced apoptosis in rats (Dong et al. 2009); could increase insulin secretion from INS-1 cells (Choi et al. 2007)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
168.	*Glycine max* (L.) Merr., Fabaceae	Genistein (soy phytoestrogen)	Activated PPAR-γ (Wang et al. 2014)
169.	*Glycyrrhiza glabra* L., Fabaceae	Glycyrin; 50-formylglabridin, echinatin, kanzonol X, kanzonol W, shinpterocarpin, licoflavanone A, glabrol, shinflavanone, gancaonin L, glabrone, and so on	Glycyrin showed potent PPAR-γ ligand binding activity (Kuroda et al. 2004); these compounds showed PPAR-γ ligand-binding activity (Wang et al. 2014)
170.	*Glycyrrhiza foetida* Desf., Fabaceae	Amorfrutins from edible root	Activation of PPAR-γ *in vitro* (Wang et al. 2014)
171.	*Glycyrrhiza inflata* Batalin, Fabaceae	Chalcones and their derivatives; licochalcone E	Inhibited protein tyrosine phosphatase 1B (Jiang et al. 2012); induced 3T3-L1 preadipocyte differentiation; showed PPAR-γ ligand-binding activity; stimulated Akt signaling in epididymal white adipose tissue (Park et al. 2012)
172.	*Glycyrrhiza uralensis* Fisch., Fabaceae	Extract from roasted *G. uralensis* and glycyrrhetinic acid; extracts from both roasted and raw *G. uralensis*; semilicoisoflavone B from root; glycyrrhisoflavone , glisoflavone, licoflavone A, 2-arylbenzofuran glycybenzofuran and licocoumarone	Enhanced glucose-stimulated insulin secretion in isolated islets, and enhanced insulinotropic action (Ko et al. 2007); PPAR-γ-activation in 3T3-L1 adipocytes (Ko et al. 2007); showed potent inhibition with the IC_{50} values of 1.8 and 10.6 μM for rat lens aldose reductase (Lee et al. 2010); these compounds inhibited PTP1B (Jiang et al. 2012)
173.	*Guazuma ulmifolia* Lam, Sterculiaceae	Water extract of leaf	Stimulated glucose uptake in both insulin-sensitive and insulin-resistant adipocytes without inducing adipogenesis (Alonso-Castro and Salazar-Olivo 2008)
174.	*Gymnema montanum* Hook. f., Asclepiadaceae	Ethanol extract of leaf	Protected rat insulinoma cells from alloxan-induced apoptotic cell death *in vitro* (Ramkumar et al. 2009)
175.	*Gymnema sylvestre* R. Br. Asclepiadaceae	Leaf and leaf extracts; gymnemic acid IV, a triterpene glycoside; gymnemoside b and gymnemic acids III, V, and VII	Promoted regeneration of islet cells and increased secretion of insulin from β-cells; inhibited absorption of glucose from intestine; modulated incretin activity which triggered insulin secretion and release (Tiwari et al. 2014); this compound increased the levels of plasma insulin in the diabetic mice (Sugihara et al. 2000); inhibited glucose absorption from the intestine (Yoshikawa et al. 1997)
176.	*Gynura divaricata* (L.) DC, Asteraceae	Ethyl acetate fraction of water extract of aerial parts	Showed α-amylase and α-glycosidase inhibition (Wu et al. 2011)
177.	*Hemidesmus indicus* (L.) R. Br., Periplocacea	β-Amyrin palmitate from root	One of the mechanisms of action of β-amyrin is blocking the entry of glucose from the intestine (Ajikumaran et al. 2014)
178.	*Hemionitus arifolia* (Burm.) Moore, Hemionitidaceae	Active fraction from ethanol extract	Stimulated glucose uptake in isolated rat hemidiaphragm (Ajikumaran 2008)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
179.	*Hovenia dulcis* Thunb., Rhamnaceae	Water extract of fruit	Inhibited lipid accumulation during adipogenesis in 3T3-L1 preadipocytes; downregulated the expression of PPAR-γ, CCAAT/enhancer-binding protein-α, adipocyte fatty acid-binding protein 2, adiponectin; upregulated the phosphorylation of AMPK-α (Kim et al. 2014; Miura et al. 2005)
180.	*Humulus lupulus* L., Cannabaceae	Isohumulones, bitter acids from the flower	Activation of PPAR-γ and PPAR-α (Shimura et al. 2005)
181.	*Hunteria umbellata* K.Schum.Hallier f., Apocynaceae	Water extract of seeds; erinidine, isolated from seed	Inhibition of intestinal glucose uptake and adrenergic homeostatic mechanisms (Adeneye and Adeyemi 2009b); inhibition of intestinal glucose absorption (?) (Adejuwon et al. 2013)
182.	*Hydnocarpus wightiana* Blume, Achariaceae	Hydnocarpin, luteolin, and isohydnocarpin from seed hull	Varying degrees of α-glucosidase and *N*-acetyl-β-D-glucosaminidase inhibitory activity, luteolin being the superior (Reddy et al. 2005)
183.	*Hydrangea macrophylla* (Thunb.) Ser., Hydrangeaceae	Hydrangeic acid, a stilbene constituent of the processed leaves	Increased the amount of adiponectin released into the medium, the uptake of 2-deoxyglucose into the cells, and the translocation of GLUT4 in 3T3-L1 cells (Zhang et al. 2009)
184.	*Hypolepis punctata* (Thunb.) Mett., Dennstaedtiaceae	Pteroporin A from the whole fern	Phosphorylation of AMPK and Akt in muscles of diabetic mice enhanced AMPK phosphorylation in cultured human muscle cells also (Hsu et al. 2013)
185.	*Ibervillea sonorae* (*S.* Watson) Greene, Cucurbitaceae	Water extract of leaf	Stimulation of glucose uptake in human preadipocytes by a PI3K-independent pathway and without proadipogenic effects (*in vitro* studies) (Zapata-Bustos et al. 2014)
186.	*Indigofera arrecta Hochst. ex* A.*Rich, Fabaceae*	Whole plant extract	Insulinotropic requiring functional β-cells (Nyarko et al. 1999)
187.	*Inula britannica* L., Asteraceae	Water extract of flower	Inhibition of IFN-γ production from stimulated splenic T lymphocytes (prevention of type 1 DM) (Kobayashi et al. 2002)
189.	*Ipomoea aquatica* Forsk, Convolvulaceae	Water/methanol extract of leaves	Inhibition of glucose absorption from intestine (one of the mechanisms) (Sokeng et al. 2007)
190.	*Ipomoea batatas* L., Convolvulaceae	Tuber; an arabinogalactan-protein from tuber; leaf (edible) hot water extract or polyphenols such as caffeoylquinic acid from leaves	Induces regeneration of pancreatic β-cells (by suppression of oxidative stress and proinflammatory cytokine) (Royhan et al. 2009; Niwa et al. 2011); amelioration of insulin resistance in diabetic db/db mice (Oki et al. 2011); stimulation of secretion of GLP-1 (Nagamine et al. 2014)
191.	*Jatropha curcas* L., Euphorbiaceae	Ethanol extract of nut	Activated PPAR-γ *in vitro* (El-Abhar and Schaalan 2014)
192.	*Juglans regia* L., Juglandaceae	Walnut polyphenol fraction; walnut leaf pellets	Improved regeneration of β-cells, and inhibited glycosidase, sucrase, maltase, and amylase (Fukuda et al. 2004); improved regeneration of β-cells in alloxan-induced diabetic rats (Jelodar et al. 2007)
193.	*Juniperus communis* L., Cupressaceae	Hydroalcohol extract of fruit	Exhibited potent inhibitory activity on α-glucosidase enzyme (Orhan et al. 2014)
194.	*Juniperus oxycedrus* L., Cupressaceae	Hydroalcohol extract of leaf	Exhibited potent inhibitory activity on α-glucosidase enzyme (Orhan et al. 2014)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
195.	*Kalanchoe pinnata* (Lam.) Pers., Crassulaceae	Ethanol extract of leaves	Inhibition α-amylase activity *in vitro* (Mathew et al. 2013)
196.	*Kalopanax pictus* (Thunb.) Nakai., Araliaceae	Hot water extract of bark	Insulin-like action and glucose uptake in 3T3-L1 cells (Ko et al. 2002)
197.	*Kielmeyera coriacea* Mart, Calophyllaceae	Hydroethanolic extract of stem bark	Strong inhibition of α-amylase activity (Silva et al. 2009)
198.	*Kochia scoparia* (L.) Schrad., Chenopodiaceae	Methanol extract of fruit and momordin Ic and its 2′-O-β-D-glucopyranoside (saponins)	Inhibition of glucose and ethanol absorption in rats (Yoshikawa et al. 1997)
199.	*Kalopanax pictus* (Thunb.) Nakai, Araliaceae	Water extract of bark	Insulin-like action and insulin sensitizer in 3T3-L1 cells (Ko et al. 2002)
200.	*Lagerstroemia speciosa* L., Lathraceae	Water extract of leaf (penta-O-galloyl-glucopyranose and lagerstroemin); corosolic acid and oleonolic acid	Insulin-like glucose transport inducing activity and anti-adipogenesis activity; penta-O-galloyl-D-glucopyranose binds to IR and activates insulin-mediated glucose transport (Klein et al. 2007; Takagi et al. 2010; Yamada et al. 2008); inhibition of PTP1B activity (Jiang et al. 2012)
201.	*Larix laricina* (Du Roi) K. Koch, Pinaceae	Extract of bark	Activation of AMPK and enhancement of adipogenesis-like activities (Eid and Haddad 2014)
202.	*Lathyrus sativus* L., Fabacea	Inositol phosphoglycan from seed	Insulin-mimetic activities (Paneda et al. 2001)
203.	*Lawsonia intermis* L., Lythraceae	Alcohol extract of leaf (lawsone and gallic acid)	Inhibition of AGEs formation and hypoglycemic activity (Sultana et al. 2009)
204.	*Leonotis leonurus* (L.) R. Br.	Water extract of flowers (active principle: Marrubiin)	Enhancement of insulin secretion (Mnonopi et al. 2012)
205.	*Lepidium sativum* L., Brassicaceae	Water extract of seed	Inhibition of renal glucose reabsorption (Eddouks and Maghrani 2008)
206.	*Leptadenia hastata* (Pers.) Decne., Asclepiadaceae	Methanol and water extract of leaf	Inhibition of α-glucosidase activity (Bello et al. 2011b)
207.	*Levisticum officinale* Koch, Apiaceae	Methanol and water extract	Inhibition of α-amylase activity (Gholamhoseinian et al. 2008)
208.	*Ligularia fischeri* (Ledeb.) Trucz., Compositae	Eremophilane sesquiterpene from root	Exhibited PTP1B inhibitory activity with IC_{50} value of 1.3 μmol/L (Jiang et al. 2012)
209.	*Limnocitrus littoralis* (Miq.) Swingle, Rutaceae	Meranzin from the leaves	Activation of PPAR-γ (review: Wang et al. 2014)
210.	*Lippia nodiflora* L., Verbenaceae	Ethanol extract of plant (active principle identified: γ-sitosterol)	γ-Sitosterol increased insulin secretion in response to glucose (Balamurugan et al. 2011)
211.	*Lithospermum erythrorhizon* Sieb. et Zucc., Boraginaceae	Shikonin, a naphthoquinone	Increases glucose uptake in muscle cells via an insulin-independent pathway (Oberg et al. 2011)
212.	*Lonicerae japonica* Thunb., Caprifoliaceae	Methanol extract of flower bud	Inhibition of the activity of p-38 MAPK-mediated inflammatory response (Tzeng et al. 2014); inhibition of α-glucosidase activity (Zhang et al. 2013)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
213.	*Lupinus mutabilis* Sweet, Fabaceae	Conglutin-γ (a seed glycoprotein); lupanine and other quinolizidine alkaloids from seed; multiflorine and derivatives of spartine and lupanine	Activation of protein synthetic pathway kinases and increase in glucose transport; it appears to stimulate insulin signaling pathways (Lovati et al. 2012; Terruzzi et al. 2011); enhanced glucose-induced insulin secretion *in vitro* (García Lopez et al. 2004; Gurrola-Diaz et al. 2008)
214.	*Lycium barbarum* L., Solanaceae	Polysaccharides (glycol-conjugates) from fruit	Reduced insulin resistance; it may have β-cell protective effects also (Zhao et al. 2009)
215.	*Lycium chinense* Mill., Solanaceae	Chemical isolates from root bark	Activated PPAR-γ (review: Wang et al. 2014)
216.	*Lythrum salicaria* L., Lythraceae	Water extract of seed	Increased insulin sensitivity (Li et al. 2006)
217.	*Macaranga adenantha* Gagnep., Euphorbiaceae	Triterpene metabolite: oleanolic acid; 3β,28-dihydroxy-12-en-olean; maslinic acid and 3β-O-acetyl aleuritolic acid	PTP1B inhibitory activity (Jiang et al. 2012)
218.	*Macaranga tanarius* (L.) Mull. Arg., Euphorbiaceae	Ellagitannins from leaves	α-Glucosidase inhibitory activity (Gunawan-Puteri and Kawabata 2012)
219.	*Machilus thunbergii* Sieb. et Zucc., Lauraceae	Water fraction of methanol extract of the plant	Exhibited α-glucosidase inhibitory activity; EC_{50} was 1.1 μg/mL (El-Abhar and Schaalan 2014)
220.	*Magnolia officinalis* Rehder & E.H.Wilson	Bark extract and 4-O-methylhonokiol; magnolol from bark	Improvement of lipid metabolism and insulin resistance (Zhang et al. 2014); magnolol enhanced adipocyte differentiation and glucose uptake in 3T3-L1 cells and activated PPAR-γ (Kotani et al. 2012)
221.	*Malmea depressa* (Baill) R.E. Fries.	Butanol extract of root	Stimulation of insulin release; inhibition of α-glucosidase activity, and so on (Andrade-Cetto et al. 2008a)
222.	*Mangifera indica* L.	Methanol/ethanol extract of bark and leaf; mangiferin from bark, leaf, and so on	Reduction in glucose absorption; dipeptidyl peptidase-4 inhibitory activity (Bhoumik et al. 2009; Yogisha and Raveesha 2010); mangiferin mediated insulin sensitivity and modulated lipid metabolism (Mirza et al. 2013)
223.	*Maytenus jelskii* Zahlbr., Celastraceae	Friedelane-type triterpenes isolated from the root	Increased insulin-mediated signaling *in vitro* (Nazaruk and Borzym-Kluczyk 2015)
224.	*Medicago sativa* L., Leguminosae	Water extract of the plant	Stimulation of insulin secretion *in vitro*; insulin-releasing and insulin-like activity (Gray and Flatt 1997)
225.	*Melampyrum pratense* L., Orobanchaceae	The plant extract	Stimulation of PPAR-α and PPAR-γ (Vogl et al. 2013)
226.	*Melia dubia* Cav., Meliaceae	Ethanol extract of leaves	Inhibited α-amylase (*in vitro*) at a lower concentration than the standard acarbose (Valentina et al. 2013)
227.	*Melissa officinalis* L., Lamiaceae	Essential oil	Hepatic glucokinase and GLUT4, adipocyte GLUT4, PPAR-γ, PPAR-α, and SREBP-1c expression, were upregulated, whereas the expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase was downregulated in the livers in db/db mice (Chung et al. 2010)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
228.	*Melothria maderaspatana* (L.) Cogn., Cucurbitaceae	Ethanol extracts of aerial parts; quercetin and phloroglucinol from the methanol extract	Inhibition of α-glucosidasae and α-amylase *in vitro*; stimulation of insulin secretion from β-cell of pancreatic islets; the extract had no effect on glucose uptake, but potentiated the action of insulin-mediated glucose uptake in isolated rat hemidiaphragm (Hemalatha et al. 2010); inhibition of glucose production by quercetin in rat liver slices, not influenced by insulin addition; phloroglucinol inhibited glucose production with or without insulin (Srilatha and Ananda 2014)
229.	*Memecylon umbellatum* Burm.f., Melastomaceae	Methanol extract of leaf	Inhibited α-amylase activity; inhibited non-enzymatic glycosylation of hemoglobin and enhanced glucose uptake by yeast cells *in vitro* (Rajesh et al. 2014)
230.	*Momordica charantia* L., Cucurbitaceae	Fruit (unripe fruit including seeds) and leaves	Water extract of fruit stimulated β-cells to release or secrete more insulin (Ahmed et al. 1998; Karunanayake et al. 1990); insulin-like peptide with insulin like bioactivity has been reported in seeds (Ng et al. 1987a); fruit extract inhibited glucose absorption from the intestine and activated AMPK pathway; cucurbitane-type triterpene glycosides activated PPAR-γ (Joseph and Jini 2013; Wang et al. 2014)
231.	*Momordica cymbalaria* Hook., Fenzl ex Naud, Chcurbitaceae	Fruit and root extracts; and oleanane-type triterpenoid saponin (roots)	Stimulation of insulin secretion (modulation of calcium channel, and β-cell rejuvenation) (Koneri et al. 2014a)
232.	*Monstera deliciosa* Liebm., Araceae	Methanol extract	Insulin secretagogue activity in INS-1 cells at 1 μg/mL level (Hussain et al. 2004)
233.	*Morinda citrifolia* L., Rubiaceae	Fruit	Regulated glucose metabolism via FOXO1 in high fat diet-induced obese diabetic mice (Nerurkar et al. 2012)
234.	*Morinda lucida* Benth., Rubiaceae	Water extract of leaf	Inhibition of α-glucosidase and α-amylase (one of the mechanisms) (Kazeem et al. 2013b)
235.	*Moringa stenopetala* Baker f., Moringaceae	Hydroalcoholic extract of leaves	Inhibited the activities of intestinal α-glucosidase and some pancreatic enzymes (one of the mechanisms) (Toma et al. 2014)
236.	*Morus alba* L., Moraceae	Leaf extract; root bark and leaf and chemical isolates chalcomoracin, moracin C, moracin D and moracin M; leaf extract (repeated administration)	Stimulates regeneration of β-cells (Mohammadi and Naik 2012); inhibition of α-amylase and α-glucosidase activity (review: Firdous 2014); reduced insulin resistance in KKAy mice (Tanabe et al. 2011)
237.	*Morus bombycis* Koidzumi, Moraceae	Kuwanons J, R, and V (chalcone-derived products)	Inhibited protein tyrosine phosphatase 1B (PTB1B) (Jiang et al. 2012)
238.	*Morus nigra* L., Moraceae	Deoxynojirimycin, an alkaloid from young leaves	A potent α-glycosidase inhibitor (Kumar and Chauhan 2008)
239.	*Myrcia bella* Cambess, Myrtaceae	Ethanol extract of leaf	Increased the expression of IRS-1, PI3-K and Akt in the liver of diabetic rats (Vareda et al. 2014)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
240.	*Myrcia multiflora* DC, Myrtaceae	Methanol extract of leaf (flavonoids) and myrciacitrin I and myrciaphenone B	Showed potent inhibitory activities on aldose reductase and α-glucosidase (Yoshikawa et al. 1998)
241.	*Myrciaria dubia* Mc Vaaugh, Myristicaceae	Ellagic acid and its derivatives	Uncompetitive inhibition of human aldose reductase (IC_{50} value: 4.1×10^{-8} M) (Ueda et al. 2004)
242.	*Myristica fragrans* Houtt, Myristicaceae	Nutmeg seed; methanol extract of nutmeg seed and meso-dihydroguaiaretic acid and otobaphenol; methanol extract of seed	Insulin-like activity *in vitro* (Broadhurst et al. 2000); inhibited PTP1B (Jiang et al. 2012); PPAR-γ agonist activity in cell based *in vitro* assays (Lestari et al. 2012)
243.	*Myrtus communis* L., Myrtaceae	Leaf oil	Reduced intestinal absorption of glucose (Sumbul et al. 2011)
244.	*Nelumbo nucifera* Gaertn., Nymphaeceae	Methanol extract of leaf and catechin	Increased insulin secretion from β-cells (HIT-T15) and human islets (Huang et al. 2011)
245.	*Nymphaea pubescens* Willd., Nymphaeaceae	Ethanol extract of tuber	β-Cell regeneration potential (increase in blood insulin levels) (Sreenathkumar and Arcot 2010)
246.	*Nymphaea stellata* OW, Nymphaeaceae	Leaf, flower, and so on (Nymphayol)	β-Cell regeneration potential? (increase in blood insulin levels) (Rajagopal et al. 2008a, 2008b)
247.	*Ocimum gratissimum* L., Lamiaceae	Ursolic acid from leaves	Inhibited formation of advanced glycation end products in diabetic rats; inhibited aldose reductase in rat lens homogenate *in vitro* (Rao et al. 2013)
248.	*Ocimum sanctum* L., Labiatea	Leaf extract	Aldose reductase inhibitor (one of the mechanisms) (Halder et al. 2003).
249.	*Olneya tesota* A. Gray, Fabaceae	A lectin from seed	Potent inhibition of insect α-amylase (Lagarda-Diaz et al. 2014)
250.	*Opuntia humifusa* (Raf.) Raf., Cactaceae	Stem powder	PPAR-γ protein expression was more in the treated streptozotocin diabetic rats (Kang et al. 2013)
251.	*Opuntia streptacantha* Lemaire, Cataceae	Stem and fruit	Inhibition of carbohydrate absorption by fiber (?); sensitization of insulin action (?) (review: Lopez 2007)
252.	*Origanum majorana* L., Lamiaceae	Methanol extract of leaves and 6-hydroxyapigenin (scutellarein)	Inhibited sucrose hydrolysis by rat intestinal α-glucosidase (Kawabata et al. 2003)
253.	*Origanum vulgare* L., Lamiaceae	Biochanin A from leaves	Activated PPAR-γ *in vitro* (Mueller et al. 2008); but the plant contains selective modulators and antagonists of PPAR-γ
254.	*Orthosiphon aristatus* (Blume) Miq., Lamiaceae	A fraction from chloroform extract	Increased glucose uptake by the rat diaphragm muscle *in vitro*; reduced glucose absorption in the everted rat jejunum (Mohamed et al. 2013)
255.	*Paeonia lactiflora* Pall, Paeoniaceae	1,2,3,4,6-Penta-*O*-galloyl-D-glucopyranose from root	An inhibitor of PTP1B (IC_{50}: 4.8 μmol/L) (Jiang et al. 2012)
256.	*Paeonia suffruticosa* Andrews, Paeoniaceae	Palbinone, a triterpene	Activation of AMPK, glycogen synthase kinase-3β (GSK-3β), and acetyl-CoA carboxylase (ACC) phosphorrylation in insulin resistant human HepG2 cells (Ha et al. 2009)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
257.	*Panax ginseng* C.A.Meyer, Araliaceae	Root and berry extracts; ginsenoside Re; ginsenoside Rh2; 20(S)-gingenoside Rg3; ginsenoside Rb1; gingenoside Rb1 and Rg1; malonyl ginsenosides from the root; a peptide	Multiple mechanisms of action: upregulation of adipocytic PPAR-γ; blocking intestinal glucose absorption; stimulation of insulin release; activation of AMPK (Chung et al. 2001; Jeong et al. 2014; Park et al. 2008a); reducing insulin resistance through activation of PPAR-γ pathway and inhibition of TNF-α production in 3T3-L1 adipocytes (Gao et al. 2013); increase of insulin secretion by ginsenoside Rh2 (Lee et al. 2006); 20(S)-Gingenoside Rg3 enhanced glucose-stimulated insulin secretion and activated AMPK (Park et al. 2008a); Rb1 stimulated basal and insulin-mediated glucose uptake in 3T3-L1 adipocytes and C2C12 myotubes; in adipocytes, Rb1 promoted GLUT1 and GLUT4 translocations to the cell surface. Rb1 increased the phosphorylation of IRsubstrate-1 and PKB and stimulated PI3K activity in the absence of the activation of IR (Shang et al. 2008); enhanced β-cell insulin secretion and viability in Min6 cells via PKA-dependent pathways (Park et al. 2008b); improved insulin sensitivity (Liu et al. 2013); peptide showed insulinomimetic properties
258.	*Panax japonicas* C.A.Meyer, Araliaceae	Root extract	Potent α-glucosidase inhibition (Chan et al. 2010)
259.	*Panax noto-ginseng* (Burk) F.H.Chen, Araliaceae	Saponins	Improving insulin and leptin sensitivity (Yang et al. 2010a)
260.	*Pandanus fascicularis* Lamk., Pandanaceae	Methanol extract of aerial roots	Increased secretion of insulin (?) (Kumari et al. 2012)
261.	*Papaver somniferum* L., Papaveraceae	Papaverine	*In vitro* inhibitory effect against recombinant h-PTP1B (IC_{50} = 1.20 μM) (Bustanji et al. 2009)
262.	*Paronychia argentea* Lam, Caryophyllaceae	Water extract of leaves	Augmented pancreatic MIN6 β-cell expansion and inhibited carbohydrate absorption *in vitro* (Kasabri et al. 2012b)
263.	*Peganum harmala* L., Zygophyllaceae	Ethanol extract of seed (harmine is the active principle)	Mimics the effect of PPAR-γ ligands (Waki et al. 2007; Moloudizargari et al. 2013)
264.	*Perilla frutescens* (L.) Britton, Lamiaceae	Ethyl acetate fraction of methanol extract (chlorogenic acid, rosmarinic acid, methyl rosmarinic acid luteolin); rosmarinic acid rich fraction	Inhibited aldose reductase activity (Higashino et al. 2011); inhibited α-glucosidase activity and glucose transport activity under *in vitro* and *in vivo* in rats (Higashino et al. 2011)
265.	*Persea americana* Mill., Lauraceae	Hydroalcoholic extract of the leaves	PKB (Akt) activation in liver and skeletal muscle (Lima et al. 2012)
266.	*Phoradendron reichenbachianum* (Seem.) Oliv., Viscaceae	Oleanolic acid and ursolic acid	Inhibited PTP 1B activity (Nazaruk and Borzym-Kluczyk 2015)
267.	*Phyllanthus emblica* Linn., Euphorbiaceae	Ethanol extract of fruit; hydrolysable tannoids from fruit; leaf extract	Inhibition of intestinal disaccharidase activity and reduced intestinal glucose absorption (Sultana et al. 2014); inhibition of lens aldose reductase activity (Suryanarayana et al. 2004); increase in serum insulin levels in diabetic rats (Nain et al. 2012)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
268.	*Pinellia ternata* (Thunb.) Ten. ex Breitenb., Araceae	Certain fatty acids (rhizome)	Activated PPAR-γ (Wang et al. 2014)
269.	*Pinus pinaster* Aiton, Pinaceae	Bark extract	Showed very potent α-glucosidase inhibitory effect compared to acarbose (Schafer and Hogger 2007)
270.	*Piper retrofractum* Vahl., Piperaceae	Piperidine alkaloids (piperine, pipermonaline, and dehydropipermonaline)	Activation of AMPK and PPAR-δ (Kim et al. 2011a)
271.	*Piper sarmentosum* Roxb., Piperaceae	Water extract of leaf or aerial parts	Inhibition of glucose absorption and enhancement of glucose consumption (Krisanapun et al. 2012); regeneration of β-cells in streptozotocin diabetic rats (?) (Hussain et al. 2013)
272.	*Pistacia atlanticia* Dest., Anacardiaceae	Plant extract	Potentiated calcium stimulated insulin secretion from the β-cells *in vitro* (Kasabri et al. 2012a)
273.	*Pistacia vera* L., Anacardiaceae	Plant extract	Inhibition on α-glucosidase activity (Gholamhoseinian et al. 2008)
274.	*Plectranthus amboinicus* (Lour.) Spreng, Lamiaceae	Ethanol extract of leaf	Restoration of the functions of pancreatic tissues and insulinotropic effect (Viswanathaswamy et al. 2011a)
275.	*Polyalthia longifolia* Sonn. var. angustifolia, Annonaceae	Ethanol and chloroform extracts of leaf	Showed α-amylase and glucosidase enzymes inhibitory activity (Sivashanmugan and Chatterjee 2013)
276.	*Polygala senega* L. var. latifolia Torry et Gray, Polygalaceae	E and Z-senegasaponins, and E and Z-senegins II, III, and IV	Inhibited glucose absorption by suppressing the transfer of glucose from the stomach to the small intestine and by inhibiting the glucose transport system at the small intestinal brush border (Matsuda et al. 1998)
277.	*Polygonatum odoratum* (Mill.) Druce, Asparagaceae/Liliaceae	Methanol extract of rhizome	Inhibited α-amylase activity (*in vitro*) (Deng et al. 2012); increased expression of PPAR γ and α (Gu et al. 2013)
278.	*Polygonum hyrcanicum* Rech. f., Polygonaceae	Methanol extract of flowering aerial parts	Showed α-glucosidase inhibitory activity (IC_{50}: 15 μg/mL) (Moradi-Afrapoli et al. 2012)
279.	*Polygonum senegalensis* Hausa, Polygonaceae	Hydroalcohol extract of leaves	Exhibited potent α-glucosidase inhibition *in vitro* (Bothon et al. 2013)
280.	*Pongamia pinnata* (L.) Pierre, Polygalaceae	Cycloart-23-ene-3beta, 25-diol isolated from stem bark; pongamol and karanjin from fruit	Increased pancreatic insulin secretion (Badole and Bodhankar 2010); PTP1B inhibitory activity (Jiang et al. 2012)
281.	*Potentilla discolor* Bunge, Rosaceae	Triterpenes and flavonoids extract	Inhibition on glycogen phosphorylase (Yang et al. 2010); protective effects on β-cells in diabetic rats (Zhang et al. 2010)
282.	*Potentilla fulgens* Wall. ex Hook., Rosaceae	Methanol extract and different solvent fractions of root	Inhibition of aldose reductase and sorbitol dehydrogenase activities in the liver, kidney and eye (Syiem and Majaw 2011)
283.	*Poterium ancisroides* Desf., Rosaceae	Tormentic acid	Stimulation of insulin secretion *in vitro* (Ivorra et al. 1989)
284.	*Poupartia birrea* (Hochst) Aubr., Anacardiacea	Leaf extract	Inhibited aldose reductase activity (Haddad et al. 2005)
285.	*Pouteria ramiflora* (Mart.) Radlk, Sapotaceae	Extract of this plant	Inhibited activity of human salivary α-amylase activity (De Gouveia et al. 2013)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
286.	*Prosopis glandulosa* Torr., Fabaceae	Dried and ground pods	Stimulated insulin secretion; the treatment lead to the formation of small β-cells in diabetic rats; improved insulin sensitivity of isolated cardiomyocytes (George et al. 2011)
287.	*Prunella vulgaris* L., Labiatae	Water–ethanol extract of spikes; caffeic acid ethylene ester	Increased insulin sensitivity (Zheng et al. 2007); inhibited aldose reductase (Li et al. 2012a)
288.	*Prunus mume* Siebold, Rosaceae	Fruit juice	Increased plasma adiponectin levels and PPAR-γ mRNA expression in adipose tissue from plum treated obese type 2 diabetic rats (El-Abhar and Schaalan 2014; Utsunomiya et al. 2005)
289.	*Pseudocedrela kotschyi* (Schweinf.) Harms, Meliaceae	Water extract of leaf	Regeneration of β-cells; inhibition of α-glucosidase (Bothon et al. 2013; Mbaka et al. 2014)
290.	*Pseudolarix amabilis* (J. Nelson) Rehder, Pinaceae	Pseudolaric acid B from root	PPAR-γ agonist activity (Wang et al. 2014)
291.	*Psidium guajava* L., Myrtaceae	Psidials B and C (terpenoids) isolated from the leaves	PTP1B inhibitory activity (one of the mechanisms) (Jiang et al. 2012)
292.	*Psoralea corylifolia* L., Fabaceae	Psoralidin, and bakuchiol from seed	Noncompetitive PTP1B inhibitors (Jiang et al. 2012)
293.	*Pterocarpus marsupium* Roxb., Fabaceae	An isoflavone from the methanol extract of the plant	Upregulated GLUT4 and PPAR γ on L6 myotubes (Anandharajan et al. 2005)
294.	*Pueraria lobata* (Willd.) Ohwi, Leguminosae	Puerarin from root	Levels of IRS-1 and IGF-1 in the pancreas were increased; endogenous mRNA levels of skeletal muscle IR and PPAR-γ were increased in the treated animals (Wu et al. 2013)
295.	*Pueraria thomsonii* Benth., Leguminosae	Daidzein	Activated PPAR-γ and PPAR-α (Shen et al. 2006)
296.	*Punica granatum* L., Lythraceae	Methanol extract of fruit rinds or valonic acid dilactone (active principle)	Inhibited α-amylase activity; inhibited PTP1B activity; inhibited aldose reductase activity (Jain et al. 2012)
297.	*Raphia hookeri* G.Mann. & H.Wendl., Arecaceae	Root extract	Stimulated insulin secretion and β-cell survival in the diabetic rats (Mbaka et al. 2011)
298.	*Retama raetam* (Forssk) Mebb., Fabaceae	Methanol extract of the fruit	Likely mechanisms include stimulation of pancreatic insulin release and reduction in intestinal glucose absorption in streptozotocin diabetic rats (Algandaby et al. 2010)
299.	*Rheum emodi* Wall ex. Meisn., Polygonaceae	Methanol extract of rhizome and chemical isolates	Inhibition of α-glucosidase (Sureshbabu et al. 2004)
300.	*Rheum palmatum* Linn., Polygonaceae	Emodin	Elevated mRNA expression level of PPAR-γ in liver and adipocytes (Xue et al. 2010)
301.	*Rheum ribes* L., Polygonaceae	Water extract of this plant	Augmented pancreatic MIN6 β-cell expansion and stimulated insulin secretion *in vitro* (Kasabri et al. 2012b)
302.	*Rhizophora mucronata* Lam., syn: Rhizophora mangle Roxb., Rhizophoraceae	80% water : ethanol extract of stem bark	Promising α-glucosidase inhibitory activity with IC_{50}: 2.24 ± 1.58 μg/mL (Lawag et al. 2012)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
303.	*Rhododendron groenlandicum* (Oeder) Kron & Judd, Ericaceae	Leaf extract	Inhibited glucose-6-phosphatase activity with a concomitant stimulation of AMPK in cultured hepatocytes *in vitro* (Eid and Haddad 2014)
304.	*Rhododendron tomentosum* Harmaja, Ericaceae	Plant extract	Inhibited glucose uptake by intestinal cells *in vitro*; decreased expression of sodium-dependent GLUT1 (Eid and Haddad 2014)
305.	*Rhoroedendron brachycarpum* G. Don., Ericacea	Triterpenes including rhododendric acid A; corosolic acid	Inhibited PTP1B activity (Choi et al. 2012)
306.	*Rhus coriaria* L., Anacardiaceae	Ethyl acetate extract of fruit	Inhibited α-amylase activity with an IC50 value of 28 μg/mL (Giancarlo et al. 2006)
307.	*Rhus verniciflua* Stokes, Anacardiaceae	Crude extract of stem	Showed strong α-glucosidase inhibitory effects (Kim et al. 2011b)
308.	*Robinia pseudoacacia* var. umbraculifer DC., Fabaceae	Amorphastilbol from seed	Exhibited dual PPAR-γ/-α agonist effects (Wang et al. 2014)
309.	*Rosa damascena* Mill, Rosaceae	Methanol extract of flower	Intensive inhibitory effect on α-glucosidase activity (Gholamhoseinian et al. 2009)
310.	*Rosmarinus officinalis* L., Lamiaceae	Carnosic acid and carnosol (phenolic diterpenes)	Activated human PPAR-γ (Wang et al. 2014)
311.	*Rubia cordifolia* L., Rubiaceae	Alcohol extract of leaf	Regeneration of β-cells in alloxan diabetic rats (Viswanathaswamy et al. 2011b)
312.	*Rubus fructicosis* L., Rosaceae	Water extract of fruit	Inhibited α-glucosidase and α-amylase activities (Zia-ul-haq et al. 2014)
313.	*Ruta graveolens* L., Rutaceae	Rutin; infusion and rutin	Increased adipose tissue PPAR-γ expression (Ahmed et al. 2010); enhanced insulin release from isolated islets and insulin binding to its receptors in rat diaphragm; decreased intestinal glucose and cholesterol absorption (Ahmed et al. 2010)
314.	*Salacia chinensis* L., Celastraceae	Methanol extract of stem; 3-β, 22-β-dihydroxyoleon-12-en-29-oic acid, tingenone, tingenine B, regeol A, triptocalline A, and mangiferin	Inhibited intestinal α-glucosidase and rat lens aldose reductase (Yoshikawa et al. 2003); inhibited rat lens aldose reductase (Morikawa et al. 2003)
315.	*Salacia oblonga* Wall. ex Wight. & Arn., Celastraceae	Salacinol; kotalanol and aqueous methanol extract of root	Inhibited α-glucosidase; inhibited aldose reductase (Matsuda et al. 1999)
316.	*Salacia reticulata* Wight, Celastraceae	Salacinal and kotanol, polyhydroxylated cyclic 13-membered sulfoxide	α-Glucosidase inhibitors (Ozaki et al. 2008)
317.	*Salvadora persica* L., Salvadoraceae	Water extract of root	Accelerated regeneration of β-cells in streptozotocin diabetic rats (Khan et al. 2014)
318.	*Salvia acetabulosa* L., Lamiaceae	Extract of the plant	Showed potent α-amylase inhibitory activity *in vitro* (El-Abhar and Schaalan 2014)
319.	*Salvia coccinia* Buchoz ex Etl., Lamiaceae	Ethanol extract	Showed insulin secretagogue activity in INS-1 cells at 1 μg/mL level (Hussain et al. 2004)
320.	*Salvia fructicosa* Mill, Lamiaceae	10% infusion of leaves	Reduced intestinal absorption of glucose in rats (Perfumi et al. 1991)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
321.	*Salvia lavandifolia* Vahl, Lamiaceae	Whole plant extract	Potentiated insulin release induced by glucose; increased peripheral uptake of glucose; decreased intestinal absorption of glucose; and hyperplasia of the pancreatic islet β-cells (seen after chronic treatment) (Zarzuelo et al. 1990)
322.	*Salvia miltiorrhiza* Bunge, Lamiaceae	Abietane-type diterpene metabolites: isotanshinone IIA, dihydroisotanshinone I, and isocryptotanshinone from methal extract of root; danshenol A(triterpene); from root	PTP1B inhibitors (Jiang et al. 2012); inhibited lens aldose reductase (Angel de la Fuente and Manzanaro 2003)
323.	*Salvia officinalis* L., Lamiaceae	Leaf tea; water and alcohol extract of leaf or carnosic acid, carnosol, 12-O-methyl carnosic acid and linolenic acid	Primary cultures of hepatocytes from healthy, sage-tea-drinking rats showed, after stimulation, a high glucose uptake capacity and decreased gluconeogenesis in response to glucagon (Lima et al. 2006). (This effect is not seen in severe streptozotocin diabetic rats); activated PPAR-γ (review: Wang et al. 2014)
324.	*Sambucus adnata* Wall. ex DC., Caprifoliaceae	Methanol extrat of whole plant and isolates (ursolic acid, oleanolic acid and (±)-boehmenan)	PTP1B inhibitory activity (Sasaki et al. 2011)
325.	*Sambucus nigra* L., Adoxaceae	Plant extract; α-linolenic acid, linoleic acid, and naringenin from methanol extract of flower	Exhibited insulin-like and insulin-releasing actions *in vitro* (Gray et al. 2000); activated human PPAR-γ (review: Wang et al. 2014)
326.	*Sarcopoterium spinosum* (L.) Spach, Rosaceae	Water extract of the plant	*In vitro* studies suggest insulin-like effects on metabolic pathways; stimulation of basal insulin secretion, and so on (Rosenzweig et al. 2007)
327.	*Sarracenia purpurea* L., Sarraceniaceae	Alcohol extract of the plant; 7β-O-Methylmorroniside, rutin, kaempferol-3-O-rutinoside, kaempferol-3-O-(6″-caffeoylglucoside), morroniside, goodyeroside, and quercetin-3-O-galactoside from alcohol extract; quercetin-3-O-galactoside and morroniside	Stimulated insulin-dependent glucose uptake in skeletal muscle cells *in vitro*; this effect was attributed to a metformin-like action on the AMPK pathway (Eid and Haddad 2014); stimulated glucose uptake by cultured skeletal muscle cells (Eid and Haddad 2014); provided cytoprotection to neuronal cells (Eid and Haddad 2014)
328.	*Saururus chinensis* (Lour.) Baill., Saururaceae	Saurufuran A (a new furanoditerpene from roots)	Exhibited agonist effect on PPAR-γ (Wang et al. 2014)
329.	*Saussurea lappa* C.B. Clarke, Asteraceae	Three anthraquinones from ethanol extract of roots; betulinic acid, methyl ester of betulinic acid, mokkolactone and dehydrocostuslactone from methanol extract of root; chrysophanol and its glucopyranoside from root	Moderately inhibited activity of hPTP1B *in vitro* (Li et al. 2006); these four compounds inhibited activity of PTP1B *in vitro* (Choi et al. 2009); inhibited activity of PTP1B (Jiang et al. 2012)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
330.	*Schisandra arisanensis* Hayata, Schisandraceae	Schiarisanrin A and B	Showed protective effect against cytokine-mediated β-cell death (Hsu et al. 2012)
331.	*Schisandra chinensis* (Turcz) Baillon, Schisandraceae	A lignan-rich fraction from fruit	PPAR-γ agonist in type 2 diabetic rats (Kwon et al. 2011)
332.	*Sclerocarya birrea* (A. Rich.) Hochst., Anacardiaceae	Water and methanol extract of stem bark	Inhibited the activities of α-amylase and α-glucosidase; both extracts increased glucose uptake in C2C12, 3T3-L1 and HepG2 cells (Mousinho et al. 2013)
333.	*Scoparia dulcis* L., Scrophuilariaceae	Water extract of the plant; scoparic acid D, a diterpenoid from alcohol extract	Stimulated insulin secretion from isolated pancreatic islet cells (Latha and Pari 2004); stimulated glucose uptake as potent as insulin at 480 min on L6 myotubes (Pari and Latha 2004); scoparic acid D exhibited insulin secretagogue activity in insulinoma cell line and isolated islets *in vitro* (Latha et al. 2009)
334.	*Scrophularia ningpoensis* Hemsl., Scrophulariaceae	Scrophuside and iridoid glycosides ningposide 1 and 2 from the roots	Showed marked α-glucosidase inhibitory activity (Firdous 2014)
335.	*Scutellaria baicalens* Georgia, Lamiaceae	Methanol extract and the active principle bailalein; the extract	Inhibited human intestinal sucrase expressed in Caco-2 cells (Nishioka et al. 1988); improved glucose stimulated insulin secretion and β-cell proliferation through IRS2 induction (Park et al. 2008)
336.	*Selaginella tamariscina* (Beauv.) Spring, Selaginellaceae	Flavonoid fraction of whole plant; amentoflavone from methanol extract	Increased the protein expression of PPAR-γ in adipose tissue, and increased the protein expressions of IRS-1 in hepatic and skeletal muscle tissues (Zheng et al. 2011); noncompetitive PTP1B inhibitor (IC_{50}: 7.3 μmol/L) (review: Jiang et al. 2012)
337.	*Semecarpus anacardium* L.F., Anacardiaceae	Nut milk	Protein levels of PPAR-γ were increased in the treated streptozotocin diabetic rats (Jaya et al. 2010); expressions of PI3K and Akt also increased in the skeletal muscle (Jaya et al. 2011)
338.	*Senna tora* (L.) Roxb., Fabaceae,	Methanol extract of seed and active fraction	Regeneration existing β-cells in alloxan-diabetic rats (?) and possibly some more unknown mechanisms of action (Jain et al. 2011)
339.	*Siegesbeckia glabrescens* Makino., Asteraceae	Kaurane-type diterpenes from methanol extract of aerial part	Exhibited PTP1B inhibitory activity ($IC_{50:}$ 8.7 μmol/L) (Jiang et al. 2012)
340.	*Silybum marianum* (Linn.) Gaertn., Asteraceae	Isosilybin A (phenolic) from the seed	Activated PPAR-γ *in vitro* (Wang et al. 2014)
341.	*Siraitia grosvenorii* (Swingle) C. Jeffrey ex. A.M. Lu. and Zhi Y., Cucurbitaceae	Mogrosides (aglycone mogrol and two cucurbitane triterpenoids)	Potent AMPK activators in the HepG2 cell line (Chen et al. 2011)
342.	*Sorbus commixta* Hedl., Rosaceae	Triterpenes: lupeol and lupenone from stem bark	Lupeol and lupenone inhibited PTP1B in a noncompetitive manner with IC_{50} values of 13.7 and 5.6 μmol/L, respectively (Jiang et al. 2012)
343.	*Sorghum bicolor* (L.) Moench, Graminae	Phenolic extract of sorghum	Reduced the expression of phosphoenolpyruvate carboxykinase and the phosphor-p38/p38 ratio; increased phosphor-AMPK /AMPK ratio in streptozotocin diabetic rats (Kim and Park 2012); sorghum extracts improved insulin sensitivity via PPAR-γ in high fat fed mice; adiponectin expression was also increased (Park et al. 2012)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
344.	*Sphagneticola trilobata* (L.) Pruski, Asteraceae	Water extract of whole plant	Inhibited α-glucosidase activity; this effect was comparable to that of acarbose (Rungprom et al. 2010)
345.	*Sphenocentrum jollyanum* Pierre, Menispermaceae	Petroleum ether extract of seed	Recovery of β-cells to some extent in alloxan diabetic rabbitsand streptozotocin diabetic rats (Alese et al. 2013)
346.	*Spinacia oleracea* L., Chenopodiaceae	Ethanol and water extracts of the leaves	Regeneration of β-cells in the extracts treated alloxan-diabetic rats (Gomathy et al. 2010)
347.	*Stephania tetrandra* Moore, Menispermaceae	Bis-benzylisoquinoline alkaloid, fangchinoline; tetrandrine (alkaloid)	Effective insulin secretagogue in diabetic rats at very low oral doses (Tsutsumi et al. 2003); reduced the cumulative incidence of spontaneous diabetes from 75.5% to 10.9% in biobreeding rats; reduced the cumulative incidence of spontaneous diabetes from 75.5% to 10.9%.
348.	*Stereospermum teteragonum* DC., Bignoniaceae	A novel iridoid glycoside and a derivative of napthoquinone from root	Inhibition of glucose absorption from the gut as well as activating PPAR-γ and GLUT4 (Bino Kingsley 2014)
349.	*Stevia rebaudiana* (Bert.) Bertoni, Asteraceae	Stevioside; rebaudioside from leaves	Stevioside decreased blood glucose levels by enhancing not only insulin secretion, but also insulin utilization in insulin-deficient rats (Chen et al. 2005); insulinotropic property (Abudula et al. 2004)
350.	*Styrax japonica* Siebold & Zucc., Styracaceae	Triterpenoids and a sterol	Inhibited PTP1B activity (Jiang et al. 2012)
351.	*Swertia bimaculata* (Siebold & Zucc.) C. B. Clarke., Gentianaceae	Ethanol and dichloromethane extracts	Stimulated glucose consumption in 3T3-L1 adipocyte (Liu et al. 2013)
352.	*Swertia chirayita* (Roxb. ex Flm.) Krast., Gentianaceae	Hexane fraction of alcohol extract	Lowered blood glucose by stimulating insulin release from islets of Langerhans (Saxena et al. 1993)
353.	*Swertia corymbosa* (Griseb.) Wight ex C.B. Clarke, Gentianaceae	Methanol extract of aerial parts	Inhibition of α-glucosidase and α-amylase activity *in vitro* and regeneration of the β-cells in streptozotocin diabetic rats (?) (Mahendran et al. 2014)
354.	*Swertia punicea* Hemsl., Gentianaceae	Methylswertianin and bellidifolin	Improved insulin resistance by enhancing insulin signaling; the expression level of IRα subunit, IRS-1 and PI3-kinase were increased (Tian et al. 2010)
355.	*Symplocos cochinchinsis* (Lour.) S. Moore, Symplocaceae	Methanol extract of leaf	*In vitro* α-glucosidase inhibition, insulin-dependent glucose uptake (threefold increase) in L6 myotubes and regeneration of RIN-m5F cells (3.5-fold increase) (Antu et al. 2014)
356.	*Symplocos paniculata* (Thunb.) Miq., Symplocaceae	Ursolic acid	Stimulation of glucose uptake in L6 myotubes and facilitated GLUT4 translocation in CHO/hIR cells via enhancing IR phosphorylation (Jiang et al. 2012)
357.	*Syzygium cumini* (L.) Skeels., Myrtaceae	Water extract of the seeds; methanol extract; whole fruit	Inhibited pancreatic α-amylase *in vitro* (review: Sharma et el. 2012); stimulated glucose uptake by activating GLUT4, PI3 kinase and PPAR-γ in L6 myocytes *in vitro* (Anandharajan et al. 2006); may stimulate insulin secretion (Gupta and Saxena 2011)

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TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
358.	*Syzygium malaccense* (L) Merr. & Perr, Myrtaceae	Bark extract; leaf extract and myricitrin (active principle)	Inhibition of aldose reductase (Guzman and Guerrero 2005); inhibited α-glucosidase more significantly than the positive control, acarbose (Arumugam et al. 2014)
359.	*Syzygium samarangense* (Blume) Merrill and Perry, Myrtaceae	Fruit extract; vescalagin from fruit	Ameliorated insulin resistance via modulating insulin signaling *in vitro* (Shen et al. 2012); enhanced glucose uptake in insulin-resistant FL83B cells (Shen and Chang 2013)
360.	*Tabernaemontana divaricata* (L.) Roemer & Schultes, Apocynaceae	Conophylline, a vinca alkaloid from leaves (*Ervatamia microphylla* also contains this compound)	Induced the differentiation of pancreatic precursor cells to insulin-producing cells *in vitro*. (Fujij et al. 2009)
361.	*Tabernantha iboga* Vault, Apocynaceae	Water extract of the plant	Stimulated insulin secretion in the presence of 11.1 mM of glucose from the rat islets *in vitro*; insulinotropic effect of the extract (1 μg/mL) was potentiated in K(+)-depolarised media and calcium removal inhibited the insulinotropic effect (Souza et al. 2011)
362.	*Tamarindus indica* L., Fabaceae	Seed powder	Inhibitory effect on intestinal glucose absorption (?) (Parvin et al. 2013)
363.	*Taraxacum officinale* F.H. Wigg, Asteraceae	Ethanol extract of leaf	Showed insulin secretagogue activity in INS-1 cells at 40 μg/mL level (Hussain et al. 2004)
364.	*Tarchonanthus camphorates* L., Asteraceae	Ethanol extract of this plant	Increased utilization of glucose in C2C12 muscle cells in culture (Huyssteen et al. 2011)
365.	*Tecoma stans* (L.) Kunth., Bignoniaceae	Tecomine (alkaloid); 5-β-Hydroxyskitanthine and boschniakine; water extract of leaf	Increased glucose uptake by normal rat white adipocytes *in vitro* (Costantino et al. 2003); exhibited insulin-like action (Pandeya et al. 2013); inhibition of glucose release from starch (Aguilar-Santamaría et al. 2009)
366.	*Telfairia occidentalis* Hook. f., Curcubitaceae	Ethanol extract of leaf	Inhibited α-amylase and α-glucosidase activities in a dose-dependent manner (Oboh et al. 2012)
367.	*Terminalia bellerica* (Gaertn) Roxb., Combrataceae	Gallic acid from fruit; gallotannins from fruit; decoction of dried fruits	Showed insulin-secretagogue action in streptozotocin-induced diabetic rats (Latha and Daisy 2011); increased PPAR-α and PPAR-γ levels and stimulated glucose uptake without enhancing adipocyte differentiation (Yang et al. 2013); stimulated the secretion and action of insulin and inhibited starch digestion and protein glycation *in vitro* (Kasabri et al. 2010)
368.	*Terminalia catappa* L., Combrataceae	Water extract of leaf	Regeneration of β-cells of pancreas in alloxan diabetic rats (Syed et al. 2005)
369.	*Terminalia chebula* Retz. or *T. chebula* Retz var. tomentella Kurt, Combretaceae	Water extract of dried fruit	*In vitro* studies with pancreatic islets showed that the insulin release was nearly two times more than that in untreated streptozotocin diabetic animals (Murali et al. 2007)
370.	*Terminalia paniculata* Roth, Combretaceae	Water extract of bark or gallic acid	Showed enhancement of glucose uptake action in presence of insulin in muscle cells *in vitro*; also, the extract inhibited pancreatic α-amylase and α-glucosidase enzymes (Ramachandran et al. 2013)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
371.	*Tetracera scandens* (L.) Merr., Dilleniaceae	Genistein-derivatives; flavonoids from methanol extract of leaves	Stimulated glucose-uptake in L6 myotubes (Jiang et al. 2012); PTP1B inhibitory activity; stimulation of glucose-uptake activity in basal and insulin-stimulated L6 myotubes; stimulated AMPK phosphorylation (Umar et al. 2010; Jiang et al. 2012)
372.	*Teucrium capitatum* L., Lamiaceae, syn: *Teucrium polium* L.	Alcohol extract of the aerial parts	Showed insulinotropic effect in INS-1E cells *in vitro* (Stefkov et al. 2011)
373.	*Teucrium cubense* Jacq., Labiatae	Water extract of the plant	Induced glucose-uptake in insulin-sensitive and insulin-resistant murine and human adipocytes (Zapata-Bustos et al. 2009; Alonso-Castro et al. 2010)
374.	*Thymelaea hirsuta* L., Endl., Thymelaeaceae	Polyphenol-rich fraction and ethyl acetate fraction	Inhibition of intestinal α-glucosidase and intestinal glucose absorption (Abid et al. 2014)
375.	*Thymus vulgaris* L., Lamiaceae	Carvacrol, a component of thyme oil	Activated PPAR-α and -γ and suppressed COX-2 expression (Wang et al. 2014)
376.	*Tinospora crispa* (L.) Hook. f. & Thomson, Menispermaceae	Borapetol B from this plant	Stimulated insulin release from pancreatic β-cells (Lokman et al. 2013, 2014)
377.	*Tithonia diversifolia* (Hemsl.) A. Gray, Asteraceae	Three new germacrane sesquiterpenes; alcohol extract of whole plant	Increased glucose uptake in 3T3-L1 adipocytes (Zhao et al. 2012); improvement in insulin resistance in type 2 diabetic KK-Ay mice (Zhao et al. 2012)
378.	*Toona ciliata* var *pubescens* (Franchet) Handel-Mazzetti, Meliaceae	(*Z*)-Aglawone from stem bark	Inhibited PTP1B activity with an IC_{50} value of 1.12 μg/mL (Jiang et al. 2012)
379.	*Toona sinensis* Roem., Meliaceae	Leaf extract (50% alcohol/water)	Increased glucose uptake in basal and insulin stimulated 3T3-L1 adiposites (Yang et al. 2003); in alloxan diabetic rats increased plasma insulin levels (Wang et al. 2008b)
380.	*Tournefortia hartwegiana* Steud, Boraginaceae	Methanol extract of aerial part	Inhibited α-glucosidase activity *in vitro* (review: El-Abhar and Schaalan 2014)
381.	*Trichosanthes cucumerina* L., Cucurbitaceae, syn: *Trichosanthes anguina* L.	Hot water extract of aerial parts	May stimulate insulin secretion (Arawwawala et al. 2009)
382.	*Trifolium pratense* L., Fabaceae	Genistein, biochanin A, 6-hydroxydaidzein soflavones, 3′-hydroxygenistein, and so on	Potent activators of PPAR-γ ligands; maximal transactivational activity of 6-hydroxydaidzein and 3′-hydroxygenistein exceeded that of rosiglitazone, a known PPAR-γ agonist (Wang et al. 2014)
383.	*Trigonella foenum-graecum* L., Leguminoceae	4-hydroxyisoleucine (2S, 3R, and 4S) from seed; trigonelline (phenolic compound); antihyperglycemic compound named GII from seeds	The ability of (2S, 3R, and 4S) isomers of this compound to stimulate glucose-induced insulin secretion in μ molar concentrations was shown (Sauvaire et al. 1998); protected β-cells from death and damage in alloxan diabetic rats; decreased intestinal α-amylase, maltase and lipase (Hamden et al. 2013); increased serum insulin levels; increased sensitivity of tissues to insulin action; and stimulated activity of enzymes of glucose utilization in diabetic rabbits (Puri et al. 2011)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
384.	*Urtica dioica* L., Urticaceae	Hydroalcoholic extract of leaf	Decreased serum glucose, insulin, and leptin, and insulin resistance index in fructose-fed insulin-resistant rats (Ahangarpour et al. 2012); could cause repair of pancreatic tissue in streptozocin-induced diabetic rats (?) (Qujeq et al. 2013)
385.	*Vaccinium angustifolium* Ait., Ericaceae	Fruit extracts; stem leaf and fruit extracts	Increased ^{3}H-thymidine incorporation in replicating β-TC-tet cells by 2.8-fold; reduced apoptosis by 20–33% in PC12 cells exposed to elevated levels of glucose for 96 h; extracts showed insulin-like and glitazone-like properties (Martineau et al. 2006)
386.	*Vaccinium arctostaphylos* L., Ericaceae	Anthocyanin: malvidin-3-O-β-glucoside	Inhibited α-amylase (Nickavar and Amin 2004); protected β-cells from oxidative stress and increased secretion of insulin; improved insulin resistance also (Sancho and Pastore 2012)
387.	*Vaccinium vitis-idaea* L., Ericaceae	Berry ethanol extract	Inhibited hepatic glucose-6-phosphatase, an effect coupled to increased AMPK activation; enhanced basal or insulin-stimulated glucose uptake in cultured myocytes like metfomin (Eid and Haddad 2014)
388.	*Vernonia amygdalina* Del., Asteraceae	Ethanol extract of whole plant	Showed protective effect over pancreatic β-cells against streptozotcin-induced damage; increased GLUT4 translocation to plasma membrane; suppressed (40% inhibition) one of the key hepatic gluconeogenic enzymes, glucose-6-phosphatase (Ong et al. 2011)
389.	*Vitex negundo* L., Labiatae	1, 2 di-substituted idopyranose; chloroform, ethyl acetate and n-butanol extracts of leaf	Showed regeneration of hepatocytes, nephrocytes, as well as β-cells and acinar region appeared normal with increased numbers of β-cells; inhibited expression of NF-kappa B (Manikandan et al. 2011); showed α amylase inhibition *in vitro*; out of these 3 extracts chloroform extracts showed better inhibitory action (Devani et al. 2013)
390.	*Vitis vinifera* L., Vitaceae	Grape-skin extract; ellagic acid and epicatechin gallate, (flavonoids) from grape	Inhibited α-glucosidase activity and suppressed postprandial glycemic response in streptozotocin-diabetic mice; activated insulin-signaling cascade and reduced hyperglycaemia in alloxan-diabetic mice; IR content and Akt phosphorylation were greater in extract-treated diabetic mice gastrocnemius muscles (Soares de Moura et al. 2012); activated PPAR-γ (Wang et al. 2014)
391.	*Weigela subsessilis* L.H.Bailey, Caprifoliaceae	24-Norursane triterpenes, ilekudinols A and B from leaves	Inhibited PTP1B activity (Jiang et al. 2012)
392.	*Xanthocercis zambesiaca* (Baker) Dumaz, Leguminosae	Fagomine (nitrogen containing sugar from this plant)	Increased plasma insulin level in streptozotocin-diabetic mice and potentiated glucose-induced insulin release from rat isolated-perfused pancreas (Nojima et al. 1998)
393.	*Zataria multiflora* Boiss, Lamiaceae	Essential oil	Increased insulin sensitivity and PPAR-γ gene expression in high-fructose-fed insulin-resistant rats (Mohammadi et al. 2014)
394.	*Zea mays* L., Poaceae	Hirsutrin; corn silk	Competive inhibition of aldose reductase (IC_{50}: 4.78 μM) (Kim et al. 2013); increased insulin level and recovered injured β-cells in alloxan diabetic rats (Guo et al. 2009)

(*Continued*)

TABLE 3.1 (*Continued*)

Mechanism of Actions of Anti-Diabetes Mellitus Plants

No.	Botanical and Family Names of Plants	Plant Drugs Used (Extracts or Compounds)	Mechanisms of Actions
395.	*Zhumeria majdae* Rech. f, Lamiaceae	Plant extract	Showed promising *in vitro* inhibition of α-amylase activity (Gholamhoseinian et al. 2008)
396.	*Zingiber officinale* Roscoe, Zingiberaceae	6-Shogaol and 6-gingerol	Inhibited TNF-α-mediated downregulation of adiponectin expression (Wang et al. 2014)
397.	*Ziziphus mucronata* Willd. subsp. *mucronata*, Rhamnaceae	Water and methanol extracts of bark	Inhibited the activities of α-amylase and α-glucosidase; this effect was comparable to that of acarbose; increased glucose uptake in C2C12, 3T3-L1 and HepG2 cells (Mousinho et al. 2013)
398.	*Ziziphus spina-christi* (L.) Willd., Rhamnaceae	Butanol extract of leaf or christinin-A (the major saponin glycoside from leaf); leaf extract	Potentiated glucose-induced insulin release in normal and type 2, but not in type 1, diabetic rats (Abdel-Zaher et al. 2005); *in vitro* experiments showed inhibitory activity of the extract against α-amylase enzyme (Michel et al. 2011)
399.	*Zygophyllum album* L., Zygophyllaceae	Extracts rich in flavonoids and phenolic compounds; ethanol extract of aerial part	Decreased leptin levels and inhibited lipase activity of obese high-fat diet fed (HDF)-rats; inhibition of α-amylase enzyme *in vitro*; and decreased α-amylase levels in serum, pancreas and intestine of diabetic rats (Mnafgui et al. 2012); decreased TNF-α levels also (Mnafgui et al. 2014)

cells to insulin-producing cells *in vitro* (Fujij et al. 2009). Canophylline from *Tabernaemontana bufalina* Lour leaf also stimulated the differentiation of progenitor cells into β-cells (Chang et al. 2013). Compound SGL-1 (uncharacterized chemical isolate from *Enicostemma littorale* Blume) stimulated islet neogenesis in cell culture conditions (Gupta et al. 2010). A compound isolated from methanol extract of the plant is named as SGL-1. Examples of anti-DM plants that induced the regeneration of β-cells include *Ficus amplissima* Smith, *Juglans regia* L., *Nymphaea pubescens* Willd., *Spinacia oleracea* L., *Symplocos cochinchinsis* (Lour.) S. Moore, *Terminalia catappa* L., and *Vitex negundo* L. (see Table 3.1). Regeneration of β-cells and increase in the number of functional β-cells could lead to increase in insulin production and secretion.

Plants reported to have insulin secretagogue activities include *Abies pindrow* Royle, *Abutilon indicum* (L.), *Acalypha indica* L., *Acalypha wilkesiana* Mull., *Acanthopanax senticosus* Rupr. & Maxim, *Achillea santolina* L., *Aegle marmelos* (L.) Correa, *Agrimonia eupatoria* L., *Amorphophallus konjac* K.Koch., *Anemarrhena asphodeloides* Bunge, *Anisopus mannii* N.E.Br., *Annona muricata* L., *Apium graveolens* L., *Artemisia amygdalina* Decne, *Artemisia santonicum* L., *Aspalathus linearis* (Burm.f.) R. Dahlgren, *Asparagus adscendens* Buch. Ham. ex Roxb., *Asparagus racemosus* Willd., *Azadirachta indica* A. Juss., *Baccharis articulata* (Lam.) Pers., *Bauhinia variegata* L., *Belamcanda chinensis* (L.) DC, *Bergenia himalaica* Boriss., *Beta vulgaris* L., *Bougainvillea spectabilis* Willd., *Brassica nigra* (L.) Koch, *Caesalpinia bonbuc* (L.), *Cassia sophera* L., *Catharanthus roseus* (L.) G. Don f., *Centaurea corcubionensis* Lainz, *Centaurea iberica* Spreng., *Centaurea seridis* L., *Chiliadenus iphionoides* (Boiss. & Blanche) Brullo, *Cinnamomum cassia* (Nees & T. Nees) J. Presl., and *Cinnamomum verum* J.S. Presl., *Citrullus colocynthis* (L.) Schrd, *Clausena lansium* (Lour.) Skeels, *Clitoria ternatea* L., *Coriandrum sativum* L., *Croton klozchianus* L., *Cucurbita ficifolia* Bouche, *Cymbopogon citratus* (DC.) Stapf, *Desmodium gangeticum* (L.) DC, *Dioscorea bulbifera* L., *Elephantopus scaber* L., *Eleutherococcus senticosus* (Rupr.& Maxim) Maxim., *E. littorale* Blume, *Ephedra distachya* L., *Eryngium creticum* Lam., *Eucalyptus globulus* Labill, *Euonymus alatus* (Thunb.) Siebold, *Euphorbia helioscopia* L., *Ginkgo biloba* L., *Glycyrrhiza uralensis* Fisch., *Gymnema sylvestre* R. Br., *Indigofera arrecta* Hochst. ex A.Rich, *Ipomoea batatas* L., *Leonotis leonurus* (L.) R., *Lippia nodiflora* L., *Lupinus mutabilis* Sweet, *Malmea depressa* (Baill) R.E. Fries., *Mandicago sativa* L., *Medicago sativa* L., *Momordica charantia* L., *Momordica cymbalaria* Hook., *Monstera deliciosa* Liebm., *Nelumbo nucifera* Gaertn., *Panax ginseng* C.A.Meyer, *Pistacia atlanticia* Dest., *Plectranthus amboinicus* (Lour.) Spreng, *Pongamia pinnata* (L.) Pierre, *Poterium ancisroides* Desf, *Prosopis glandulosa* Torr., *Pseudocedrela kotschyi* (Schweinf.) Harms, *Raphia hookeri* G.Mann.&

H.Wendl., *Rheum ribes* L., *Ruta graveolens* L., *Salvadora persica* L., *Salvia coccinia* Buchoz ex Etl., *Salvia lavandulifolia* Vahl, *Sambucus nigra* L., *Scoparia dulcis* L., *Scutellaria baicalens* Georgia, *Stevia rebaudiana* (Bert.) Bertoni, *Stephania tetrandra* Moore, *Swertia chirayita* (Roxb. ex Flm.) Krast, *T. bufalina* Lour., *Tabernantha iboga* Vault, *Taraxacum officinale* F.H. Wigg, *Terminalia bellerica* (Gaertn) Roxb., *Terminalia chebula* Retz., *Teucrium capitatum* L., *Tinospora crispa* (L.) Hook. f. & Thomson, *Trigonella foenum-graecum* L., *Vaccinium arctostaphylos* L., *Xanthocercis zambesiaca* (Baker) Dumaz, *Zea mays* L., and *Ziziphus spina-christi* (L.) Willd. (see Table 3.1).

3.2.2 Sensitization of Insulin Action (Decreasing Insulin Resistance)

Insulin action is mediated through insulin-signaling pathways; there are several key molecules such as insulin receptor (IR), insulin receptor substrates (IRSs), phosphoinositide 3 kinase (PI3-K), protein tyrosine phosphates-1B (PTP1B), protein kinase B (Akt), and glucose transporter-4 (GLUT4) involved in insulin signaling. Malfunction or reduced function or reduced levels of any of these molecules can result in varying degrees of insulin resistance. Increase in the levels of insulin-signaling pathway key elements can lead to increase in the sensitivity of insulin action. For example, ethanol extract of *Myrcia bella* Cambess leaf increased the expression of IRS1, PI3-K, and Akt in the liver of diabetic rats (Vareda et al. 2014). Increase in the levels of GLUT4 caused by phytomolecules could lead to increase in the insulin-mediated glucose uptake in cells (El-Abhar and Schaalan 2014).

PTP1B is a phosphatase with 435 amino acids. Substantial evidence shows that PTP1B is a negative regulator in insulin signaling. In the insulin-signaling pathway, this enzyme can associate with and dephosphorylate activated IR and IRSs. Overexpression of PTP1B decreases insulin-stimulated phosphorylation of IR and IRS1, whereas a reduction or inhibition of this enzyme activity augments insulin-initiated signaling. PTP1B inhibitors can act as insulin sensitizers and insulin mimetics. Many plant extracts and isolated compounds belonging to different chemical classes, phenolics in particular, from plants inhibit PTP1B (Jiang et al. 2012). Plants that inhibited this enzyme include *Acanthopanax koreanum* Nakai, *Aegiceras corniculatum* (L.) Blanco, *Artemisia minor* Jacq. ex Besser, *Astilbe grandis* Stapf ex E.H.Wilson, *Brassica oleracea* L., var. botrytis, *Broussonetia papyrifera* L., *Bruguiera gymnorrhiza* (L.) Lam., *Cichorium glandulosum* Boiss. & A. Huet, *Cichorium intybus* L., *Cornus officinalis* Sieb., *Dendrobium moniliforme* (L.) Sw., *Dodonaea viscosa* (L.) Jacq., *Erythrina abyssinica* DC, *Coptis chinensis* Franch, *Coptis deltoides* C.Y., *Glycyrrhiza inflata* Batalin, *G. uralensis* Fisch., *Lagerstroemia speciosa* L., *Ligularia fischeri* (Ledeb.) Trucz., *Macaranga adenantha* Gagnep., *Morus bombycis* Koidzumi, *Paeonia lactiflora* Pall, *Papaver somniferum* L., *Phoradendron reichenbachianum* (Seem.) Oliv., *P. pinnata* (L.) Pierre, *Psidium guajava* L., *Psoralea corylifolia* L., *Punica granatum* L., *Rhoroedendron brachycarpum* G. Don., *Salvia miltiorrhiza* Bunge, *Sambucus adnata* Wall. ex DC., *Saussurea lappa* C.B. Clarke, *Selaginella tamariscina* (Beauv.) Spring, *Siegesbeckia glabrescens* Makino., *Sorbus commixta* Hedl., *Styrax japonica* Siebold & Zucc., *Tetracera scandens* (L.) Merr., *Toona ciliata* var *pubescens* (Franchet) Handel-Mazzetti, and *Weigela subsessilis* L.H.Bailey (see Table 3.1).

Plants known to sensitize insulin action (without inhibiting PTP1B) include the following: *Abelmoschus moschatus* Medik., *Abies balsamea* (L.) Mill, *Agrimonia pilosa* Ledeb (decrease in fatty acid induced resistance and stimulation of Akt), *Amomum villosum* var. xanthioides (Wall. ex Baker) T.L.Wu & S.J.Chen., *A. asphodeloides* Bunge, *Angelica sinensis* (Oliv.) Diels, *Artemisia dracunculus* L., *Artemisia sphaerocephala* Krasch, *A. adscendens* Buch. Ham. ex Roxb., *Campsis grandifolia* (Thunb.) K. Schum, *Celastrus vulcanicola* J.D. Smith, *Cinnamomum burmannii* (Nees & Th. Nees) Nees ex Blume, *C. cassia* (Nees & T. Nees) J. Presl., *C. verum* J.S. Presl., *Costus pictus* D. Don., *Curcuma longa* L., *E. senticosus* (Rupr. & Maxim) Maxim., *E. littorale* Blume, *Inula racemosa* Hook., *I. batatas* L., *Kalopanax pictus* (Thunb.) Nakai, *L. speciosa* L., *Lycium barbarum* L., *Lythrum salicaria* L., *Magnolia officinalis* Rehder & E.H.Wilson, *Mangifera indica* L., *Melothria mederaspatana* (L.) Cogn., *Morus alba* L., *P. ginseng* C.A.Meyer, *Panax noto-ginseng* (Burk) F.H. Chen, *Prunella vulgaris* L., *Pueraria lobata* (Willd.) Ohwi, *Semicarpus anacardium* L.F. (PI3K and Akt expression), *Swertia punicea* Hemsl., *S. cochinchinsis* (Lour.) S. Moore, *Syzygium samarangense* (Blume) Merrill and Perry, *T. bellerica* (Gaertn) Roxb., *Terminalia paniculata* Roth, *Tithonia diversifolia* (Hemsl.) A. Gray, *T. foenum-graecum* L., *Urtica dioica* L., *V. arctostaphylos* L., and *Zataria multiflora* Boiss (see Table 3.1).

PPAR-γ and adiponectin are also sensitizers of insulin action. Plants that activate and/or increase the expression of PPAR-γ are given in Section 3.1.4. Hormones such as adiponectin and leptin from adipocytes modulate the actions of insulin. Adiponectin, the sensitizer of insulin, simulates the fatty acid oxidation through AMPK and PPAR-γ-dependent pathways (Duan et al. 2008). Plants that influence adiponectin levels include the following: Hydrangeic acid, a stilbene constituent of the processed leaves of *Hydrangea macrophylla* (Thunb.) Ser, increased the amount of adiponectin released into the medium, the uptake of 2-deoxyglucose into the cells, and the translocation of GLUT4 in 3T3-L1 cells (Zhang et al. 2009b). Fruit juice of *Prunus mume* Siebold increased plasma adiponectin levels (El-Abhar and Schaalan 2014). Phenolic extract of sorghum, *Sorghum bicolor* (L.) Moench, increased adiponectin expression (Park et al. 2012a). Also, 6-shogaol and 6-gingerol from *Zingiber officinale* Roscoe inhibited TNF-α-mediated the downregulation of adiponectin expression (Wang et al. 2014).

Leptin secreted from white adipocytes helps to regulate body fat. It inhibits appetite through hypothalamous, stimulates the break down of fatty acids and decreases body fat and insulin resistance. However, important actions of leptin involve the inhibition of insulin biosynthesis and secretion in the β-cells. In turn, insulin stimulates leptin secretion from adipose tissue, establishing a hormonal regulatory feedback loop. Extracts rich in flavonoids and phenolic compounds from *Zygophyllum album* L. decreased leptin levels and inhibited lipase activity of obese HDF rats (Mnafgui et al. 2012). Water extract of seeds of *Coix lacryma-jobi* var. *mayuen* (Rom. Caill.) Stapf ex Hook. f. reduced the expression of neuropeptide Y and leptin receptor levels in the hypothalamus of high-fat-fed rats (Kim et al. 2007b). *Panax notoginseng* (Burk) F.H.Chen saponins improved insulin and leptin sensitivity (Yang et al. 2010).

3.2.3 Insulin-Like Action/Insulin Mimetic (Partial or Complete)

Insulin mimetic (insulinomimetic) agents are able to function like insulin, partly or completely, even in the absence of insulin. They utilize insulin-signaling pathways at receptor or postreceptor levels. They may stimulate key molecules in the signaling pathways such as IR, IRSs, PI3K, PTP1B, protein kinase B (PKB/Akt), GLUT4, and so on. An example to an insulin mimetic protein is a peptide isolated from *M. charantia*, which showed insulin-like bioactivity. An example of insulin mimetic extract is water extract of *Eucommia ulmoides* Oliv leaf; the extract stimulated glucose uptake in L6 rat muscle cells by stimulating the activity PI3-K and its downstream effectors, PKB, and atypical form of PKC (Hong et al. 2008).

Other plants reported to have varying levels of insulin mimetic activity include *Bauhinia forficata* Link, *Berberis aristata* DC (and other berberine containing plants), *C. grandifolia* (Thunb.) K. Schum, *C. vulcanicola* J.D. Smith, *Chelidonium majus* L., *C. cassia* (Nees & T. Nees) J. Presl., and *C. verum* J.S. Presl., *C. sativum* L., *C. chinensis* Franch, *C. deltoides* C.Y., *K. pictus* (Thunb.) Nakai, *L. speciosa* L., *Lathyrus sativus* L., *L. mutabilis* Sweet, *M. sativa* L., *M. charantia* L., *Myristica fragrans* Houtt, *P. ginseng* C.A.Meyer (peptide), *Persea americana* Mill. (Akt activation), *S. nigra* L., *Sarcopoterium spinosum* (L.) Spach, *Symplocos paniculata* (Thunb.) Miq. (IR phosphorylation), *Syzygium cumini* (L.) Skeels. (PI3-K stimulation), *Tecoma stans* (L.) Kunth., *Vaccinium angustifolium* Ait, and *Vitis vinifera* L. (activates insulin signaling cascade) (see Table 3.1).

There could be limitations in the interpretations of animal experimental results regarding insulin mimetic activity because in type 1 DM animal models such as alloxan-diabetic animals, complete loss of all β-cells cannot be ensured. Therefore, increase in insulin levels could, possibly, occur; this could overlap with the assessment of insulin mimetic action. Furthermore, the activation of other pathways can indirectly activate crucial molecules in the insulin-signaling pathways. For example, AMPK activation will in turn activate and translocate GLUT4 without any direct effect on insulin-signaling pathway molecules. Therefore, insulin mimetic action should be confirmed using carefully planned and executed *in vitro* studies.

3.2.4 Activation of PPAR-γ

PPARs are ligand-activated transcription factors of the nuclear receptor (NR) family. There are three PPAR subtypes (PPAR-α, PPAR-β, and PPAR-γ) that have different ligand specificity and tissue distribution (Berger and Moller 2002). PPAR-γ is highly expressed in adipose tissue, macrophages, and cells of the vasculature and plays major roles in adipogenesis, glucose, and lipid homeostasis (Lehrke and Lazar

2005). PPAR-γ is an essential transcription mediator of adipogenesis, lipid metabolism, and insulin sensitivity (Duan et al. 2008). PPAR-γ agonists such as the thiazolidinediones are efficient and clinically useful insulin sensitizers and are under investigation for the treatment of inflammation with potential applications in atherosclerosis, arthritis, and bowel disease (Borniquel et al. 2010; Giaginis et al. 2009).

PPAR-α is the receptor for the fibrate class of lipid-lowering drugs, and PPAR-δ orchestrates the regulation of high-density lipoprotein (HDL) metabolism. Synthetic ligands of PPAR-α and PPAR-γ such as fibric acid and thiazolidinediones showed significant improvement in insulin sensitivity, HbA1c, and glucose levels in type 2 DM and prediabetes. One of the essential aspects of anti-diabetes action of thiazolidinediones is described as the glyconeogenesis-dependent fatty acid-lowering effect. The PPARs, in the absence of ligand, bind with 9-*cis* retinoic acid receptor (RAR) and a multicomponent corepressor complex in a heterodimeric fashion to a specific response element within the promoter region of their target genes. When the PPAR is activated by ligands, PPAR–RAR heterodimer becomes free due to the dissociation of multicomponent corepressor complex from the promoter region leading to an increase in the rate of gene transcription involved in the regulation of lipid and carbohydrate metabolism. PPAR-γ also enhances the production and release of the cytokine adiponectin. PPAR-γ agonist increases the production of adiponectin from adipocytes, which also increases insulin sensitivity (Berger and Moller 2002; Jay and Ren 2007). Stimulation of PPAR-γ potentiates its direct binding with the response element in the promoter region of the adiponectin gene. Adiponectin possesses anti-DM and antiatherogenic properties. Adiponectin enhances glucose uptake in skeletal muscles, activates IRS1-mediated PI3-K, and activates AMPK (El-Abhar and Schaalan 2014). Plants known to activate PPAR-γ and/or increase the expression of PPAR-γ include the following (those plants known to increase PPAR-γ expression are indicated in brackets):

Alisma plantago-aquatica L., *Amorpha fruticosa* L., *Astragalus membranaceus* Bunge, *Bixa orellana* L., *Camellia sinensis* (Linn.) Kuntze, *Cannabis sativa* L., *Chromolaena odorata* (L.) R.M. King & H. Rob., *Citrus lemon* (L.) Burm.f. (PPAR-γ level increased), *Clematis pickeringii* A.Gray (increased expression of PPAR-γ), *C. lacryma-jobi* var. ma-yuen (Rom. Caill.) Stapf ex Hook. f., *Commiphora mukul* (Hook. ex Stocks) Engl., *Cornus alternifolia* L.f., *Cornus kousa* F. Buerger ex Miquel, *C. longa* L., *C. citratus* (DC.) Stapf, *D. viscosa* (L.) Jacq., *Echinacea purpurea* (L.) Moench, *E. scaber* L., *Glycine max* (L.) Merr., *Glycyrrhiza glabra* L., *Glycyrrhiza foetida* Desf., *G. inflata* Batalin, *G. uralensis* Fisch., *Hovenia dulcis* Thunb. (stimulated expression), *Humulus lupulus* L., *Jatropha curcas* L., *Limnocitrus littoralis* (Miq.) Swingle, *Lycium chinense* Mill., *M. officinalis* Rehder & E.H.Wilson, *Melampyrum pratense* L., *Melissa officinalis* L. (increased expression of PPAR-γ), *M. charantia* L., *M. fragrans* Houtt, *Opuntia humifusa* (Raf.) Raf. (increased expression of PPAR-γ), *P. ginseng* C.A.Meyer, *Peganum harmala* L., *Pinellia ternata* (Thunb.) Ten. ex Breitenb., *Polygonatum odoratum* (Mill.) Druce (increased expression of PPAR-γ), *P. mume* Siebold (increased PPAR-γ mRNA expression), *Pseudolarix amabilis* (J. Nelson) Rehder, *P. lobata* (Willd.) Ohwi (increased expression of PPAR-γ mRNA), *Pueraria thomsonii* Benth., *Rheum palmatum* Linn.(increased PPAR-γ mRNA expression), *Robinia pseudoacacia* var. umbraculifer DC., *Rosmarinus officinalis* L., *R. graveolens* L. (expression increased), *Salvia officinalis* L., *S. nigra* L., *Saururus chinensis* (Lour.) Baill., *Schisandra chinensis* (Turcz) Baillon, *S. tamariscina* (Beauv.) Spring (protein expression), *S. anacardium* L.F. (increased expression of PPAR-γ), *Silybum marianum* (Linn.) Gaertn., *S. bicolor* (L.) Moench, *Stereospermum teteragonum* DC., *S. cumini* (L.) Skeels., *T. bellerica* (Gaertn) Roxb., *Thymus vulgaris* L., *Trifolium pratense* L., *V. vinifera* L., and *Z. multiflora* Boiss (increased PPAR-γ gene expression) (see Table 3.1).

3.2.5 Increasing the Levels of GLP-1

GLP-1 (major incretin hormone) is secreted from the L-cells of intestine. GLP-1 is rapidly degraded in the blood. Dipeptidyl peptidase-4 (DPP-4) is the major enzyme responsible for degrading the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Inhibition of DPP-4 can result in an increase in the duration of action of GLP-1. Furthermore, agents that stimulate the secretion of GLP-1 also increase its level in the blood. GLP-1 plays important roles in glucose homeostasis by improving β-cell differentiation, mitogenesis, and survival as well as through the stimulation of glucose-dependent insulin secretion. It also delays the gastric emptying and inhibits glucagon secretion. Thus, increase in the levels of GLP-1 could ameliorate type 2 DM (Ahrén 2007; Green 2007).

Glucose regulatory mechanisms of incretin hormones (GLP-1 and GIP) are utilized to generate new anti-diabetic drugs such as DPP-4 inhibitors in the treatment of type 2 DM. DPP-4 inhibitors therapy results in appreciable glycemic control, glucose tolerance, or increase in insulin secretion in type 2 DM (Pratley and Salsali 2007). Dipeptidyl peptidase-4 has a wide range of substrates other than GLP-1, GIP, and peptide YY. Therefore, the inhibitors of DPP-4 may not only influence the regulation of energy homeostasis but also other functions unrelated to energy homeostasis-like immunity (Michel et al. 2008). In obese diabetic ob/ob mice, administrated with a new DPP-4 inhibitor, alogliptin benzoate showed reduced activity of DPP-4 and increased GLP-1 activities. Alogliptin benzoate improves β-cell function, glycemic control, and reduces serum triglycerides in ob/ob mice (Moritoh et al. 2008). Orally active DPP-4 inhibitors show antihyperglycemic effect without severe hypoglycemia, reduce glycated hemoglobin, improve islet function, and modify the course of diabetes. These drugs also show normal body weight with lesser side effects compared to other oral hypoglycemic agents (OHA). The oral DPP-4 inhibitors improve islet function by increasing α- and β-cell responsiveness to glucose that culminate in proper insulin release and reduced glucagon secretion. However, long-term controlled studies on specific DPP-4 inhibitors are needed to demonstrate sustained glycemic control and β-cell functions (Fisman and Tenenbaum 2015; Rosenstock and Zinman 2007).

Anti-DM plants that increase the levels of GLP-1 include *Agave tequilana* Gto. (GLP-1 synthesis increased), *A. asphodeloides* Bunge (secretion of GLP-1 increased), *Buddleja officinalis* Maxim (inhibition of DPP-4 activity), *C. majus* L., *Citrus aurantium* L. (secreation of GLP-1 increased *in vitro*), *Dasylirion* spp. (synthesis of GLP-1 increased), *C. chinensis* Franch (GLP-1 levels increased), *C. deltoides* C.Y. (GLP-1 levels increased), *G. sylvestre* R. Br., *I. batatas* L (secreation of GLP-1 increased), and *M. indica* L. (DPP4 inhibition) (see Table 3.1).

3.2.6 Activation of AMPK

AMPK is a serine/threonine protein kinase involved in metabolism; this enzyme is activated by several natural compounds such as berberine, resveratrol, epigallo-catechin gallate, and quercetin (Hardie 2013). AMPK helps in regulating the cellular uptake of glucose and oxidation of free fatty acids (Arif et al. 2014). Furthermore, AMPK can stimulate GLUT4 expression and translocation and thereby stimulate glucose uptake independent of insulin action (Eid and Haddad 2014). Since it increases GLUT4 levels, it is also considered as an insulin sensitizer. Plants that are known to activate AMPK include *A. balsamea* (L.) Mill, *Alnus incana* sub sp. *rugosa* (Du Roi) R.T. Clausen, *Anacardium occidentale* L., *Aquilaria sinensis* (Lour.) Gilg, *A. dracunculus* L., *B. aristata* DC., *C. majus* L., *Combretum lanceolatum* Pohl ex Eichler, *C. chinensis* Franch, *C. deltoides* C.Y., *Coffea arabica* L., *Gastrodia elata* Blume, *H. dulcis* Thunb.(upregulation), *Hypolepis punctata* (Thunb.) Mett., *Larix laricina* (Du Roi) K. Koch, *M. charantia* L., *Paeonia suffruticosa* Andrews, *P. ginseng* C.A.Meyer, *Piper retrofractum* Vahl., *Rhododendron groenlandicum* (Oeder) Kron & Judd, *Sarracenia purpurea* L., *Siraitia grosvenorii* (Swingle) C. Jeffrey ex. A.M. Lu. and Zhi Y., *S. bicolor* (L.) Moench, *T. scandens* (L.) Merr., and *Vaccinium vitis-idaea* L. (see Table 3.1).

3.2.7 Inhibition of Carbohydrate Digestion in the Intestine

Complex carbohydrates (polysaccharides) are absorbed from the intestine after digestion into monosaccharides by carbohydrate hydrolyzing enzymes. Inhibition of these enzymes could retard the absorption of glucose from the intestine and delay carbohydrate absorption. The α-amylase is one of the major secretory products of the pancreas and salivary glands involved in the digestion of starch and glycogen. The α-amylase constitutes a family of endoamylases that catalyze the initial hydrolysis of starch into shorter oligosaccharides and maltose. Alpha-glucosidase enzyme is a member of the glucosidases located in the brush-border surface membrane of the intestinal cells and is primarily involved in the conversion of oligosaccharides and disaccharides into monosaccharides necessary for intestinal absorption (El-Abhar and Schaalan 2014; Michelle de-Sales et al. 2012). The pancreatic α-amylase and membrane-bound intestinal α-glucosidase hydrolase enzymes are inhibited by many phytochemicals. Numerous plant extracts and phytochemicals have been reported to inhibit carbohydrate digestion enzymes; plants with considerable enzyme activity are given below in alphabetical order. It is very difficult to select some

best extracts or compounds in view of the differences in the assay methods and conditions used and the plant extracts used. Diverse phytochemicals with varying solubility in different solvents are involved in the inhibition of the enzymes.

Plants reported to inhibit both α-glucosidase and α-amylase include *Bergenia ciliata* (Haw.) Sternb., *B. spectabilis* Willd, *Centella asiatica* (L.) Urban, *Chaenomeles sinensis* (Thouin) Koehne, *C. iphionoides* (Boiss. & Blanche) Brullo, *C. cassia* (Nees & T. Nees) J. Presl., *C. verum* J.S. Presl., *Citrullus lanatus* (Thunb.) Matsumara & Makai, *D. bulbifera* L., *Ficus exasperata* Vahl., *Ficus lutea* Vahl, *Gynura divaricata* (L.) DC, *M. mederaspatana* (L.) Cogn., *Morinda lucida* Benth., *M. alba* L., *Polyalthia longifolia* Sonn., *Rubus fructicosis* L., *Sclerocarya birrea* (A. Rich.) Hochst., *Swertia corymbosa* (Griseb.) Wight ex C.B. Clarke, *Telfairia occidentalis* Hook. f., and *T. paniculata* Roth (see Table 3.1).

Plants reported to inhibit α-glucosidase activity include *Acer saccharum* Marshall, *A. santolina* L., *Alisma orientale* (Sam.) Juzepcz, *A. linearis* (Burm.f.) R. Dahlgren, *B. forficata* Link, *Boerhaavia diffusa* L., *Cassia alata* L., *Cecropia obtusifolia* Bertol., *Commelina communis* L., *Cuminum cyminum* L., *C. longa* L., *Cyclocarya paliurus* (Batal.) Ijinskaja, *Eclipta alba* (L.) Hassk., *Epimedium brevicornum* Maxim, *Euclea undulata* Thunb, *Hydnocarpus wightiana* Blume, *Juniperus communis* L., *Juniperus oxycedrus* L., *Leptadenia hastata* (Pers.) Decne., *Lonicerae japonica* Thunb., *Macaranga tanarius* (L.) Mull. Arg., *Machilus thunbergii* Sieb. et Zucc., *M. depressa* (Baill) R.E. Fries., *Moringa stenopetala* Baker f., *Morus nigra* L., *Myrcia multiflora* DC, *Olneya tesota* A. Gray, *Origanum majorana* L., *Panax japonicas* C.A.Meyer, *Perilla frutescens* (L.) Britton, *Pinus pinaster* Aiton, *Pistacia vera* L., *Polygonum hyrcanicum* Rech. f., *Rheum emodi* Wall ex. Meisn., *Rhizophora mucronata* Lam., *Rhus verniciflua Stokes, Rosa damascena Mill, Salacia oblonga* Wall. ex Wight. & Arn., *Salacia reticulata* Wight, *Scrophularia ningpoensis* Hemsl., *Sphagneticola trilobata* (L.) Pruski, *Syzygium malaccense* (L.) Merr. & Perr, *Thymelaea hirsuta* L.Endl., *Tournefortia hartwegiana* Steud., and *V. vinifera* L. (Table 3.1).

Plants reported to inhibit α-amylase activity include *A. pilosa* Ledeb., *Amaranthus spinosus* L., *Anthocleista schweinfurthii* Gilg., *Aralia elata* (Miq.) Seem, *Areca catechu* L., *Kielmeyera coriacea* Mart, *Levisticum officinale* Koch, *Melia dubia* Cav, *Memecylon umbellatum* Burm.f., *P. odoratum* (Mill.) Druce, *Pouteria ramiflora* (Mart.) Radlk, *P. granatum* L., *Rhus coriaria* L., *Salvia acetabulosa* L., *S. cumini* (L.) Skeels., *V. arctostaphylos* L., *V. negundo* L., *Zhumeria majdae* Rech. f., *Z. spina-christi* (L.) Willd., and *Z. album* L.

Digestion of starch was inhibited by *A. adscendens* Buch. Ham. ex Roxb., *T. stans* (L.) Kunth., *T. bellerica* (Gaertn) Roxb and *Phyllanthus emblica* Linn. (inhibited disaccharidases). *T. foenum-graecum* L. inhibited α-amylase and maltase; *Eruca sativa* Mill. inhibited α-glucosidase, α-amylase, and galactosidase (see Table 3.1).

3.2.8 Inhibition of Glucose Absorption from the Intestine

The sodium-linked glucose transporter system works actively in the intestine. This is involved in the absorption of glucose from the intestine. Inhibition of this transport system will reduce glucose absorption from the intestine. However, absorption of glucose depends on the availability of glucose in the intestinal tract. This is determined by the conversion of carbohydrates into monosaccharides by the enzymes mentioned above. These two events are not separated in some of the studies. Plants reported as inhibitors of glucose absorption include *Abroma augusta* L. f., *A. indicum* (L.), *Allium porrum* L. (both), *A. racemosus* Willd., *E. globulus* Labill, *C. arabica* L., *G. sylvestre* R. Br., *Hunteria umbellata* K.Schum.Hallier f., *Ipomoea aquatica* Forsk, *Kochia scoparia* (L.) Schrad., *M. indica* L., *M. charantia* L., *Myrtus communis* L., *Orthosiphon aristatus* (Blume) Miq., *P. ginseng* C.A.Meyer, *P. frutescens* (L.) Britton, *P. emblica* Linn., *Piper sarmentosum* Roxb., *Polygala senega* L. var. latifolia Torry et Gray (inhibition of glucose transporter activity), *Rhododendron tomentosum* Harmaja (inhibition of glucose trasnsporter expression and transport), *R. graveolens* L., *S. lavandifolia* Vahl, *S. teteragonum* DC, and *T. hirsuta* L.Endl (see Table 3.1). The extracts of *R. tomentosum* Harmaja inhibited glucose uptake by intestinal cells *in vitro*; it decreased the expression of sodium-dependent GLUT1 (Eid and Haddad 2014).

3.2.9 Inhibition of Glucose Reabsorption in the Kidney

The kidney reabsorbs glucose from the urine. Generally, the quantity of glucose filtered by kidney does not exceed the kidneys' threshold to reabsorb it and thus little glucose appears in urine. Sodium–glucose cotransporter-2 present in the kidney is involved in this reabsorption (Kahn et al. 2014). The drugs that inhibit glucose reabsorption could lower blood glucose levels. Anti-DM plants that inhibit sodium–glucose cotransporter-2 in the kidney include *Alstonia macrophylla* Wall & G. Don, *C. cyminum* L., *Fraxinus excelsior* L., and *Lepidium sativum* L. (Table 3.1).

3.2.10 Inhibition of Aldose Reductase Activity

High concentrations of glucose in blood in diabetic patients result in several complications including diabetic cataract. The enzyme aldose reductase is the first enzyme of the polyol pathway that converts excess D-glucose into D-sorbital with concomitant conversion of nicotinamide adenine dinucleotide phosphate (NADPH) into NADP+ (Patel and Mishra 2009). Experiments on animals have shown that aldose reductase inhibitors can prevent the development of cataract and certain other secondary complications of diabetes. Therefore, these inhibitors can be used to retard or prevent the development of diabetic cataract in combination therapy. Plants reported to have aldose reductase inhibitory activity include *B. orellana* L., *Boswellia serrata* Roxb. ex Colebr., *B. officinalis* Maxim., *C. asiatica* (L.) Urban, *C. chinensis* Franch, *Coptis japonica* (Thunb.) Makino, *Dendrobium nobile* Lindl, *E. alba* (L.) Hassk., *Eremophila alternifolia* R. Br., and *Eremophila longifolia* (R.Br.) F.Muell, *G. uralensis* Fisch., *M. multiflora* DC, *Myrciaria dubia* Mc Vaaugh, *Ocimum gratissimum* L., *Ocimum sanctum* L., *P. frutescens* (L.) Britton, *P. emblica* Linn., *Potentilla fulgens* Wall. ex Hook., *Poupartia birrea* (Hochst) Aubr., *P. vulgaris* L., *P. granatum* L., *Salacia chinensis* L., *S. oblonga* Wall. ex Wight. & Arn., *S. miltiorrhiza* Bunge, *S. malaccense* (L) Merr. & Perr, and *Z. mays* L. (see Table 3.1).

3.2.11 Other Mechanisms

Another important mechanism of action is the modulation of immune reactions. For example, butanol fraction from whole plant and cytopiloyne and other polyynes isolated from *Bidens pilosa* L. prevented type 1 DM development in mice by immune modulation (inhibition of T-cell differentiation, downregulation of Th1, upregulation of Th2 cells, reduced invasion of CD4+ T cells into β-cells) mediated protection of β-cells. Cytopiloyne protected against islet atrophy and increased insulin levels; it suppressed hunger in type 2 DM and thus showed anti-type 2 DM activity (Yang 2014). Water extract of the flower of *Inula britannica* L. inhibited interferon gamma (IFN-γ) production from stimulated splenic T lymphocytes (Kobayashi et al. 2002). There are many such plants, which modulate immune system specifically. Such plants are promising, among other things, to delay or prevent the development of type 1 DM in genetically type 1 DM prone individuals.

Other mechanisms of action include the inhibition of insulin degradation, cortisol-lowering activities, and so on. When catecholamines bind the β-receptors, glycogen breakdown and production of glucose is induced. Epinephrine (adrenaline) induces glycogenolysis in the liver and skeletal muscle and an increase in circulating free fatty acid levels by stimulating lipolysis. Clausena coumarine from leaves of *C. lansium* (Lour.) Skeels antagonized the elevation of blood glucose caused by adrenaline in normal mice (Shen et al. 1989). Water extract of leaf of *A. indica* A. Juss abrogated the inhibitory effect of serotonin and epinephrine on insulin secretion mediated by glucose (Chattopadhyay 1999). Methanol extract of *I. racemosa* Hook root lowered corticosteroid concentration in humans (Gholap and Kar 2005).

Activation of farnesoid X-receptor results in the release of fibroblast growth factor 19 (FGF-19), which has insulin-like actions and insulin-sensitizing properties (Kingwell 2014; Xu et al. 2014). Furthermore, when bile acids bind farnesoid X-receptor in L-cells GLP-1 secretion from the cells increase (Kahn et al. 2014). Kaempferol-3-O- β-D-glucopyranoside from *C. alternifolia* L.f. (leaf) activated liver farnesoid X-receptor (Wang et al. 2014). Fruit of *Morinda citrifolia* L. regulated glucose metabolism via forkhead transcription factor 1 (FOXO1) in high-fat-diet-induced obese diabetic mice (Nerurkar et al. 2012). Breviscapine (a flavonoid) from *Erigeron breviscapus* (Vaniot) Hand attenuated renal injury in the

diabetic rats by suppressing oxidative stress and protein kinase C (PKC) activities as well as overexpression of transforming growth factor-β1 (TGF-β1) in renal tissue (Xu et al. 2013).

Plant products are also known to inhibit advanced glycation end products formation in *in vitro* and *in vivo* conditions and reduce complications of diabetes. For example, erigeroflavanone from the flowers of *Erigeron annuus* (L.) Pers inhibited advanced glycation end products formation and rat lens aldose reductase activity (Yoo et al. 2008). Alcohol extract of *Lawsonia intermis* L. leaf containing lawsone and gallic acid inhibited advanced glycation end products (AGEs) formation (Sultana et al. 2009).

Plants may have molecules that inhibit key enzymes involved in carbohydrate and other metabolism. Severe inhibition of key enzymes can lead to toxicity including extreme hypoglycemia. For example, hypoglycin A from unripe fruit and hypoglycin B from seeds (unusual amino acids) of *Blighia sapida* Koenig are toxic compounds. The injection of hypoglycin A forms a metabolite called methylene cyclopropane acetyl CoA that inhibits several enzymes, which are essential for metabolism of lipids, gluconeogenesis, and so on. This toxin induces hypoglycemia, depletion of glucose reserves, and inability of cells to regenerate glucose (Atolani et al. 2009). These compounds are attractive materials for the modification of structure and synthetic transformation leading to possible and novel anti-DM molecules.

3.3 Plants with Multiple Mechanisms of Action

Most of the anti-DM mechanical studies were carried out using extracts/active fractions and, in limited cases, using pure isolated compounds. The additive, synergistic, and antagonistic effects of various combinations of active principles acting via different mechanisms are of interest. It is of interest to note that some of the important anti-DM plants studied for their mechanisms of action exhibit multiple anti-DM principles and mechanisms of action. In these cases, the active principles present in the same plant directly or indirectly influence several or a few crucial molecules involved in metabolism, glucose metabolism, in particular. Plants that act on multiple target molecules in DM include *C. cassia, C. verum, C. longa, G. uralensis, G. sylvestre, I. batatas, M. indica, M. charantia, P. ginseng, T. bellerica, T. foenum-graecum*, and *V. vinifera*. Some of the active molecules isolated from anti-DM plants also show more than one mechanism of actions.

3.3.1 *Cinnamomum verum* J.S. Presl.

Cinnamon, used as a common spice, is obtained from the inner bark of trees from the genus *Cinnamomum*. *Cinnamomum verum* and *C. cassia* (Nees & T. Nee) J.Presl are two important anti-DM plants. *In vitro* and *in vivo* experiments suggest multiple mechanisms of action of these plants as shown in Figure 3.2. Cinnamon inhibited intestinal glucose absorption *in vitro* by inhibiting the activity of enzymes involved in carbohydrate metabolism (pancreatic α-amylase and α-glucosidase); it stimulated cellular glucose uptake by translocation of GLUT4 to the membrane. Furthermore, cinnamom inhibited gluconeogenesis by influencing key regulatory enzymes involved in gluconeogenesis. Besides, cinnamom stimulated insulin secretion and potentiated insulin signaling. Cinnamtannin B1 was identified as the potential active compound responsible for these effects (Bandara et al. 2012; Ranasinghe et al. 2012). The *in vivo* effects of *Cinnamomum* bark include the attenuation of weight loss associated with diabetes, the reduction of fasting blood glucose levels in diabetic animals, reduction in low-density lipoprotein (LDL) levels and increase in HDL cholesterol, reduction in the levels of HbA1c, and increase in the levels of insulin in blood. In addition, cinnamon showed beneficial effects against diabetic neuropathy and nephropathy. Besides, cinnamon reduced total cholesterol, LDL cholesterol, and triglycerides while increasing HDL cholesterol in diabetic rats (Mhammad et al. 2015).

Methylhydroxychalcone polymer from *Cinnamomum* sp. was found to be an effective mimetic of insulin in 3T3-LI adipocytes. This compound may be useful in the treatment of insulin resistance and in the study of the pathways leading to glucose utilization in cells (Jarvill-Taylor et al. 2001).

Water-soluble polyphenol type A polymers isolated from cinnamon increased insulin-dependent *in vitro* glucose metabolism roughly 20-fold and displayed antioxidant activity (Anderson et al. 2004). Thus, cinnamom exhibits multiple mechanisms of action. It is predicted that cinnamtannin B,

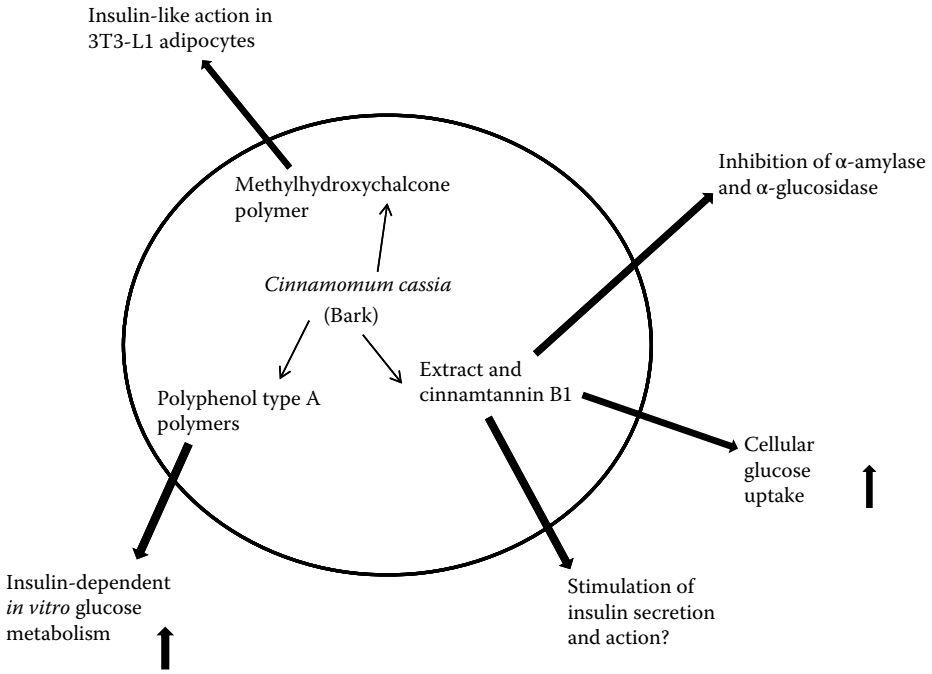

FIGURE 3.2 Likely mechanisms of actions of *Cinnamomum verum*.

methylhydroxychalcone, polyphenol type A molecules, and other compounds present in cinnamom may be involved in bring about multiple effects observed in the experimental studies.

3.3.2 *Curcuma longa* L.

Hypoglycemic and anti-diabetes properties of the rhizome of *C. longa* have been reported. The multiple actions of turmeric (*C. longa* rhizome) are shown in Figure 3.3. Active principles such as curcumin, demethoxycurcumin, sesquiterpenoids, bisdemethoxycurcumin, and arturmerone act via stimulation of PPAR-γ (Arun and Nalini 2002; Kuroda et al. 2005; Nishiyama et al. 2005). Curcumin, the principal constituent of the rhizomes of *C. longa*, was found to inhibit PTP1B also. The compound improved insulin and leptin sensitivity in the liver of rats; it prevented triglyceride accumulation and hepatic steatosis in fructose-fed rats (Li et al. 2010). Turmeric volatile oils inhibited α-glucosidase enzymes more effectively than the reference standard drug acarbose. Drying of rhizomes was found to enhance α-glucosidase and α-amylase inhibitory capacities of volatile oils. Arturmerone, the major volatile component in the rhizome, also showed potent α-glucosidase (IC_{50}: 0.28 μg/mL) and α-amylase (IC_{50}: 24.5 μg/mL) inhibition (Lekshmi et al. 2012). Furthermore, curcumin can prevent some of the diabetic complications such as cardiomyopathy and nephropathy primarily due to its antioxidant and anti-inflammatory properties. Curcumin (150 mg/kg, p.o. [by mouth]) prevented diabetic nephrophathy in streptozotocin-induced diabetic rats by inhibiting the activation of Sphk1-S1P-signaling pathway (Huang et al. 2013).

3.3.3 *Glycyrrhiza uralensis* Fisch.

The multiple actions of this plant are shown in Figure 3.4. The anti-diabetic effects and mechanisms of action of raw *G. uralensis* and roasted *G. uralensis* extracts and their major components, glycyrrhizin and glycyrrhetinic acid, were examined. In partial pancreatectomized diabetic mice, both raw and roasted *G. uralensis* extracts improved glucose tolerance but only the roasted extract enhanced glucose-stimulated insulin secretion. Extracts from both roasted and raw *G. uralensis* enhanced insulin-stimulated

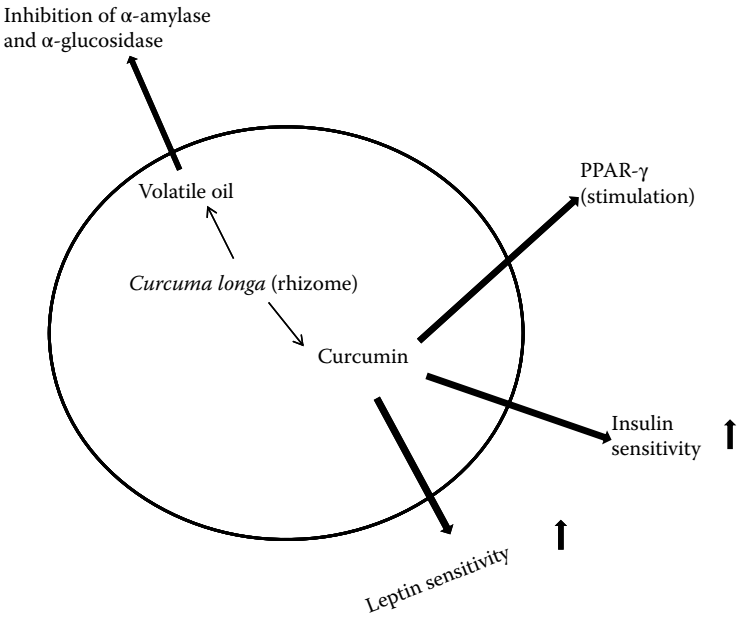

FIGURE 3.3 Likely mechanisms of actions of *Curcuma longa*.

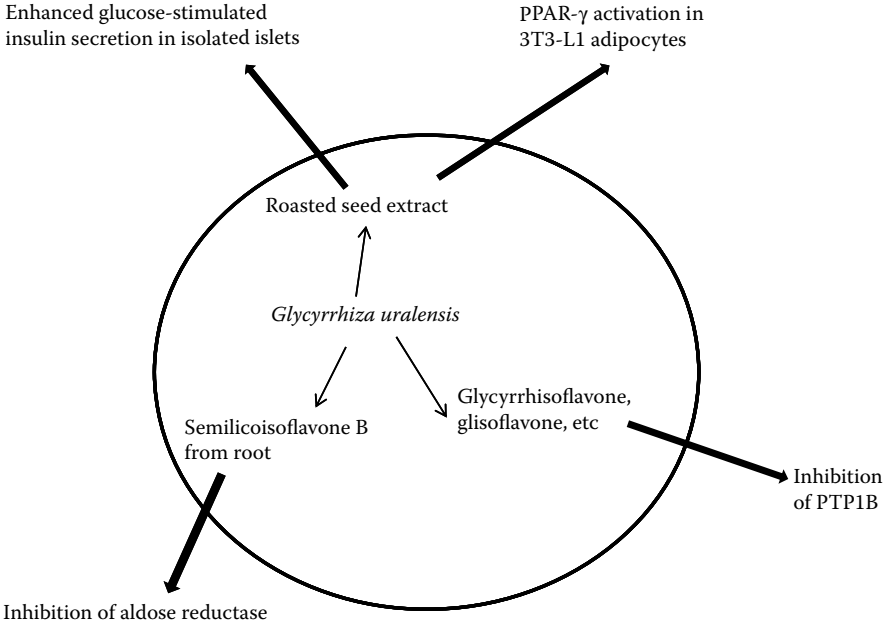

FIGURE 3.4 Likely mechanisms of actions of *Glycyrrhiza uralensis*. PTP1B, protein-tyrosine phosphatase 1B.

glucose uptake through PPAR-γ activation in 3T3-L1 adipocytes. Consistently, only extract from roasted *G. uralensis* and glycyrrhetinic acid enhanced glucose-stimulated insulin secretion from isolated islets. In addition, they induced mRNA levels of IRS2, pancreas duodenum homeobox-1, and glucokinase in the islets, which contributed to improving β-cell viability. Roasted *G. uralensis* extract containing glycyrrhetinic acid improved glucose tolerance better than raw *G. uralensis* extract by enhancing insulinotropic action (Ko et al. 2007). The inhibitory effects of 10 components from the root of *G. uralensis* on aldose

reductase and sorbitol formation in rat lenses with high levels of glucose were investigated. Of the compounds tested, semilicoisoflavone B showed the most potent inhibition with the half maximal inhibitory concentration (IC_{50}) values of 1.8 and 10.6 μM for rat lens aldose reductase and human recombinant aldose reductase, respectively. It showed noncompetitive inhibition against rat lens aldose reductase. Furthermore, semilicoisoflavone B inhibited sorbitol formation of rat lens incubated with a high concentration of glucose, indicating that this compound may be effective for preventing osmotic stress in hyperglycemia (Lee et al. 2010). PTP1B inhibitors, glycyrrhisoflavone, glisoflavone, and licoflavone A were isolated from the roots of *G. uralensis*. Besides, 2-arylbenzofuran glycybenzofuran and licocoumaron isolated from the roots also inhibited PTP1B (Jiang et al. 2012).

3.3.4 *Gymnema sylvestre* R. Br.

The indicated mechanisms of action of *G. sylvestre* leaf are shown in Figure 3.5. Gymnemic acids, a mixture of triterpene glycosides extracted from the leaves of *G. sylvestre*, inhibited the intestinal absorption of glucose in human and rats (Tiwari et al. 2014). In another study, gymnemoside b and gymnemic acids III, V, and VII were found to inhibit glucose absorption from the intestine (Yoshikawa et al. 1997).

A crude saponin fraction derived from the methanol extract of leaves of *G. sylvestre* reduced blood glucose levels after intraperitonal administration to streptozotocin diabetic mice. Gymnemic acid IV was found to be the major active principle that at doses of 3.4–13.4 mg/kg reduced the blood glucose levels by 13.5–60% 6 h after the administration comparable to the potency of glibenclamide and did not change the blood glucose levels of normal rats. This compound (13.4 mg/kg) increased the levels of plasma insulin in the diabetic mice. Furthermore, it stimulated insulin secretion from isolated human islets of Langerhans (Ghorbani et al. 2013). The stimulatory effects of *G. sylvestre* leaf on insulin release have been reported (Persaud et al. 1999).

The likely mechanisms of action of *G. sylvestre* leaf extracts include promotion of regeneration of islet cells and stimulation of insulin secretion from β-cells. The leaf extracts activated enzymes responsible for utilization of glucose by insulin-dependent pathways. The extracts also modulated incretin activity, which triggers insulin secretion (Porchezhian and Dobriyal 2003; Tiwari et al. 2014). A novel dihydroxy gymnemic triacetate (5–20 mg/kg) isolated from the leaves of *G. sylvestre* showed normoglycemic and hypolipidemic activities in streptozotocin diabetic rats (Daisy et al. 2009b).

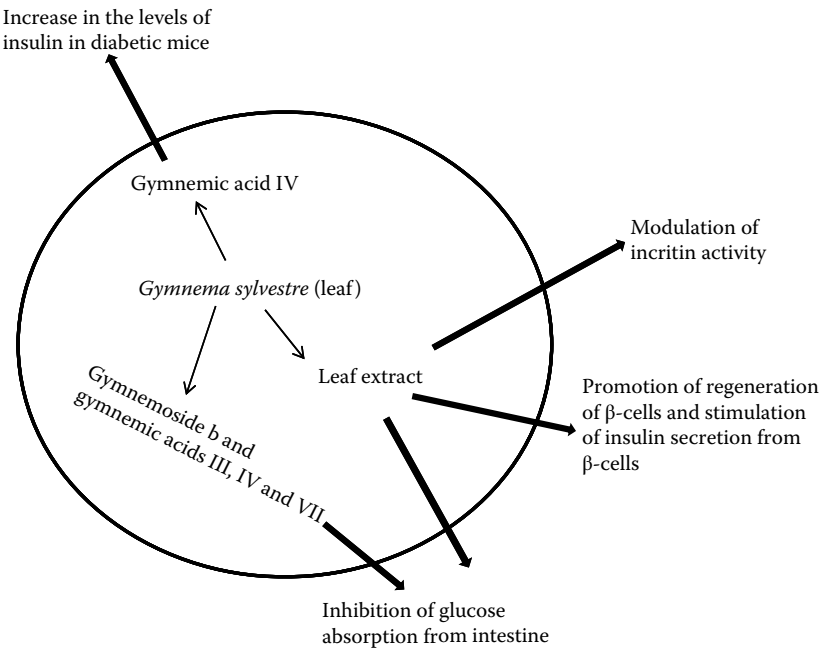

FIGURE 3.5 Likely mechanisms of actions of *Gymnema sylvestre*.

In clinical trials, *G. sylvestre* showed promise in improving blood sugar homeostasis and regeneration of pancreas (Ghorbani 2013).

3.3.5 *Ipomoea batatas* L.

Ipomoea batatas tuber is an important anti-DM food medicine. This plant showed multiple mechanisms of action as shown in Figure 3.6. White-skinned sweet potato showed remarkable anti-DM activity in Zucker fatty rats and it improved the abnormality of glucose and lipid metabolism by reducing insulin resistance (Kusano and Abe 2000). Furthermore, the potato has been shown to have hypoglycemic activity in streptozotocin diabetic rats and it increased blood insulin levels. The active component was a high molecular weight glycol–protein found mainly in the cortex of the tuber (Kusano et al. 2001). In the streptozotocin-diabetic rats also, the sweet potato treatment (flour suspension, 100–800 mg/kg) resulted in a dose-dependent marked decrease in blood glucose levels, an increase in the number of pancreatic β-cells, and an increase in the expression of insulin (Royhan et al. 2009). Thus, sweet potato induces the regeneration of pancreatic β-cells and increases insulin expression.

Studies suggest that hypoglycemic effects of *I. batatas* result from the suppression of oxidative stress and proinflammatory cytokine production followed by improvement of pancreatic β-cells mass (Bachri et al. 2010). Powdered sweet potato (5 g/kg, p.o. for 2 months) increased serum insulin levels, and improved oral glucose tolerance and body weight in the streptozotocin-diabetic rats. Moreover, the treatment reduced superoxide production from leukocytes and vascular homogenates, serum 8-oxo-2′-deoxyguanosine, and vascular nitrotyrosine formation of diabetic rats to comparable levels of normal control animals. Stress- and inflammation-related p38 mitogen-activated protein kinase activity and tumor necrosis factor-α (TNF-α) production of diabetic rats were significantly depressed by *I. batatas* administration. Histological examination also exhibited improvement of pancreatic β-cells mass after the treatment (Niwa et al. 2011).

An arabinogalactan–protein isolated from white-skinned sweet potato decreased plasma glucose levels and improved glucose tolerance and insulin sensitivity in spontaneously diabetic db/db mice. This suggests that amelioration of insulin resistance by the arabinogalactan–protein leads to its hypoglycemic effects (Oki et al. 2011). In this connection, it should be noted that *I. batatas* peel proteins are susceptible to digestive enzymes to a considerable extent (Maloney et al. 2014).

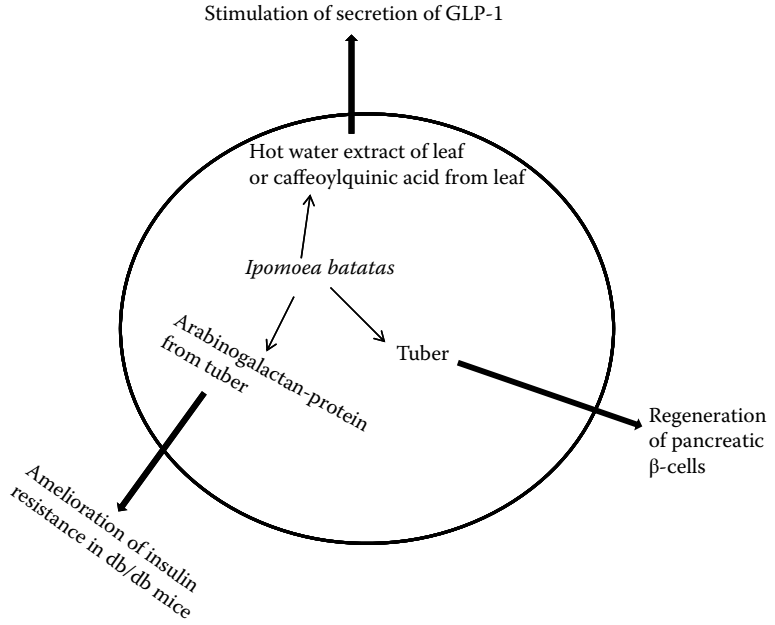

FIGURE 3.6 Likely mechanisms of actions of *Ipomoea batatas*.

The ethyl acetate fraction from leaves of sweet potato accelerated hexokinase activity stimulated insulin secretion and inhibited gluconeogenesis enzymatic activity (glucose-6-phosphatase) in streptozotocin diabetic rats (Lien et al. 2011). Administration of flavone extract from *I. batata* leaf (50 mg/kg; daily for 2 weeks) to rats with noninsulin-dependent DM resulted in a significant decrease in the concentration of plasma triglyceride, cholesterol, LDL, fasting glucose levels, and malondialdehyde levels in the diabetic rats; the treatment increased the insulin sensitive index and superoxide dismutase level in the diabetic rats (Zhao et al. 2007). In alloxan-induced diabetic rats also hot water extract of leaf at a dose of 300 mg/kg produced the best hypoglycemic effect (69.67%) in the diabetic rats (Ijaola et al. 2014).

Interestingly, a recent report indicated that sweet potato leaf (edible) extract attenuated hyperglycemia by enhancing the secretion of GLP-1. In an *in vitro* study, the extract and polyphenols such as caffeoylquinic acid present in the leaf enhanced GLP-1 secretion. Furthermore, administration of the extract to rats resulted in stimulation of GLP-1 secretion and enhanced insulin secretion (Nagamine et al. 2014).

A placebo-controlled, randomized, and double-blinded clinical study confirmed the beneficial effects of an extract of white sweet potato on plasma glucose as well as cholesterol levels in patients with type 2 diabetes (Ludvik et al. 2004).

3.3.6 *Mangifera indica* L.

The multiple mechanisms of action of this plant are shown in Figure 3.7. The ethanol extracts of stem barks reduced glucose absorption from the intestine in type 2 diabetic rats. Potent therapeutically promising anti-DM activity of the methanol extract of bark and leaves was shown in type 1 and type 2 diabetic rats (Bhoumik et al. 2009). *Mangifera indica* (methanol extract) exhibited dipeptidyl peptidase-4 inhibitory activity (Yogisha and Raveesha 2010).

The predominant anti-diabetes constituent of the extract of the mango plant is mangiferin. Experiments demonstrate that mangiferin isolated from the plant leaves possess significant anti-diabetic properties (Muruganandan et al. 2005). Mangiferin from the leaves prevented diabetic nephropathy progression in streptozotocin-diabetic rats (Li et al. 2010b). Recent studies shed light on the likely emergence of this compound as a very important molecule in mediating insulin sensitivity and modulating lipid metabolism (Mirza et al. 2013). 1,2,3,4,6-Penta-O-galloyl-β-D-glucose isolated from *M. indica* inhibited 11-β-hydroxysteroid dehydrogenase (HSD)-1 and ameliorated high-fat-diet-induced diabetes in C57BL/6 mice (Mohan et al. 2013). Anti-diabetic compounds 6-O-galloyl-5-hydroxy mangiferin, mangiferin, 5-hydroxy mangiferin, and methyl gallate were isolated from the kernel of *M. indica*. (The known major mechanisms actions of these compounds are described under Chapter 2.)

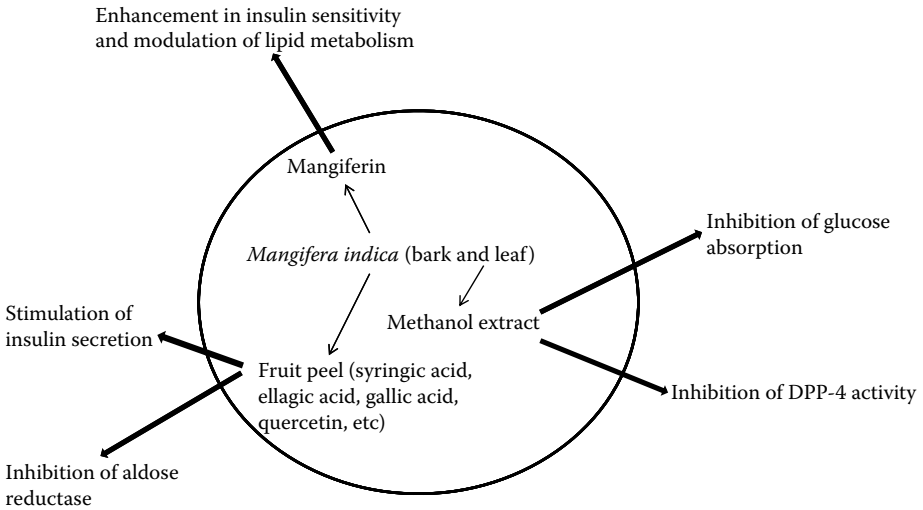

FIGURE 3.7 Likely mechanisms of actions of *Mangifera indica*. DPP-4, dipeptidyl peptidase-4.

Mango fruit peel supplementation resulted in remarkable anti-diabetic effects in streptozotocin-induced diabetic rats. In a recent study, mango fruit peel (5% and 10% levels in basal diet) ameliorated streptozotocin-induced increase in urine sugar, urine volume, fasting blood glucose, total cholesterol, LDL, triglycerides, and decrease in HDL in the rats. Besides, the treatment increased antioxidant enzyme activities and decreased lipid peroxidation in plasma, kidney, and liver in the streptozotocin-diabetic rats compared to untreated diabetic rats (Gondi et al. 2015). Phenolic compounds identified in the raw and ripe mango peel include gallic acid, syringic acid, mangiferin, ellagic acid, gentisyl–protocatechuic acid, and quercetin (Ajila et al. 2010). It is of interest to note that these compounds are known anti-diabetic agents. Mangiferin exerts its anti-diabetic activity through multiple mechanisms, including the modulation of insulin sensitivity and lipid metabolism. Syringic acid from *D. nobile* prevented diabetic cataract pathogenesis by inhibiting aldose reductase (Wei et al. 2012); syringin from *E. senticosus* was reported to augment insulin release from the β-cells (Liu et al. 2008). Quercetin and quercetin glycosides from *Eucommia almoidea* inhibited AGEs formation (Kim et al. 2004). Quercetin from *M. multiflora* inhibited aldose reductase. In addition, quercetin effectively blocked polyol accumulation in intact rat lenses incubated in medium containing high concentration of sugars (Varma et al. 1975). Quercetin glycosides from *B. forficata* were reported to inhibit intact microsomal glucose-6-phosphatase and activate insulin-signaling pathways (Estrada et al. 2005). Ellagic acid from *M. dubia* inhibited aldose reductase (Ueda et al. 2004). Gallic acid isolated from *Terminalia* species stimulated insulin secretion (insulin secretagogue) (Latha and Daisy 2011). Thus, mango peel (nutraceutical) exerts its anti-DM activity via multiple mechanisms.

3.3.7 *Momordica charantia* L.

More than one active principle and mechanism of actions are involved in the anti-diabetic property of *M. charantia*. Important mechanisms of action are projected in Figure 3.8. Like sulfonyl urea drugs, the water extract of the fruit stimulated β-cells to release or secrete more insulin, and viable β-cells may be required for its action (Ahmed et al. 1998; Karunanayake et al. 1990). It is known to protect and stimulate β-cells in streptozotocin-challenged rats (Ahmed et al. 1998; Sitasawad et al. 2000). The presence of molecules with insulin-like bioactivity in *M. charantia* seeds has been reported (Ng et al. 1987a). A hypoglycemic polypeptide has been isolated from the fruit and it is described as plant insulin (Khanna

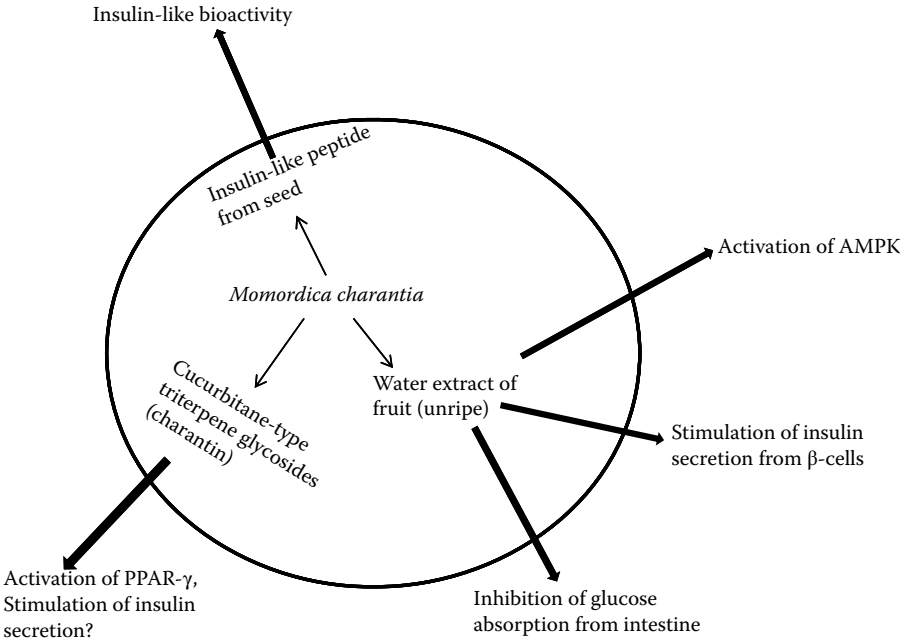

FIGURE 3.8 Likely mechanisms of actions of *Momordica charantia*.

et al. 1981; Sheng et al. 2004). The plant insulin may act in the absence of β-cells. However, the protein's action in the oral route is not explained and its heat sensitivity is not studied in detail.

It is also reported that the fruit inhibited glucose absorption from the intestine. This activity is attributed to some other active principles. Fruit juice (10 mg/kg, p.o., for 30 days) produced significant lowering of blood sugar level in alloxan-induced diabetic rabbits. Alkaloids like charantin (50 mg/kg, p.o.) produced marked lowering of blood glucose on normal fasting rabbits. In addition to charantin, several triterpenoids (cucurbitan-type triterpenoids in fruits, including momordicine and momordicosides) and conjugated linolenic acid (a fatty acid found in high concentrations in the seeds), which improved insulin resistance have been isolated from the fruit and stem of this plant and some of them stimulated AMPK activity; this also contributes to hypoglycemic activity (Joseph and Jini 2013). Momordicine 1 and momordicine 2 stimulated insulin secretion in MIN6 β-cells (Firdous 2014). Recently, a new cucurbitacin, 5β,19-epoxycucurbit-23-en-7-on-3β,25-diol and three already known cucurbitacins showed concentration-dependent inhibition of glucose production from liver cells (Chan et al. 2015).

Other effects of *M. charantia* fruit observed include suppression of key gluconeogenic enzymes, stimulation of key enzymes of hexose monophosphate (HMP) pathway and preservation of islet cells and their functions. Studies also indicate the involvement of mechanisms such as stimulation of PPAR-α and PPAR-γ. Cucurbitane-type triterpene glycosides activated PPAR-γ. These receptors are known to mitigate insulin resistance (Joseph and Jini 2013; Wang et al. 2014). Thus, the mechanisms of action of *M. charantia* include insulin-like action, activation of AMPK, stimulation of PPAR-γ, and inhibition of sugar absorption from the intestine. Clinical studies show efficacy and safety of bitter gourd (Subramoniam 2016).

3.3.8 *Panax ginseng* C.A. Meyer

Multiple mechanisms of action and several compounds are involved in the action of ginseng on the metabolic syndrome. Important mechanisms of actions of ginseng extracts and isolated compounds are shown in Figure 3.9. Some compounds in the plants have even opposing effects. Furthermore, the optimum dose required and the combinations of compounds present in the preparation or extract or fraction are important in exerting its specific anti-diabetic effects.

The anti-diabetic effect of ginseng berry extract was shown in obese-diabetic mice. Administration of the extract (150 mg/kg; 12 days) resulted in decrease in blood glucose and insulin levels and improvement in glucose (i.p.) tolerance. A hyperinsulinemic–euglycemic clamp study revealed a more than two-fold increase in the rate of insulin-stimulated glucose disposal in treated ob/ob mice. Treatment with the extract also significantly reduced plasma cholesterol levels and body weight in ob/ob mice. Additional studies demonstrated that ginsenoside Re plays a significant role in antihyperglycemic action. This anti-diabetic effect of ginsenoside Re was not associated with body weight changes, suggesting that other constituents in the extract have distinct pharmacological mechanisms on energy metabolism (Attele et al. 2002). In another study, the antioxidant and antihyperlipidemic efficacies of ginsenoside Re were shown in streptozotocin-diabetic rats. In addition to lowering glucose and lipid levels, ginsenoside Re decreased the levels of TNF and IL-6 involved in inflammation (El-Khayat et al. 2011). A study suggests that the compound can protect the diabetic rats from oxidative stress-mediated microvasculopathy in the eye, kidney, and so on (Cho et al. 2006). Ginsenoside Re exhibited anti-diabetic activity by reducing insulin resistance and increasing the expression of PPAR-γ and its responsive genes and inhibition of TNF-α production in 3T3-L1 adipocytes (Gao et al. 2013). Malonyl ginsenosides, from the root of this plant, lowered fasting blood glucose level, improved insulin sensitivity, and improved lipid profile in high fat diet and streptozotocin-induced type 2 diabetic rats (Liu et al. 2013).

Improvement of insulin resistance by *P. ginseng* in fructose-rich chow-fed rats has been reported (Liu et al. 2005a). Panacene (a peptidoglycan from ginseng) exhibited hypoglycemic activity (Konno et al. 1984); a peptide with insulinomimetic properties has also been isolated (Ando et al. 1980).

Another study suggests that white ginseng (ginseng radix alba) can improve hyperglycemia in Kuo Kundo mice with obese Ay_{gene} (KKAy mice), possibly by blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase. The ginseng rootlet (ginseng radix palva) exhibited anti-DM activity through the upregulation of adipocytic PPAR-γ protein expression as well as inhibition of intestinal glucose absorption (Chung and Choi 2001). Another study reported that extract of dried root of *P. ginseng* improved

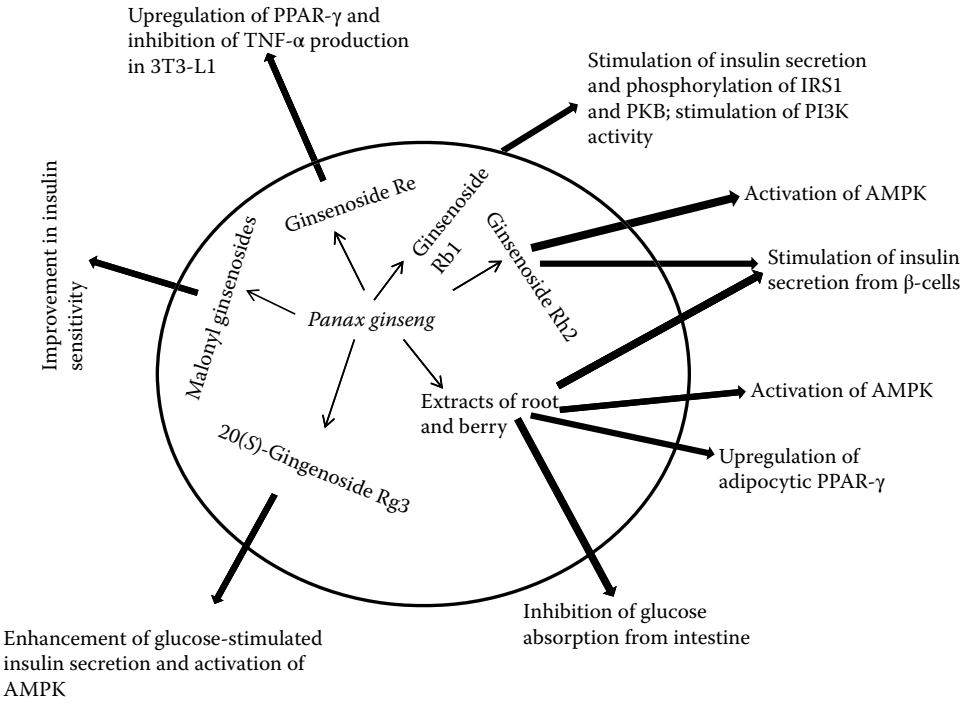

FIGURE 3.9 Likely mechanisms of actions of *Panax ginseng.* TNF-α, tumor necrosis factor-α.

glucose-stimulated insulin secretion and β-cell proliferation through IRS2 induction (Park et al. 2008). A study indicates that some ginseng fractions stimulated insulin release, especially glucose-induced insulin release from pancreatic islets (Kimura et al. 1981). Subsequent studies also confirmed the modulation of insulin secretion by ginseng. Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in Wister rats has been reported (Lee et al. 2006). Compound K (one of the ginsenosides) enhanced insulin secretion with beneficial metabolic effects in db/db mice (Kan et al. 2007). Korean red ginseng stimulated insulin release from isolated rat pancreatic islets (Kim and Kim 2008). Increase in acetylcholine release by *P. ginseng* root enhanced insulin secretion in rats (Su et al. 2007).

Ginsenoside Rh2 is one of the ginsenosides that exerts anti-diabetes, anti-inflammatory, and anti-cancer effects. In cell culture system, ginsenoside Rh2 effectively inhibited adipocyte differentiation via PPAR-γ inhibition. Interestingly, ginsenoside Rh2 significantly activated AMPK in 3T3-L1 adipocytes. Furthermore, ginsenoside Rh2 effectively induced lipolysis and this induction was abolished by AMPK inhibitor treatment (Hwang et al. 2007). Another study suggests that the antiobesity effect of red ginseng-rich constituent, ginsenoside Rg3 also involves the AMPK-signaling pathway and PPAR-γ inhibition (Hwang et al. 2009). In an *in vitro* study, 20(S)-gingenoside Rg3 enhanced glucose-stimulated insulin secretion and activated AMPK (Park et al. 2008a). In a recent review, the ginseng extracts and ginsenosides that activate AMPK and the various likely mechanisms of their action are discussed (Jeong et al. 2014).

In an *in vitro* study, ginsenoside Rb1 stimulated glucose uptake through insulin-like signaling pathway in 3T3-L1 adipocytes. Rb1 stimulated basal and insulin-mediated glucose uptake in a time- and dose-dependent manner in 3T3-L1 adipocytes and C2C12 myotubes; in adipocytes, Rb1 promoted GLUT1 and GLUT4 translocations to the cell surface. Rb1 increased the phosphorylation of IRS1 and PKB/Akt, and stimulated PI3K activity in the absence of the activation of the IR. Rb1-induced glucose uptake and GLUT1 and GLUT4 translocations were inhibited by the PI3K inhibitor (Shang et al. 2008).

PKA may also be involved in the anti-diabetes actions of ginseng. Gingenoside Rb1 and Rg1 suppressed triglyceride accumulation in 3T3-L1 adipocytes and enhanced β-cell insulin secretion and viability in MIN6 cells via PKA-dependent pathways (Park et al. 2008b).

Red ginseng (steam-treated *P. ginseng* root) has been clinically shown to have beneficial effects in type 2 DM and improved cardiovascular disease and other risk factors (Sotaniemi et al. 1995).

3.3.9 *Terminalia bellerica* (Gaertn) Roxb.

Terminalia bellerica is extensively used in Indian traditional systems of medicine to treat various diseases, including DM. The fruit appears to exert its anti-DM action via multiple mechanisms as shown in Figure 3.10. *T. bellerica* (decoction of dried fruits) stimulated the secretion and action of insulin and inhibited starch digestion and protein glycation *in vitro* (Kasabri et al. 2010). Gallic acid (5–20 mg/kg) isolated from the fruits of *T. bellerica* showed insulin-secretagogue and antihyperlipidemic effects in streptozotocin-induced diabetic rats (Latha and Daisy 2011). Gallotannins present in the fruits of this plant increased PPAR-α and PPAR-γ levels and stimulated glucose uptake without enhancing adipocyte differentiation (Yang et al. 2013).

Administration of *T. bellerica* fruit (hexane extract, 200 mg/kg; ethylacetate extract, 300 mg/kg; and methanol extract, 300 mg/kg) for 60 days to streptozotocin-induced diabetic rats resulted in the increase in the plasma insulin, C-peptide, and glucose tolerance levels compared to the diabetic control; the effect was more pronounced in methanol extract-treated rats. In addition, the plant extracts significantly increased body weight and serum total protein and significantly decreased the serum levels of total cholesterol, triglycerides, LDL cholesterol, urea, uric acid, and creatinine in the diabetic rats. The authors attribute these beneficial therapeutic effects of the fruits extracts to the synergistic action of more than one bioactive compound present in the extract (Latha and Daisy 2010).

3.3.10 *Trigonella foenum-graecum* L.

Trigonella foenum-graecum (fenugreek) seeds are used as spice in the preparation of various side dishes in India and elsewhere. Its regular consumption has been suggested to be beneficial in the management of diabetes and prevention of atherosclerosis and coronary heart disease (Patil and Jain 2014). Several human clinical studies have shown the usefulness of fenugreek seeds in the management of both type 1 and type 2 DM (Ghorbani 2013).

The major multiple mechanisms of actions of *T. foenum-graecum* are summarized in Figure 3.11.

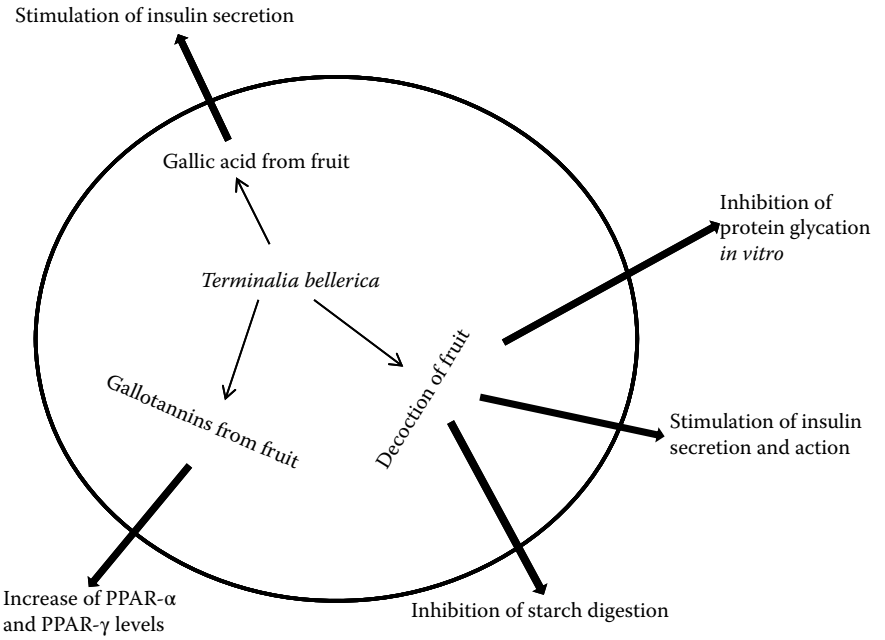

FIGURE 3.10 Likely mechanisms of actions of *Terminalia bellerica*. PPAR-α, peroxisome proliferator–activated receptor-α.

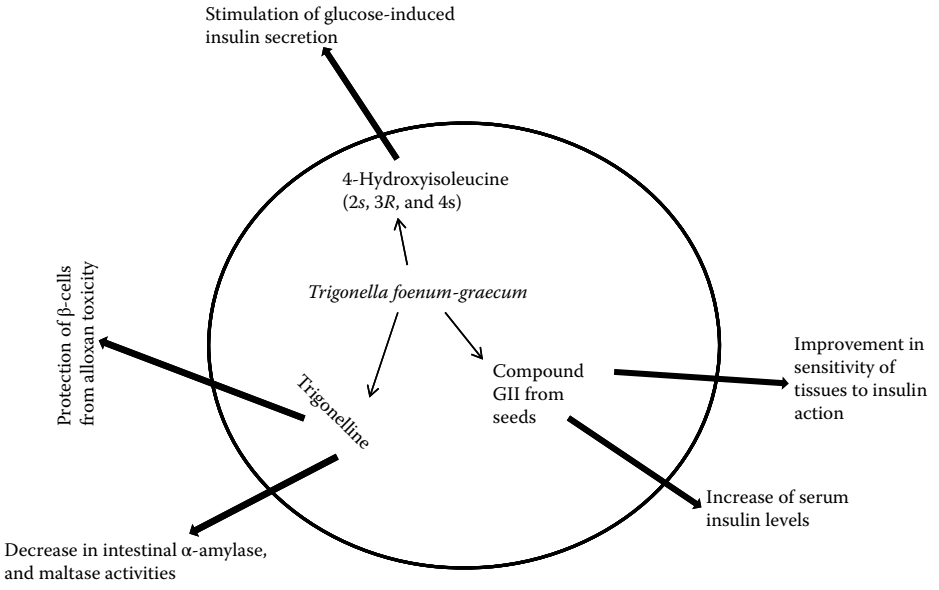

FIGURE 3.11 Likely mechanisms of actions of *Trigonella foenum-graecum*.

Fenugreek's major free amino acid 4-hydroxyisoleucine has been shown to stimulate insulin secretion from perfused pancreas *in vitro*. Fenugreek seeds contain 4-hydroxy isoleucine in two diastereoisomers: the major one being the (2S, 3R, and 4S) configuration and the minor one being the (2R, 3R, and 4S) configuration. The ability of the major isomer to stimulate glucose-induced insulin secretion in micromolar concentrations was shown (Sauvaire et al. 1998). The semisynthetic derivatives of this compound were reported to have more anti-diabetic activity than the parental compound (Sridevi et al. 2014).

Trigonelline is a major alkaloid present in fenugreek. The isolated pure trigonelline (10 mg/kg., twice a day, for 4 weeks) exhibited a significant hypoglycemic effect in normal and alloxan diabetic rabbits, but its effect was more in diabetic animals (Al-Khateeb et al. 2012). In another study, the administration of trigonelline to alloxan diabetic rats helped to protect β-cells from death and damage. Furthermore, trigonelline treatment decreased intestinal α-amylase, maltase, and lipase; the treatment resulted in decrease in blood glucose, cholesterol, and triglycerides in the diabetic rats. Trigonelline was also found to protect the liver and kidney functions of the diabetic rats efficiently (Hamden et al. 2013).

An unidentified antihyperglycemic compound named GII was purified from the water extract of the seeds of *T. foenum-graecum* and shown to be different from trigonelline isolated earlier from the same plant. GII (50 mg/kg, p.o.) reduced blood glucose in glucose tolerance test in the subdiabetic and moderately diabetic rabbits. Treatment for 7 days of the subdiabetic rabbits with GII (50 mg/kg, p.o.) improved glucose tolerance without reducing fasting blood glucose that was nearly normal (Moorthy et al. 2010a). Mechanism of action of GII (100 mg/kg, p.o. for 15 days) seeds was studied in the subdiabetic and moderately diabetic rabbits. GII seems to decrease lipid content of liver and stimulate the enzymes of glycolysis (except glucokinase) and inhibit enzymes of gluconeogenesis in the liver of the diabetic especially moderately diabetic rabbits (Moorthy et al. 2010b). In another study, the administration of GII (50 mg/kg for 15 days) to subdiabetic and moderately diabetic rabbits or (50 mg/kg for 30 days) to severe diabetic rabbits corrected or almost normalized the altered serum lipids, tissue lipids, liver glycogen, enzymes of glycolysis, glyconeogenesis, glycogen metabolism, polyol pathway, and antioxidant enzymes. Histopathological abnormalities seen in the pancreas, liver, heart, and kidneys were normalized by the treatment. The compound increased serum insulin levels, increased sensitivity of tissues to insulin action, and stimulated activity of enzymes of glucose utilization (Puri et al. 2011).

3.3.11 *Vitis vinifera* L.

The likely mechanisms of actions of *V. vinifera* (grape) are shown in Figure 3.12. Grape-skin extract inhibited α-glucosidase activity and suppressed postprandial glycemic response in streptozotocin-diabetic mice (Zhang et al. 2011). The extract activated the insulin-signaling cascade and reduced hyperglycemia in alloxan-induced diabetic mice. IR content and Akt phosphorylation were significantly greater in the extract-treated diabetic mice (gastrocnemius muscles) compared with the untreated alloxan-diabetic mice. Furthermore, the treatment improved the GLUT4 content. The extract treatment did not change glucose-induced insulin secretion in isolated pancreatic islets (Soares de Moura et al. 2012). Ellagic acid and epicatechin gallate (flavonoids present in grapes) activated PPAR-γ (Wang et al. 2014). Grape seed extract could play a role in the management of peripheral neuropathy, similar to other antioxidants known to be beneficial for diabetic peripheral neuropathy (Jin et al. 2013). Anti-Diabetes and antioxidant activities of this plant leaf (ethanol extract; 250 mg/kg) in streptozotocin-diabetic rats have been reported (Sendogdu et al. 2006).

3.3.12 Compound with Multiple Mechanisms

There are anti-DM phytochemicals that act through more than one mechanism. Compounds such as berberine, chlorogenic acid, and curcumin act through multiple mechanisms. As an example, the multiple actions of berberine are shown in Figure 3.13. Berberine improved insulin action by activating AMPK, inhibiting PTP1B activity and increasing phosphorylation of IR, IRS1, and Akt in 3T3-L1 adipocytes (Arif et al. 2014). Berberine mimicked insulin action by increasing glucose uptake by 3T3-L1 adipocytes and L6 myocytes in an insulin-independent manner. It increased GLP-1 secretion in streptozotocin-diabetic rats, which is dependent on PKC or AMPK. Some signaling pathways including PKC-dependent pathways are involved in promoting GLP-1 secretion and biosynthesis (Yu et al. 2010b). Furthermore, berberine was found to inhibit human recombinant DPP-4 *in vitro* (Almasri et al. 2009). Besides, berberine reduced the expression of the enzymes involved in fatty acid and cholesterol synthesis (Prabhakar and Doble 2011).

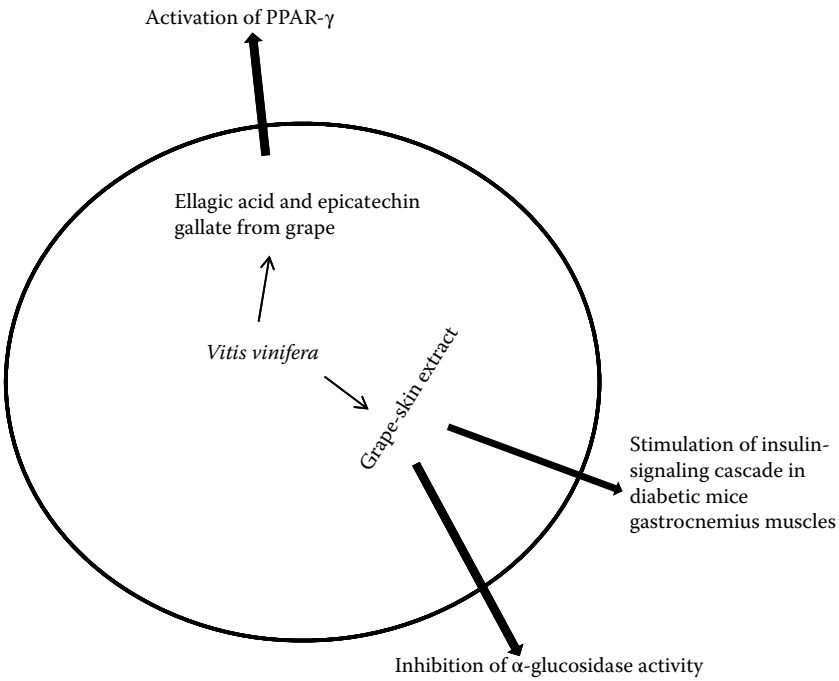

FIGURE 3.12 Likely mechanisms of actions of *Vitis vinifera*.

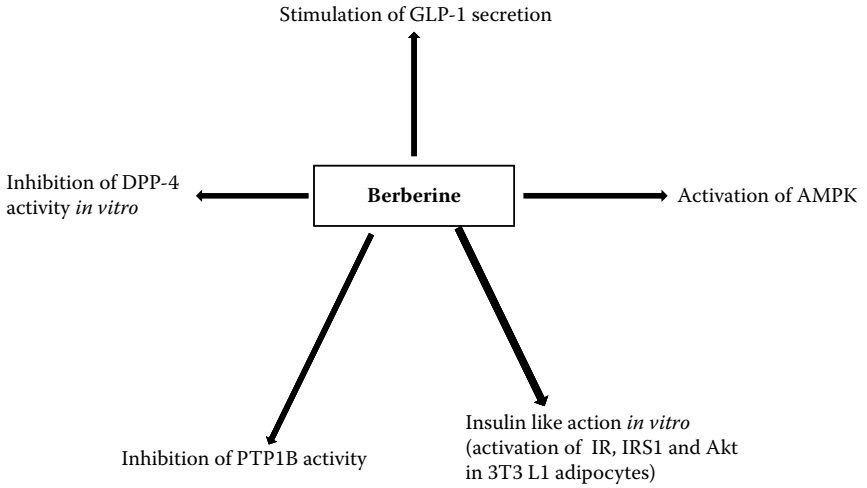

FIGURE 3.13 Multiple mechanisms of actions of berberine. Akt, protein kinase B; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; IR, insulin receptor; IRS1, insulin receptor substrate 1; PTP1B, protein-tyrosine phosphatase 1B.

3.4 Anti-DM Plants without Known Mechanisms of Action

Many plants (at least more than 40) with well-confirmed anti-diabetes activity based on experiments on animal models of DM remain to be studied to unravel their mechanisms of action. These include the following plants:

Acacia catechu (L. f.) Willd.
Ajuga iva L.
Allium cepa L.
Amaranthus viridis L.
Artemisia herba-alba Asso
Artocarpus heterophyllus Lam
Bauhinia tomentosa L.
Bridelia ferruginea Benth.
Butea monosperma (Lam) Taub.
Capparis deciduas (Forsk) Edgew.
Capparis spinosa L.
Caralluma adscendens var. attenuate (Wight) Grav. & Mayur.
Casearia esculenta L.
Cassia auriculata L.
Cassia fistula L.
Cassia kleinii W. & A.
Cassia occidentalis L.
Caylusea abyssinica (Fresen.) Fisch & C.A.Mey
Clerodendron phlomidis Linn.f., Syn: *C. multiflorum* (Burm. f.) O. Kuntze;
Costus speciosus (Koenig.) Sm. (specific mechanism not known)
Cucumis sativus L.
Enicostema hyssopifolium (Willd.) Verd. *Syn: E. littorale* Blume (check)

Ficus carica L., (known anti-DM compounds are there)
Ficus racemosa L. Moraceae, syn. *Ficus glomerata* Roxb.
Hemidesmus indicus (L.) R. Br.
Hemionitus arifolia (Burm.) Moore Hemionitidaceae
Hibiscus rosa-sinensis L.
Hintonia latiflora (Sesse & Moc.) Bullock.
Holarrhena antidysentrica (L.) Wall.
Hordeum vulgare L.
Murraya koenigii (Linn.) Spreng.
Olea europaea L.,
Panax quinquefolius L. (checked)
Phyllanthus amarus Schum & Thonn,
Prunus amygdalus Batsch.,
Smallanthus sonchifolius (Poepp. & Endl.) Robinson
Tectona grandis L.
Tephrosia purpuria (L.) Pers
Tinospora cordifolia (Willd.) Miers. ex Hook. f. & Thoms.
Ziziphus jujuba Mill.

In most of the anti-DM plant species, multiple mechanisms of action and active principles are involved in their anti-DM activities. In many cases, the mechanisms of action studies are incomplete and the major mechanisms were not brought to light. Examples of these important anti-DM plants include *A. augusta* L. f., *Aloe vera* (L.) Burm. f., *Alstonia scholaris* L., *B. variegata* L., *Brassica juncea* Czern. & Coss., *Brucea javanica* (L.) Merr., *C. bonbuc* (L.) Roxb., *C. roseus* (L.) G. Don f., and *S. tetragonum* DC.

3.5 Conclusions

The available literature on the mechanisms of action of anti-DM plant extracts and active molecules reveals diverse mechanisms of action such as (1) insulin secretagogue and/or regeneration of the β-cells, (2) sensitization of insulin action, (3) insulin-like action, (4) activation of AMPK, (5) increasing the levels of GLP-1, (6) activation of PPAR-γ, (7) inhibition of starch digestion and glucose absorption from the intestine, and (8) inhibition of glucose reabsorption in the kidney. Furthermore, multiple mechanisms of action exist in some of the anti-DM plants. This is due to the existence of more than one active molecule and, to some extent, existence of more than one target to an individual anti-DM compound such as berberine. However, in the case of a majority of anti-DM plants, the mechanism of action is not known or only very limited knowledge exists. Mechanism-of-action studies should move hand in hand with phytochemical studies and pharmacological evaluation in each case. Understanding the mechanisms of action is an essential part in the management of DM effectively using herbal or plant-based anti-DM medicine. Furthermore, the mechanism of action studies will facilitate the development of mechanism of action-based polyherbal formulation as well as combination therapy and knowledge-based treatment of DM.

4

Polyherbal and Combination Medicines for Diabetes Mellitus

4.1 Introduction

Numerous polyherbal formulations are in use in different parts of the world in traditional medicine from ancient time onward to control or treat diabetes. They are also used in well-organized traditional systems of medicine such as Ayurveda, Siddha, and Chinese medicine. Even in the recent years, there has been a great interest toward phytomedicines including polyherbal formulations not only for diabetes but also for other diseases like arthritis and cancer; since the shortcomings of conventional chemical entity medicines have started getting more apparent, many anti-diabetes mellitus (anti-DM) herbal formulations available in the markets are immensely used by diabetic patients on the advice of physicians in India and elsewhere (Srivastava et al. 2012).

When products from more than one herb (plant) are used in a medicinal preparation, it is generally considered as a polyherbal formulation. In most of the cases, products from many plants (along with or without nonplant materials) are used as ingredients in a polyherbal formulation. These polyherbal formulations contain products from plant species as ingredients with specific methods of preparation. Polyherbal formulations could be better than single chemical entity drugs in many medical conditions. The multivalent and multitarget actions of mixtures of phytochemicals could provide therapeutic superiority compared with single compound drugs in the treatment of DM. Now, it is increasingly recognized that, in many complex disease conditions (e.g., DM, arthritis, liver diseases, and old-age-related diseases), combination therapy is more suitable compared with monosubstance therapy. It is considered that complex physiological and pathophysiological processes of the body can be influenced more effectively with less adverse side effects by a combination of several low-dose compounds than by a single high-dose compound. Low doses of several phytochemicals acting on multiple targets involved in a complex disease such as DM may prove better and safer compared with a high dose of a pure chemical entity drug acting on a major target. This gives relevance to phytomedicines (generally containing standardized extracts/fractions/crude homogenates). In this chapter, the advantages of rational polyherbal formulations are projected with an emphasis to develop rational and standardized polyherbal/combination medicines for DM.

4.2 Synergistic, Additive, Stimulatory, and Antagonistic Effects of Phytochemicals

Interaction of different phytochemicals can lead to synergistic effects, additive effects, antagonistic effects, and so on. One compound can influence the bioactivity of another compound positively or negatively. The pharmacological activity of one compound could, possibly, be abolished by the interaction with other compound or compounds. Molecular interactions can result into, in rare cases, emergence of a new pharmacological activity or even toxicity.

Synergistic effect: It is the cooperative interaction between two and more chemicals in a system, and the combined effect is more than the sum of the effect of each individual molecule.

Additive effect: If the combined effect of two or more chemicals is equal to or almost equal to the sum of the effects of each individual molecule, it is known as additive effect.

Inhibitory effect: If a compound partially or completely inhibits the activity of another compound, it is known as inhibitory effect. If the combined effect of two or more phytochemicals is less than the sum of the effects of each individual molecule, it could be inhibition of the activity of one compound by the other or a mutual inhibition if both the compounds are active.

Stimulatory effect: If a compound (which is not an active principle) increases the activity of an active compound, it is stimulatory effect.

Active principles present in the crude extracts of anti-DM plants exert additive effects or synergistic effects in many cases; however, molecules that antagonize or block the anti-DM action of active principles have also been reported in the same plant. In these contexts, the mechanism of action studies on individual compounds and their various combinations are required in the development of best anti-DM medicines, particularly, combination therapies.

Examples of molecular interactions in anti-DM activity of natural products:

1. The main bis-benzylisoquinoline alkaloid, fangchinoline (0.3–3 mg/kg) isolated from water extract of *Stephania tetrandra* Moore significantly brought down the blood glucose level and increased the low level of blood insulin in a dose-dependent manner in streptozotocin-induced diabetic mice. The effect of fangchinoline was 3.9-fold greater than that of water extract of *S. tetrandra*. However, another main compound, tetrandrine (1–100 mg/kg), did not show any effect (Tsutsumi et al. 2003). The water extract of *Astragalus membranaceus* did not affect singly but potentiated the antihyperglycemic action of fangchinoline (0.3 mg/kg) in streptozotocin-diabetic ddY mice. Fangchinoline appears to be an effective insulin secretagogue in diabetic rats at very low oral doses. Formononetin and calycosin (0.03–0.1 mg/kg) isoflavones from *A. membranaceus* alone did not affect the blood glucose or blood insulin level of the diabetic mice. These compounds (0.03–0.1 mg/kg) potentiated or stimulated the antihyperglycemic action of fangchinoline (0.3 mg/kg). Furthermore, formononetin (0.1 mg/ kg) facilitated the fangchinoline-induced insulin release (Ma et al. 2007). Bioassay-guided fractionation resulted in the isolation of the isoflavones, formononetin, and calycosin from *A. membranaceus* as the peroxisome proliferators-activated receptor-gamma (PPAR-γ) activating compounds (Shen et al. 2006).
2. *Balanites aegyptiaca* (fruit extract) showed hypoglycemic, hypolipidemic, and liver protective properties in senile diabetic rats. The fruit flesh was found to increase serum insulin levels and stimulate glucose metabolism (Gajalakshmi et al. 2013). Two new steroidal saponins were isolated from the active fraction and their structures were determined. In addition, two known saponins and their methyl ether were isolated. Interestingly, the individual saponins did not show anti-diabetic activity, but the combination of these saponins showed significant anti-diabetic activity (Kamel et al. 1991).
3. Rooibos is a slightly sweet and mildly astringent fragrant tea produced by fermentation of the commercially cultivated leaves and twigs of *Aspalathus linearis* (Burm.f.) R. Dahlgren. A study was carried out to confirm the anti-diabetes activity of aspalathin-rich rooibos extract. The extract showed the synergic action of mixture of compounds present in the extract. Under *in vitro* conditions, the extract-induced a dose-dependent increase in glucose uptake on C2C12 myocytes. Aspalathin was effective at 1, 10, and 100 μM, whereas rutin was effective at 100 μM. *In vivo* the extract sustained a glucose-lowering effect comparable with metformin over a 6-h period after administration (25 mg/kg) to streptozotocin-diabetic rats. In an oral glucose tolerance test (OGTT), the extract (30 mg/kg) was more effective than vildagliptin (10 mg/kg), a dipeptidyl peptidase-4 inhibitor. A mixture of aspalathin and rutin (1:1) at a low dose (1.4 mg/kg), but not the single compounds separately, reduced blood glucose concentrations over a 6-h monitoring period in streptozotocin diabetic rats. The improved hypoglycemic activity of the mixture and the extract showed synergic actions of the polyphenols (Muller et al. 2012).
4. In alloxan-induced diabetic rats, the 70% ethanol extract of *Artemisia herba-alba* showed superior hypoglycemic activity compared with any of its fractions (Awad et al. 2012).

4.3 Dose Effects of Anti-DM Molecules/Extracts

Some compounds are known to have atypical or abnormal dose effects. For example, resveratrol, a phenolic compound (3,4,5-trihydroxy-stilbene), a nutraceutical present in grapes, peanuts, and so on, has many beneficial biological effects depending on the dose used. Too much could be harmful. Animal experiments have shown that this compound has a protective effect at low doses against cardiovascular injury, gastric lesions, ischemic stroke, Alzheimer's disease, and osteoporoses, but an adverse or no beneficial effect was observed in these medical conditions at high doses (Calabrese et al. 2010). In cell proliferation assays, under *in vitro* conditions, resveratrol stimulated growth of a variety of cell types including cancer cells, whereas high concentrations inhibited cancer cell proliferation (Calabrese et al. 2010). In a clinical study, resveratrol (10 mg/day, for 4 weeks) improved insulin sensitivity in humans (Brasnyo et al. 2011). However, in another study, a high dose of resveratrol supplementation did not influence endogenous glucose production and metabolic markers of diabetes (Poulsen et al. 2013). The differential effects observed in these two clinical trials could likely to be due to dose effect. Further studies are needed regarding this. Thus, the low doses of certain active molecules present in a polyherbal formulation (or even in extracts and crude preparations of the same plant) could, possibly, provide better anti-DM effect compared with high doses of a single isolated phytochemical.

Intraperitoneal administration of the hydromethanolic extract of *Indigofera pulchra* leaves at a high dose (1 g/kg) did not change blood glucose levels in alloxan-induced diabetic rats at 4, 8, and 24 h after administration. But, 250 mg/kg of the extract lowered blood glucose levels significantly at 4, 8, and 24 h after administration. In normoglycemic rats, the high dose (1 g/kg) decreased blood glucose levels at 8 and 24 h after administration, whereas the lower dose (250 mg/kg) decreased at 4, 8, and 24 h (Tanko et al. 2009a). The ethyl acetate portion (active fraction) of hydromethanolic extract of *I. pulchra* leaf extract at a dose of 50 mg/kg decreased blood glucose levels in normal and alloxan-diabetic rats after 24 h of treatment, whereas higher doses (100 and 200 mg/kg) did not influence the levels of blood glucose in alloxan diabetic rats; in normal rats 100 mg/kg, but not 200 mg/kg, also showed a decrease in blood glucose levels (Tanko et al. 2009b).

Oral administration of leaf suspension of *Piper betle* for 30 days resulted in significant reduction in blood glucose and glycated hemoglobin and decreased activities of liver glucose-6-phosphatase and fructose-1,6-bisphosphatase, while liver hexokinase increased in streptozotocin diabetic rats compared with untreated diabetic rats. *P. betle* (75 mg/kg) exhibited better sugar reduction than a higher dose (150 mg/kg) (Santhakumari et al. 2006).

4.4 Development of Rational Polyherbal Formulations

Numerous polyherbal formulations are used in traditional medicine; these have been used from time immemorial. However, these preparations are not rational polyherbal medicines. Although the traditional medicine may have its own explanation, they are not explicable in light of modern science. Empirical knowledge may have a major place in the origin of these formulations. Even in recent times, Ayurvedic type polyherbal formulations are being developed using known anti-DM plant parts. The reason behind the inclusion of each ingredient of the formulation in the said ratio is not clear. Although phytomedicine is easy to develop compared with conventional pure chemical entity drug, development of rational scientific formulations involves huge amounts of research.

The development of rational polyherbal formulations requires a lot of pharmacological and toxicological studies and phytochemical standardization. As shown in Figure 4.1, in the preparation of a rational polyherbal formulation, pharmacological evaluation is required in a sequential manner. For example, in the development of a polyherbal formulation using active extract/fraction/compound from three herbs (herb 1, 2, and 3), first pharmacological evaluation of each plant extract has to be carried out using three or four reasonable doses; if active, the optimum dose should be fixed in each case. Then, combinations of two plants (1 + 2, 2 + 3, and 1 + 3) in different ratios (generally optimum dose in each case, 1:1 ratio and lower doses than that) have to be evaluated. Finally, the combinations with the three plants (1 + 2 + 3) in different ratios and doses (generally optimum dose in each case, 1:1:1: ratio and doses lower than that) are

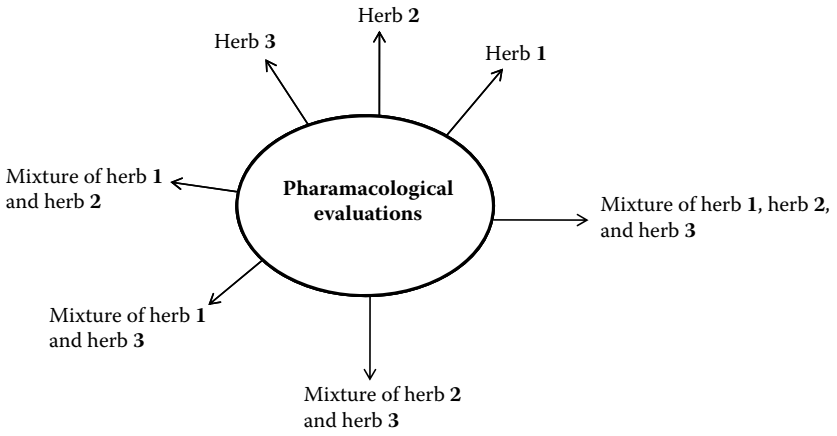

FIGURE 4.1 Pharmacological evaluations in the systematic development of polyherbal formulation with three plant species.

to be done to determine the superiority, if any, of the specific three-plant combination. The safety study (toxicological evaluation) for the most promising combinations should be carried out. Thus, even in the case of a three-plant, polyherbal medicine development, several samples have to be evaluated using at least three doses for each sample. When the number of plant ingredients in the combination increases, the work to be carried out increases tremendously when various permutations and combinations are considered. This will help to develop rational polyherbal formulations for diabetes with standards of safety and efficacy. Plant products with antioxidant and antihyperlipidemic properties should be added in the formulation (in case the formulation does not have these properties) to improve the ability of the combination medicine to combat diabetic complications. When such additions are made, again, efficacy and safety evaluation should be done to establish its enhanced health benefits.

In a recent study, a polyherbal formulation was prepared from the ethanol extracts of the stem bark of *Glycomis pentaphylla*, whole plant of *Tridax procumbens*, and leaves of *Mangifera indica*. The polyherbal formulation contains the ethanol extracts of *G. pentaphylla, T. procumbens*, and *M. indica* in the ratio of 2:2:1. The anti-diabetic activity of the individual plant parts is well known, but the synergistic or combined effects are unclear. The quality of the finished product was evaluated as per the World Health Organization's guidelines for the quality control of herbal materials. The acute toxicity studies of the polyherbal formulation did not show any toxic symptoms in doses up to 2000 mg/kg over 14 days. The oral anti-diabetic activity of the polyherbal formulation (250 and 500 mg/kg) was screened against streptozotocin (50 mg/kg; i.p.) + nicotinamide (120 mg/kg; i.p.) induced DM in rats. The investigational drug was administered for 21 consecutive days, and the effect of the polyherbal formulation on blood glucose levels was studied at regular intervals. At the end of the study, the blood samples were collected from all the animals for biochemical estimation, and the animals were sacrificed and the liver and pancreatic tissues were collected for histopathologic analysis. The polyherbal formulation showed significant anti-diabetic activity at 250 and 500 mg/kg, and this effect was comparable with that of glibenclamide. The anti-diabetic activity of the polyherbal formulation is supported by biochemical and histopathologic analysis (Petchi et al. 2014). But, in this study, a comparison with individual plant extract and two-plant extracts were not done. Thus, the superiority of the three-plant combination was not established. Thus, it is not a very rational polyherbal formulation as per the aforementioned criteria.

In another study, anti-diabetic effects of four different polyherbal combinations of six medicinal plants used in traditional medicine were investigated. Aqueous extracts of *Stevia rebaudiana, Momordica charantia, Tamarindus indica, Gymnema sylvestre, Allium sativum,* and *Murraya koenigii* were used for polyherbal combinations. All these four combinations were studied for their acute toxicity and a 250 mg/kg dose was selected. OGTT, anti-diabetic activity and anti-α amylase and α-glucosidase

activity and liver function tests were performed for all the combinations. Reduction in blood glucose level was determined for 0–20 days and histopathology of the pancreas was performed on the 20th day. IC_{50} value was determined in anti-α amylase activity. Results revealed that all combinations were safe. One of the combinations, polyherbal combinations II (250 mg/kg), showed significant anti-diabetic activity in OGTT and lowered blood glucose levels in streptozotocin-diabetic rats. Combination-II showed significant anti-α amylase and α-glucosidase activity, which is better than other combinations. Treatment with combination-II in diabetic animals produced beneficial improvement in lipid profile also. Histopathological observations showed improvement in the rat treated with combination-II. It may be concluded that combination-II was most effective and safe in comparison to other combinations. However, the rationale for the preparation of specific combinations and the ratios in each combinations are not given. The combination was not compared with important individual anti-DM plant extract such as *S. rebaudiana, M. charantia, T. indica*, and *G. sylvestre* to establish its superiority. Furthermore, only one dose (250 mg/kg) was studied (Patil et al. 2012).

Development of rational polyherbal medicine should consider the different anti-DM mechanisms of actions, oxidative stress, hyperlipidemia, complications of DM, adverse drug interactions, effect on immune system, and so on. Ideally rational anti-DM polyherbal combinations should contain agents to provide required pharmacological activities such as insulin-secretagogue and/or regeneration of the β-cells, sensitization of insulin action (decreasing insulin resistance), insulin-like action (partial or complete), activation of adenosine monophosphate-activated protein kinase (AMPK) (this has also a role in insulin sensitization), increasing the levels of glucagon-like protein 1 (GLP-1), activation of PPAR-γ, inhibition of carbohydrate absorption in the intestine, inhibition of glucose reabsorption in the kidney, and inhibition of aldose reductase activity. In addition, agents that reduce oxidative stress and reduce lipid levels may be included, if the anti-DM ingredients do not have this activity. Each formulation with different ratios of the ingredients should be tested for efficacy in animals through *in vivo* experimental models. The best formulation may be selected for detailed long-term safety evaluation. Therapeutically promising formulations based on safety and efficacy evaluation in animal experiments should be carried forward for clinical trials as shown in Figure 4.2. Development of a systematic rational polyherbal formulation involves a lot of studies.

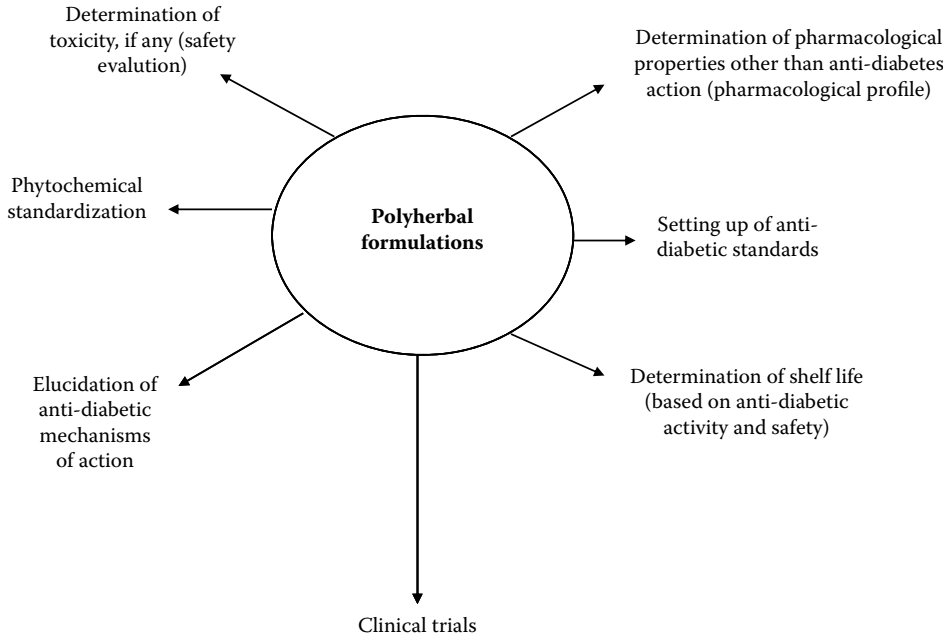

FIGURE 4.2 Systematic representation of studies on polyherbal formulations leading to polyherbal medicine development.

4.5 Polyherbal Therapy for DM

Currently, many polyherbal formulations are used to treat diabetes in complementary and alternative medicine. Pharmacological evaluations (reverse pharmacology) have been carried out on some of the anti-DM polyherbal formulations and these studies showed varying levels of anti-DM activities. However, the specific reasons for the presence of many ingredients in specific ratios are not clear. The major anti-DM formulations are used in traditional medicine in the form of decoctions, infusion, tinctures, extracts, and powders. In some formulations such as diabecon more than 25 plant species are included. It should be noted that some of the polyherbal formulations were studied for their efficacy and safety along with the establishment of their chemical profile. Comparisons of crude herbal drugs with standard drugs reported in the literature are inadequate, to a large extent, because the efficacy at the optimum doses was not compared. The optimum dose has not been experimentally determined in the case of many of the polyherbal formulations. It is of interest to note that most of the plant ingredients of the polyherbal formulations in use are reported to have anti-DM activities in experimental pharmacological studies (Subramoniam 2016). Furthermore, it is believed that most of the ancient polyherbal formulations were developed to take care of all systems of the body in its entirety, and not just to give symptomatic relief from DM. Many of the existing major polyherbal formulations and the available scientific studies on them are given below.

4.5.1 Polyherbal Formulations (Ayurvedic Type) Used in India and Elsewhere

4.5.1.1 Aavaraiyathi churnum

Aavaraiyathi churnum is one of the well-known polyherbal formulations used in Siddha system of medicine to treat DM. The ingredients of this formulation are *Cassia arriculata* leaves, *Odina wodier* (*Lannea coromandelica*) bark, *Coscinium fenestratum* stem, *Ficus glomarata* leaves, and *Cocculus cordifolia* stem. Oral administration of Aavaraiyathi churnum (100 and 200 mg/kg, for 21 days) to alloxan-induced diabetic rats resulted in a significant reduction in blood glucose levels and increase in body weight compared with untreated diabetic rats. Thus, this polyherbal formulation exhibits anti-DM activity (Anbu et al. 2012).

4.5.1.2 Annoma squamosa *and* Nigella sativa *Formulation*

A herbal formulation containing *Annoma squamosa* and *Nigella sativa* is used to treat diabetes. Aqueous extract of the formulation (200 mg/kg, daily for 30 days) showed significant reduction in blood glucose levels and increase in plasma insulin levels in streptozotocin-induced diabetic rats (Sinha et al. 2012).

4.5.1.3 APKJ-004

This is an anti-DM medicine prepared from the seeds of *Eugenia jambolana* (hydro-alcohol extract) and barks of *Cinnamomum zylanicus* (water extract). This medicine did not exhibit any acute or sub-acute toxic symptoms in rats. APKJ-004 showed prominent *in vitro* anti-diabetic activity. The *in vivo* evaluation results showed that the extract APKJ-004 reduced the elevated glucose levels and improved glucose tolerance in streptozotocin-induced diabetic rats. Furthermore, the insulin levels were considerably increased in the polyherbal drug-treated diabetic rats. These effects were comparable to the effects of glibenclamide. The authors concluded that APKJ-004 extract acts as a potent anti-diabetic agent with minimal or no side effects and useful in the pharmacotherapy of diabetes (Amarachinta and Jamil 2012).

4.5.1.4 Cogent db

This is a polyherbal formulation containing *Azadirachta indica, Curcuma longa, Phyllanthus emblica, Rotula aquatica, Syzigium cumini, Terminalia chebula, Terminalia bellerica, Tribulus terrestris*, and *Trigonella foenum-graecum* (Ghorbani 2014). Oral administration of the polyherbal formulation

(0.15–0.45 g/kg, daily for 40 days) to alloxan-induced diabetic rats resulted in marked decrease in the levels of fasting blood glucose (64% at 0.45 g/kg) and glycated hemoglobulin (71% at 0.45 g/kg); the treatment increased blood insulin and high-density lipoprotein (HDL) levels, whereas it decreased the levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL) (Pari and Saravananan 2002).

4.5.1.5 DIA-2

DIA-2 is a herbal formulation containing *A. sativum* (bulb) and *Lagerstroemia speciosa* (leaves) as ingredients (Ghorbani 2014). Oral administration of this formulation (62.5–500 mg/kg, daily for 14 days) to high-fat-diet and low-dose streptozotocin-induced type 2 diabetic rats resulted in 50% reduction in fasting blood glucose levels at 125 mg/kg; the treatment also reduced total cholesterol and triglyceride levels (more than 70%) and increased insulin levels (Kesavanarayanan et al. 2013).

4.5.1.6 Diabecon

This polyherbal formulation contains *G. sylvestre, Pterocarpus marsupium, Glycyrrhiza glabra, Casearia esculenta, S. cumini, Asparagus racemosus, Boerhavia diffusa, Sphaeranthus indicus, Tinospora cordifolia, Swertia chirata, T. terrestris, Phyllanthus amarus, Gmelina arborea, Gossypium herbaceum, Berberis aristata, Aloe vera, Triphala* (a mixture of *T. bellerica, T. chebula*, and *Phyllanthus embilica*), *Commiphora wightii, M. charantia, Piper nigrum, Ocimum sanctum, Abutilon indicum, C. longa, Rumex maritimus*, and shilajit (a rare organic mineral obtained at high altitude at Himalaya mountains, composed of humus and organic plant material that has been compressed by layers of rock). This formulation is reported to increase peripheral utilization of glucose and hepatic and muscle glycogen contents, promote β-cells repair and regeneration, and increase in C-peptide level. It has antioxidant properties; it protects β-cells from oxidative stress. It exerts insulin-like action by reducing the glycated hemoglobin levels, normalizing the microalbuminurea, and modulating the lipid profile. It minimizes long-term diabetic complications (Kaur and Valecha 2014).

Feeding high-fructose diet-fed diabetic rats with diabecon (100 mg/kg, daily for 56 days) resulted in decrease in serum fasting blood glucose (36%), blood insulin (40%), and glycated hemoglobulin (30%) levels; furthermore, the treatment increased blood HDL and muscle PPAR-γ protein and decreased the levels of LDL, triglycerides, and lipids in liver (Yadav et al. 2007).

4.5.1.7 Diabecon-400 (D-400)

D-400 is composed of *A. racemosus, Balsamodendron mukul, E. jambolana, G. sylvestre, M. charantia, O. sanctum*, and *P. marsupium* as ingredients. In a clinical trial on 30 diabetic patients with retinopathy D-400, the dosage of two tablets, three times a day for 3 months was found to be effective against retinopathy; the treatment decreased hemorrhages, microaneurysm, exudation, and retinitis proliferation (Kant et al. 2002). In another clinical study on 43 type 1 and type 2 DM patients, D-400 (two tablets, twice daily for 2 weeks) reduced fasting blood glucose levels (more than 30%) (Ghorbani 2014).

4.5.1.8 Diabecure

This formulation containing *Juglans regia, Berberis vulgaris, Erytherea centaurium, Achillea millefolium*, and *Taraxacum officinale* was effective in lowering the blood sugar level (Modak et al. 2007).

4.5.1.9 Diabet

This polyherbal formulation contains *C. longa, C. fenestratum, Strychnos potatorum, Phyllanthus reticulatus, T. indica*, and *T. terrestris.* Diabet was investigated for its glucose tolerance and anti-diabetic activity in alloxan-induced diabetic rats. The glucose tolerance test and hypoglycemic studies were carried out in normal rats. The product showed effectiveness at a dose of 500 mg/kg but did not show hypoglycemic effect (Patel et al. 2009).

4.5.1.10 Diabeta

Diabeta is a polyherbal formulation containing *G. sylvestre, Vinca rosea* (periwinkle), *C. longa* (turmeric), *A. indica* (neem), *P. marsupium* (kino tree), *M. charantia* (bitter gourd), *S. cumini* (black plum), *Acacia arabica* (black babhul), *T. cordifolia*, and *Zingiber officinale* (ginger). This formulation is available in the capsule form and is an anti-DM medicine with combination of proven anti-diabetic plant products fortified with potent immunomodulatory, antihyperlipidemic, antistress, and hepatoprotective plants. The formulation of Diabeta is based on ancient Ayurvedic references, further corroborated through modern research and clinical trials. Diabeta acts on different sites in differing ways to effectively control DM. It is reported to ameliorate the various factors that precipitate the diabetic condition, and correct the degenerative complications that result from diabetes. Diabeta is safe and effective in managing DM as a single agent supplement to currently used conventional anti-diabetic drugs. Diabeta helps to overcome resistance to oral hypoglycemic drugs when used as adjuvant in uncontrolled diabetes. Diabeta confers a sense of well-being in patients and promotes symptomatic relief of complaints like weakness, giddiness, pain in legs, body ache, polyuria, and pruritis (Modak et al. 2007).

4.5.1.11 Diabetes-Daily Care

Diabetes-Daily Care containing α-lipoic acid, cinnamon (4% extract), *T. foenum-graecum* seed (50% extract), *G. sylvestre* (25% extract), *M. charantia* fruit (7% extract), *G. glabra* root (20% extract), chromium, and vanadium is a unique, natural formula, which effectively and safely improves sugar metabolism (Modak et al. 2007).

4.5.1.12 Diabrid

A herbal-based anti-diabetic formulation (comprising of four plant species namely *G. sylvestre, M. charantia, E. jambolana*, and *T. foenum-graecum*) for maturity onset diabetic patients was clinically evaluated in 60 diabetic patients for 6 months. The clinical studies revealed that Diabrid was well tolerated in high doses and was found to be a potential anti-diabetic drug in mild and moderate diabetic cases (10–15.6 mM glucose). The blood sugar level was controlled within 2–8 weeks depending upon initial blood sugar level. No side effect was observed. The hypoglycemic activity was dose-dependent and gradual. The drug also maintained the body weight and blood pressure of diabetic patients. No deleterious effect was observed on kidney and liver (Qadri et al. 2006).

4.5.1.13 Dia-Care

A herbal formulation containing 18 plant products (*Eugenia jambolona, Tinospora cordifolia, G. sylvestre, Cressa cretica, Casearia esculenta, C. longa, S. chirata, Centratherum anthelminticum, Picrorrhiza kurroa, T. foenum-graecum, T. chebula, Holarrhena antidysentrica, P. marsupium, G. glabra, T. terrestris, Withania somnifera, Nordotachyns jatamansi* and *Bacopa monniera*), and Shilajit (an organic mineral obtained at high altitude at Himalaya mountains containing humus and specific plant materials (Reddy et al. 2014). Dia-Care is claimed to be effective for both type 1 and type 2 diabetes within 90 days of treatment and cures within 18 months. Persons taking insulin will eventually be liberated from the dependence on it. The whole treatment completes in six phases, each phase being of 90 days. Approximately 5 g (one teaspoon) powder is mixed with half a glass of water, stirred properly, kept overnight, and filtered. The filtrate is taken in the morning on an empty stomach. To the remaining medicine, fresh water is added and kept for the whole day and is consumed half an hour before dinner. The taste of the drug is very bitter. It is considered as a pure herbal formula without any side effects (Kant et al. 2002).

4.5.1.14 Diakyur

The polyherbal formulation, Diakyur is composed of *Cassia javanica, Cassia auriculata, Salacia reticulata, G. sylvestre, Mucuna pruriens, Syzygium jambolaum*, and *Terminalia arjuna*. This formulation

is scientifically proved to be potential anti-diabetic medicine in animal experiments. Reports indicate that Diakyur has shown significant hypoglycemic activity as well as antilipid peroxidative activity in alloxan-induced diabetic rats. It can be used as an adjuvant along with conventional pure chemical entity treatment as well as to delay the late complications of diabetes (Joshi et al. 2007). Studies have concluded that Diakyur at a dose of 1600 mg/kg, p.o. is safe for long-term treatment in diabetic condition (Chandra et al. 2007).

4.5.1.15 Dianex

Dianex, a polyherbal formulation consisting of aqueous extracts of *G. sylvestre, E. jambolana, M. charantia, A. indica, C. auriculata, Aegle marmelos, W. somnifera*, and *C. longa*, was screened for hypoglycemic activity in normal and streptozotocin-induced diabetic mice. Dianex produced significant hypoglycemic activity in both normal and diabetic mice. In another study, Dianex was screened for anti-diabetic activity in rats. It was administered orally in different doses (100, 250, and 500 mg/kg) up to 6 weeks. The study concluded that the continuous administration of Dianex up to 6 weeks was effective in the long term (Srivastava et al. 2012).

4.5.1.16 Diashis

The polyherbal formulation, Diashis was composed of *Syzygium cumuni, G. sylvestre, Holarrhena antidysenterica, T. cordifolia, Pongamia pinnata, Psoralea corylifolia, M. charantia,* and Asphultum (Shilajit) (Bera et al. 2010). A study was conducted to determine the efficacy of Diashis on streptozotocin-induced diabetes in rats. As oxidative stress is one of the consequences of diabetes, the activities of hepatic antioxidant enzymes and metabolic enzymes were evaluated. Treatment with Diashis in streptozotocin-induced diabetic rats resulted in a significant recovery in the activities of hepatic hexokinase, glucose-6-phosphate dehydrogenase, and glucose-6-phosphatase along with correction in the levels of fasting blood glucose, glycated hemoglobin, and liver and skeletal muscle glycogen. The oxidative stress status in the liver was corrected by Diashis, which was highlighted by the recovery in the activities of catalase (CAT), peroxidase, and glutathione-S-transferase along with the correction in the quantity of thiobarbituric acid-reactive substances and conjugated diene. Diashis was not found to have any metabolic toxicity (Bera et al. 2010).

4.5.1.17 Diasol

Diasol is a polyherbal anti-diabetic formulation containing extracts of *E. jambolana, T. foenum-graceum, T. chebula, Quercus infectoria, Cuminum cyminum, T. officinale, Emblica officinalis, Gymnea sylvestre, Phyllanthus niruri*, and *Enicostemma littorale* (Babuji et al. 2010). Diasol produced 63.4% reduction of blood glucose level at doses of 125 and 250 mg/kg, i.p. and proved to be effective anti-diabetic polyherbal formulation (Babuji et al. 2010).

4.5.1.18 Diasulin

Diasulin is a polyherbal formulation containing *C. auriculata, Coccinia indica, C. longa, E. officinalis, G. sylvestre, M. charantia, Scoparia dulcis, S. cumini, T. cordifolia*, and *T. foenum-graecum*. Studies suggest that it controls the blood glucose level by increasing glycolysis and decreasing gluconeogenesis with a lower demand of pancreatic insulin than in untreated rats. It regulates the activities of hepatic glucose metabolic enzymes (Pari and Saravanan 2004). Diasulin treatment also resulted in significant decrease in tissue lipids and lipid peroxide formation (Saravanan and Pari 2005). In alloxan-induced diabetic rats, alcohol extract of the formulation (200 mg/kg, daily, p.o., for 30 days) decreased the levels of fasting blood glucose (60%) and increased insulin levels (98%); the treatment also decreased oxidative stress and lipid levels in liver; the anti-DM activity was marginally better than that of 600 µg/kg glibenclamide (Pari and Saravanan 2004; Saravanan and Pari 2005).

4.5.1.19 Dihar

Dihar contains eight different herbs (*S. cumini, M. charantia, E. officinalis, G. sylvestre, E. littorale, A. indica, T. cordifolia*, and *C. longa*) in the formulation (Patel et al. 2009). It has been reported that combination of these eight herbs shows effective antihyperglycemic activity in streptozotocin-induced type 1 diabetic rats. Treatment with Dihar (100 mg/kg) for 6 weeks produced decrease in streptozotation-induced serum glucose and lipid levels and increased insulin levels as compared with untreated control. Dihar produced significant decrease in serum creatinine, urea, and lipid peroxidation in the diabetic rats. Administration of Dihar to diabetic rats significantly increased the activity of antioxidant enzymes also (Patel et al. 2009).

4.5.1.20 DRF/AY/5001

This is a polyherbal formulation containing *G. sylvestre, S. cumini, P. marsupium, M. charantia, E. officinalis, T. bellirica, T. chebula*, and shilajit developed by Dabur Research Foundation, Gaziabad, India. This polyherbal medicine elicited hypoglycemic/anti-diabetic effects in both normal and experimentally induced hyperglycemic rats. DRF/AY/5001 inhibited significantly the hyperglycemia induced by epinephrine. It showed significant reduction in fasting blood glucose level at 1–3 h with single dose treatment in alloxan-induced diabetes rats and 15 days treatment of rats with 600 mg/kg of DRF/AY/5001 resulted in 40% reduction in fasting blood glucose levels and 20% reduction in the levels of glycated hemoglobulin. DRF/AY/5001 gave nearly comparable results with that of synthetic drug glibenclamide (Mandlik et al. 2008).

4.5.1.21 EFPTT/09

EFPTT/09 is a polyherbal formulation containing five ingredients of herbal origin (*E. jambolana, T. cordifolia, T. arjuna, P. nigrum*, and *Ficus religiosa*) that are used in traditional medicine to treat diabetes. Studies show that EFPTT/09 elicits hypoglycemic and anti-diabetic effect in both normal and alloxan-induced diabetes rats. It also elicited significant antioxidant effect in diabetic rats by its ability to inhibit lipid peroxidation and elevate the enzymatic antioxidants in pancreatic tissue. It has been reported that at a dose of 600 mg/kg, the hypoglycemic effect of EFPTT/09 was nearly comparable with that of glibenclamide (5 mg/kg) (Yoganandam and Jha 2010).

4.5.1.22 ESF/AY/500

The polyherbal formulation ESF/AY/500, intended to be used for diabetic patients, has been screened for antioxidant activity. The formulation is composed of eight medicinal plants, namely *Aerva lanata, A. marmelos, Ficus benghalensis, Catharanthus roseus, Bambusa arundinacea, Salacia reticulata, S. cumini*, and *Eruca sativa*. Ethanol extract of ESF/AY/500 exhibited significant antioxidant activity showing increased levels of superoxide dismutase (SOD), CAT, glutathione peroxidase, and reduced glutathione and decreased level of lipid peroxidation (Sajeeth et al. 2010).

4.5.1.23 Glucolevel

Glucolevel contains leaves of *Atriplex halimus, J. regia, Olea europea*, and *Urtica dioica* as ingredients (Ghorbani 2014). In a clinical trial, 16 patients with type 2 DM were treated with the formulation (one tablet three times a day for 4 weeks). The treatment reduced both fasting blood glucose (27%) and glycated hemoglobulin (18%) (Said et al. 2008).

4.5.1.24 Gluconorm-5

The hypoglycemic effect of single dose of Gluconorm-5 (150, 300, and 600 mg/kg) made up of five plants—namely *Camellia sinensis, Punica granatum, Macrotyloma uniflorum, Foeniculum vulgare*,

and *T. foenum-graecum*—was studied in normal, glucose-loaded normal, and streptozotocin-induced diabetic rats. Fifteen days of oral feeding of Gluconorm-5 (300 and 600 mg/kg) to streptozotocin-induced diabetic rats resulted in a significant reduction of blood glucose, lipid profile, liver weight, and liver function marker enzymes compared with these parameters in untreated streptozotocin diabetic rats. The diabetic rats treated with the drug showed expanded islets compared with the untreated diabetic rats, which showed the shrunken islets. The animals that received 300 mg/kg of Gluconorm-5 showed anti-diabetic, antihyperlipidemic, and hepatoprotective effects, which were comparable with the effects of glibenclamide, a standard drug (Gengiah et al. 2014).

4.5.1.25 Glyoherb

This polyherbal formulation contains *G. sylvestre, M. charantia, P. kurroa, P. emblica*, and *E. littorale.* Glyoherb was evaluated for its antihyperglycemic, antihyperlipidemic, and antioxidant effects against normal and streptozotocin-induced diabetic rats. Glyoherb granules lowered serum glucose levels and increased glucose tolerance in streptozotocin-induced type 1 diabetic rats. This polyherbal formulation also showed significant antihyperlipidemic activity; it lowered serum cholesterol and triglyceride levels. Glyoherb did not exert any toxic effects in streptozotocin-induced impaired kidney and liver functions and was found to improve kidney and liver functions. In addition, glyoherb possessed potential antioxidant activity as it decreased lipid peroxidation and enhanced antioxidant status in diabetic rats. The anti-diabetic activity of glyoherb may be due to its antioxidant properties also. Thus, the studies concluded that glyoherb may be regarded as a promising natural and safe remedy for the prevention or delay of diabetic complications. In streptozotocin-induced diabetic rats, the formulation (600 mg/kg, daily for 28 days) showed anti-DM effect, which is comparable with that of 5 mg/kg glibenclamide (Thakkar and Patel 2010).

4.5.1.26 HAL or HA-lipids

A polyherbal formulation, named HA, comprises lyophilized hydroalcoholic (50%, v/v) extracts of *M. charantia* (fruit)*, T. foenum-graecum* (seed), and *W. somnifera* root 2:2:1, respectively. The optimized formulation (HA) entrapped in phasphatidyl choline and cholesterol vesicle system is known as HA lipids (HAL). Oral administration of this HAL (500 mg/kg of lyophilized hydroalcoholic extract, daily for 21 days) to streptozotocin-induced diabetic rats resulted in a marked decrease in fasting blood glucose level (52%), and triglycerides, LDL, and total cholesterol levels. Furthermore, the treatment increased hepatic glycogen content and blood HDL level (Gauttam and Kaila 2013).

4.5.1.27 Hyponidd

Hyponidd is an Ayurvedic herbo-mineral formulation (manufacturer: Charak Pharma). The polyherbal formulation contains Yashad Bhasma (Zinc Calx), Shilajit, bitter gourd (*M. charantia*), turmeric (*C. longa*), Indian broad beans (*C. auriculata*), Indian gooseberry (*E. officinalis*), Raja Jambu (*E. jambolana*), Mamejavo (*E. littorale*), Meshashringi (*G. sylvestre*), Vijaysar (*P. marsupium*), guduchi (*T. cordifolia*), neem (*A. indica*), and Kirat Tikata (*S. chirata*) (Jonnalagadd and Selkar 2013). Metformin-like effects have been reported for this medicine. Oral administration of hyponidd (100 or 200 mg/kg, daily for 45 days) to streptozotocin-induced diabetic rats resulted in amelioration of the diabetic condition. The treatment (200 mg/kg) reduced fasting blood glucose (72%), and glycated hemoglobulin (47%) levels and increased blood insulin levels and hepatic glycogen content. These effects were marginally better than 600 μg/kg glibenclamide (Babu and Prince 2004). A clinical trial on type 2 DM patients suggests that hyponidd could moderately decrease glycated hemoglobin levels after 12 weeks of treatment without any adverse events. However, the treatment did not significantly influence fasting blood glucose levels (Poongothai et al. 2002).

4.5.1.28 Jamboola

Jamboola is a polyherbal formulation (syrup) composed of five medicinal plants; it is used as an Ayurvedic formulation in Andhra Pradesh, India, to treat diabetes. The constituents of jamboola are

E. jambolana, C. auriculata, E. officinalis, M. charantia, and *T. cordifolia*. The herbal constituents of jamboola are known to possess anti-diabetic and antioxidant properties and are used in indigenous systems of medicine for the treatment of DM. A study was undertaken to evaluate the hypoglycemic and antihyperglycemic activity of jamboola and to add a scientific proof to its efficacy. Jamboola exhibited significant hypoglycemic activity in normal rats and antihyperglycemic activity in alloxan-induced diabetic rats at 3 mL/kg (Candasamy et al. 2011).

4.5.1.29 Karnim Plus

This polyherbal formulation (containing *M. charantia, A. indica, P. kurroa, O. sanctum,* and *Z. officinale*) was evaluated for anti-diabetic activity. The herbal product showed effectiveness at two dose levels (200 and 400 mg/kg, p.o., daily for 11 days) in alloxan-induced diabetic rats. The treatment reduced fasting blood glucose (19% at 400 mg/kg), total cholesterol (37%), urea, and creatinine in the diabetic rats (Bangar et al. 2009).

4.5.1.30 LI85008F or Adipromin

This polyherbal formulation is comprised of ethanol extract of *Moringa olefera* leaves, water extract, *M. koenigii* leaves, and ethanol extract of *C. longa* rhizomes in the ratio of 6:3:1, respectively. In a double-blind placebo-controlled randomized study on obese human subjects, the formulation (900 mg/day for 8 weeks) exhibited significant reduction in body weight, reduced fasting blood glucose, and reduced LDL/HDL ratio. No major adverse events were reported by the participants in the study (Barik et al. 2015).

4.5.1.31 MAC-ST/001

This is a recently developed polyherbal formulation which contains *A. indica* (seed), *Caesalpinia bonducella* (seed), *M. charantia* (fruit), *S. cumini* (seed), and *T. foenum-graeucm* (seed) (Ghorbani 2014). Feeding streptozotocin-induced diabetic rats with the formulation (100–400 mg/kg, daily for 21 days) resulted in marked reduction in fasting blood glucose levels (51% reduction at 400 mg/kg), triglycerides, total cholesterol, creatinine, transaminases, and alkaline phosphatase; furthermore, the treatment minimized histological damage in the pancreas (Yadav et al. 2013).

4.5.1.32 NIDDWIN

This is a polyherbal formulation containing 11 anti-DM plants (*T. cordifolia, G. sylvestre, Terminalia tomentosa, T. terrestris, E. officinalis, M. pruriens, Sida cordifolia, W. somnifera, T. bellerica, T. chebula*, and *M. charantia*). In alloxan-induced diabetic rats, this polyherbal preparation showed promising anti-DM activity. It also showed antioxidant and antihyperlipidemic activities (Barik et al. 2015).

4.5.1.33 Okchun-San

This polyherbal formulation contains *Coix lachryma-jobi* (or *Oryza sativa*), *Glycyrrhiza uralensis, Pueraria thunbergiana, Rehmannia glutinosa, Schizandra chinensis*, and *Trichosanthes kirilowii* (Ghorbani 2014). Administration of the water extract of the formulation (200 mg/kg, p.o., daily for 12 days) to db/db type 2 diabetic mice resulted in improvement of glucose tolerance and decrease (60%) in the levels of fasting blood glucose (Chang et al. 2006).

4.5.1.34 Okudiabet

Studies on this formulation containing *Stachytarpheta angustifolia, Alstonia congensis* bark, and *Xylopia acthiopica* fruit extracts showed that it was effective in decreasing plasma glucose levels in the diabetic rats. It proved to have a better plasma glucose-lowering effect than that of glibenclamide; it also showed beneficial effects on cardiovascular system. The high LD_{50} (lethal dose, 50%) value (16.5 g/kg) indicates that the formulation could be safe for use (Srivastava et al. 2012).

4.5.1.35 PMO21

This herbal formula containing components of Mori Folium (*Chrysanthemum morifolium)* and Aurantii Fructus (*Citrus aurantium*) is routinely used to treat diabetes in Korea. The anti-diabetic effect of PM021 was investigated on the type 2 diabetic Otsuka Long–Evans Tokushima Fatty (OLETF) rats. The results showed that PM021 significantly prevented increases in body weight, blood glucose, and urine and food intake that resulted from the induction of obesity and diabetes. PM021 also improved glucose tolerance in OLETO rats. However, PM021 had no effect on LETO rats, a control group of OLETF rats. Taken together, these findings indicate that PM021 has distinct anti-diabetic effects without any adverse effects or toxicities (Kim et al. 2011c).

4.5.1.36 SMK001

SMKOOl is a polyherbal combination containing several types of water extracts including Coptidis Rhizome (*Coptis chinensis*) and Trichosanthis Radix (*T. kirilowii*). It is known as Dang-Nyo-So-Ko in Korea. SMK001 has been used for treatment of diabetes in Korea as Chinese medicine. The effect of SMK001 was evaluated in the streptozotocin-induced diabetic rats. Treatment with SMK001 (100–500 mg/kg, daily for 4 weeks) resulted in significant and dose-dependent amelioration of streptozotocin-induced DM. SMK001 showed favorable effect to inhibit the changes on the blood and urine glucose levels, body weight, and the histopathological changes of pancreas in the streptozotocin-diabetic rats. At a dose of 100 mg/kg, SMK001 showed anti-DM effect comparable with that of glibenclamide 5 mg/kg (Kim et al. 2006).

4.5.1.37 SR10

SR10 contains *A. membranaceus* root, *Codonopsis pilosula* root, and *Cortex lycii* root (Ghorbani 2014). Oral administration of SR10 (927 mg/kg, daily for 4 weeks) to db/db type 2 diabetic mice resulted in decrease in the levels of fasting blood glucose (22%) and insulin (36%); however, the treatment did not improve glucose tolerance (Chan et al. 2009).

4.5.1.38 Sugar Remedy

Sugar Remedy is a polyherbal formulation manufactured by Umalaxmi Organics Pvt. Ltd., Jodhpur, Rajasthan, India. The ingredients of Sugar Remedy are *G. sylvestre* leaves, *M. charantia* fruit, *W. somnifera* leaves, *S. cumini* fruit, *P. emblica* fruit, *T. bellirica* fruit, *T. chebula* fruit, *C. zylanicus* bark, *P. marsupium* heart wood, and Asphaltum (shilajit). The polyherbal medicine was evaluated for its antihyperglycemic, antihyperlipidemic, and antioxidant effects against normal and streptozotocin-induced type 2 diabetic rats. Effects of three different doses of Sugar Remedy suspension (185, 370, and 740 mg/kg/day, orally for 21 days) and metformin (500 mg/kg/day, orally) were studied on parameters such as blood glucose, lipid profile, and antioxidant levels. No significant changes were noticed in blood glucose, serum lipid levels, and kidney parameters in normal rats treated with Sugar Remedy suspension alone. The efficacy of Sugar Remedy as an antihyperglycemic, antihyperlipidemic, and antioxidant agent in streptozotocin-induced diabetes was comparable with that of 500 mg/kg of metformin. This study provided experimental evidence that Sugar Remedy has significant antihyperglycemic, antihyperlipidemic, and antioxidative effects in streptozotocin-induced diabetic rats (Singhal et al. 2014).

4.5.1.39 Ziabeen

The ingredients of ziabeen are *Aloe barbadensis, A. indica, E. jambolana, G. sylvestre, M. charantia, H. antidysenterica, P. nigrum*, and *S. chirata* (Ghorbani 2014). Oral administration of Ziabeen (4 g/kg, daily for 30 days) to alloxan-induced diabetic rats improved glucose tolerance, lowered fasting blood glucose levels (56% on day 30), and increased body weight (Akhtar et al. 2012).

4.5.1.40 5EPHF

A polyherbal formulation (5EPHF) consisting of five medicinal plant extracts *viz., A. marmelos, M. koenigii, A. vera, P. pinnata,* and *Elaeodendron glaucum* was developed (Srivastava et al. 2012). Treatment with 5EPHF (200 mg/kg) to alloxan-induced diabetic rats resulted in significant reduction in the levels of serum glucose, glycated hemoglobin, total cholesterol, triglyceride, and LDL, whereas significant increase in the level of insulin and HDL was observed. The formulation treatment significantly inhibited lipid peroxidation and elevated the level of antioxidant enzymes in alloxanized rats. Furthermore, the treatment reduced histological damage in the pancreas of alloxan-diabetic rats (Lanjhiyana et al. 2011).

4.5.1.41 Other Formulations

An Indian traditional anti-DM herbal formulation containing *T. foenum-graecum, Sesamum indicum* seed, *Acacia catechu, A. indica* leaves, and *M. charantia* (fruit) was evaluated for hypoglycemic activity on adult Wistar albino rats by using normoglycemic, glucose-loaded, and alloxan-induced hyperglycemic rats. This formulation showed promising results that is comparable with that of reference standard glibenclamide. However, the exact biological active constituent responsible for hypoglycemic effect of the formulation has not been reported (Khan et al. 2011).

An Ayurvedic polyherbal formulation containing *A. indica* (leaf), *G. sylvestre* (leaf), *M. charantia,* (fruit), *S. cumini* (seed), and *T. foenum-graecum* (seed) is used to treat diabetes (Ghorbani 2014). Oral administration of this herbal product (500 mg/kg, daily for 4 weeks) to alloxan-induced diabetic rats resulted in marked reduction in the levels of fasting blood glucose (60%) and oxidative stress (Katiyar et al. 2012).

A novel polyherbal formulation containing *E. jambolana* (seed), *G., sylvestre* (leave), *M. charantia* (fruit), *M. pruriens* (seed), *T. foenum-graecum* (seed), and *W. somnifera* showed anti-DM activity in clinical trials. In one study, 93 patients with type 2 DM were administered 1 or 1.5 g of the polyherbal preparation three times a day for 12 weeks. The treatment (1.5 g) reduced fasting blood glucose (38%), postprandial blood glucose (43%), and glycated hemoglobin (21%) levels. No significant effect was observed on serum transaminases, alkaline phosphatase, urea, and creatinine levels (Ismail et al. 2012).

A polyherbal cream containing *A. vera, Cocos nucifera, C. longa*, *G. glabra, Musa paradisiaca*, and *Pandanus odoratissimus* was evaluated in a clinical trial (Ghorbani 2014). In the clinical trial, 20 patients with type 2 DM and foot ulcers were treated with the polyherbal cream for 5 months. The treatment stimulated wound healing and the effect was comparable with that of silver sulfadiazine (Viswanathan et al. 2011).

A traditional polyherbal formulation, consisting of *T. terrestris, P. nigrum, and Ricinus communis*, was evaluated for its anti-DM activity in alloxan-induced diabetic rats. Oral administration of the polyherbal formulation (100, 200, and 300 mg/kg) to diabetic animals up to 4 weeks dose-dependently reduced the blood glucose level, which was comparable with that of glibenclamide (5 mg/kg). Significant decrease in body weight was also observed in the diabetic control, which was partially restored upon administration of the polyherbal formulation. The polyherbal formulation also reduced elevated levels of selected biochemical parameters and prevented other complications of hyperglycemia. These findings provide scientific evidence to anti-diabetic use of the traditional formulation (Baldi and Goyal 2011).

An Ayurvedic polyherbal formulation (anti-diabetic churna) consists of eight ingredients: *E. jambolana* (seed), *M. charantia* (fruit), *A. indica* (leaf), *T. foenum-graecum* (seed), *E. officinalis* (pulp of fruit), *Casearea esculanta* (root and stem), *Veronia anthelmentica* (seed), and *Corallocarpus epigaea* (seed). This anti-diabetic churna is believed to be effective and has been standardized (Pradeep et al. 2011).

Dabur Madhu Raksha: The ingredients of Dabur Madhu Raksha (Manufacturer: Daber) are Amla (*P. emblica*), Tejpatra (*Cinnamomum tamala*), Vijaysar (*P. marsupium*), Gurmar (*G. sylvestre*), Jamun seed (*E. jambolana*), Kali marich (*P. nigrum*), neem leaves (*A. indica*), Methi (*T. foenum-graecum*), bahera (*T. belerica*), Karela fruit (*M. charantia*), hareetaki (*T. chebula*), and Shudh Shilajit. Controlled clinical trials or animal experiments are not available (Jonnalagadd and Selkar 2013).

Epinsulin: Episulin is a *P. marsupium*-containing formulation for DM (Bordoloi and Dutta 2014). Epicatechin is the major active principle in this formulation. Epicatechin increases the cyclic adenosine monophosphate content of the islet, which is associated with increased insulin release. It plays a role in the conversion of proinsulin to insulin by increasing cathepsin activity. Additionally, it has an insulin-mimetic effect on osmotic fragility of human erythrocytes and it inhibited Na/K ATPase activity from patient's erythrocytes. It corrected the neuropathy, retinopathy, and disturbed metabolism of glucose and lipids. It maintained the integrity of all organ systems affected by the disease. It is reported to be a curative for type 2 DM and a good adjuvant for type 1 DM to reduce the amount of needed insulin. It is advised along with existing oral hypoglycemic drugs and is known to prevent diabetic complications. It has gentle hypoglycemic activity and hence induces no risk of being hypoglycemic (Dwivedi and Daspaul 2013; Rajesham et al. 2012).

Madhumeha Kusumakara Rasa: The ingredients of Madhumeha Kusumakara Rasa (Manufacturer: Shree Dhoothapapeshwar Limited) are heavy metals, Mamajjaka ghana (dried water extract of *E. littorale*), Haridra (*C. longa*), Amalaki *(E. officinalis*), Guduchi (*T. cordifolia*), Bilva patra swaras (*A. marmelos*), Asana kwath (*P. marsupium*), Yashada bhasma (Zinc bhasma), and Shuddha Shilajatu (processed asphaltum) (Jonnalagadd and Selkar 2013). Controlled clinical trials or animal experiments are not available.

Madhumehari Granules: The ingredients of Madhumehari (Manufacturer: Baidyanath Ayurved Bhawan Pvt. Ltd., Kolkata, India) are gudmar (*G. sylvestre*), Jamun guthali (*S. cumini*), Gulvel (*T. cordifolia*), Karela Beej (*M. charantia*), Khadir Chuma (*A. catechu*), Haldi (*C. longa*), Amla (*E. officinalis*), Vijaysar (*P. marsupium*), Tejpatra (*C. tamala*), Gularphal Chuma (*Ficus glomerata*), Kutki (*P. kurroa*), Chitrak (*Plumbago zeylanica*), Methi (*T. foenum-graecum*), Bhavna of Neem Patti (*A. indica*), Bilwa Patra (*A. marmelos*), and Shilajit (Asphaltum) (Jonnalagadd and Selkar 2013). Controlled clinical trials or animal experiments are not available.

Mehagni: This is a polyherbal anti-DM tablet marketed in India. It is composed of *C. longa, P. emblica, G. sylvestre*, and *Salacia chinensis.* It is believed to be effective (Rashmi et al. 2014). Controlled clinical trials or animal experiments are not available.

Ojamin: The ingredients of Ojamin (Manufacturer: Tates Remedies) are *A. marmelos, T. foenum-graecum, Carum carvi, E. officinalis, T. chebula, T. bellirica, S. chirata, T. cordifolia, E. jambolana, P. kurroa, G. sylvestre, Sa. chinensis, C. longa, Melia azedarach,* and *A. indica* (Jonnalagadd and Selkar 2013). It appears that controlled clinical trials or animal experiments have not been not done on this formulation.

Pancreas Tonic: Pancreas Tonic, an Ayurvedic herbal supplement, is a botanical mixture of traditional Indian Ayurvedic herbs currently available as a dietary supplement. Treatment with Pancreas Tonic (two capsules, three times a day for 3 months) significantly improved glucose control in type 2 diabetic patients with glycated hemoglobin levels between 10% and 12%, but the treatment did not influence fasting blood glucose levels (Hsia et al. 2004).

Zpter: The ingredients of Zpter (Manufacturer: Om Pharmaceuticals Limited, India) are Vijayasar (*P. marsupium*), Dalchini (*Cinnamomum zeylanicum*), Haridra (*C. longa*), Haritaki (*T. chebula*), Bibhitaki (*T. bellerica*), Amalaki (*E. officinalis*), Chitrak (*Plumbago zeylanica*), Guduchi (*T. cordifolia*), and Madhunashini (*G. sylvestre*) and Jasad Bhasma (Jonnalagadd and Selkar 2013). Controlled clinical trials or animal experiments are not available.

4.5.2 Polyherbal Anti-DM Formulations Used in Chinese Medicine

Many polyherbal formulations are used to treat diabetes in Chinese medicine; use of polyherbal treatment is more than that of treatment with single herb. The most frequently used 10 medicinal plants in the Chinese herbal formulations to treat DM are Membranous Milkvetch (*A. membranaceus*) root, Rehmannia (*R. glutinosa*) root, Mongolian Snake gourd (*T. kirilowii)* fruit, *Panax ginseng* root, Chinese Magnolia vine (*Sc. chinensis*) fruit, Kudzu vine (*Pueraria montana*) root, Dwarf Lilyturf (*Ophiopogon japonicas*) tuber, Common Anemarrhena (*Anemarrhena asphodeloides*) rhizome,

Barbary Wolfberry (*Lycium barbarum*) fruit, and India Bread (*Triticum aestivum*) (Xie et al. 2011). Some of the important polyherbal formulations widely used to treat diabetes in Chinese medicine are given as follows.

4.5.2.1 Gan Lu Xiao Ke Capsule

This is one of the widely used formulations to treat type 2 DM in China. The ingredients of the formulation are rehmannia root (*R. glutinosa*), lycium root bark and berry (*Lycium carolinianum*), white ginseng (*P. ginseng*), astragalus root (*A. membranaceus*), cuscuta seed (*Cuscuta reflexa*), cornus fruit (*Cornus florida*), codonopsis root (*C. pilosula),* and coptis root (*C. chinensis*). Four to five 0.3 g capsules are consumed three times a day (Manufacturer: Xian Xinlong Pharmaceutical Co., Ltd.) (An 1985).

4.5.2.2 Yuquan Wan

Yuquan Wan has been long used to treat diabetes in Chinese medicines. The herbal ingredients of Yuquan Wan are *P. montana* root, *T. kirilowii* root, *R. glutinosa* root, *Ophiopogon japonicas* tuber, *Sc. chinensis*, and *G. uralensis* root. In a clinical study, among 18 diabetic patients treated with Yuquan Wan for 1 month, 72% of cases showed significant or moderate improvement in fasting blood glucose, and other diabetic symptoms such as thirst and hunger disappeared. Besides, Yuquan Wan improved the index of kidney injures of early diabetic nephropathy in diabetic patients, which suggested that it would prolong the development of diabetic nephropathy. The formulation improved the insulin resistance in patients with type 2 DM. Yuquan Wan reduced the levels of the increased proinflammatory cytokines in patients with type 2 DM. This herbal medicine had a significant effect on the pharmacokinetics of metformin hydrochloride in diabetic rats. Taken together, Yuquan Wan mainly improved diabetic complications and exerted a antihyperglycemic effect mediated likely by enhancing insulin sensitivity. No significant adverse effects were reported of this polyherbal formulation (Xie et al. 2011).

4.5.2.3 Tangmaikang Jiaonang

The ingredients of Tangmaikang Jiaonang include *A. membranaceus* root, *R. glutinosa* root, *Salvia miltiorrhiza* root (Danshen root), *Achyranthes bidentata* root (Cyathula), *Ophiopogon japonicas* tuber, and *Polygonatum cirrhifolium* rhizome (King Solomon's seal). Tangmaikang Jiaonang is used to treat type 2 DM and its complications. There were many clinical reports of Tangmaikang Jiaonang with good effects in treatment of type 2 DM, insulin resistance, dyslipidemia, diabetic peripheral neuropathy, and blood fluid parameters. These results were drawn only by comparing between before and after combined treatment with routine anti-diabetic drugs such as sulfonylureas or biguanides. Tangmaikang Jiaonang could reduce hypoglycemia and the dose of insulin at the base of controlled blood glucose. This formulation combined with metformin had better effect than metformin alone in newly diagnosed type 2 DM patients. Tangmaikang Jiaonang enhanced the effect of routine drug on diabetic peripheral neuropathy. The formulation combined with routine drugs had more improvement in blood fluid parameters than routine drugs alone. Tangmaikang Jiaonang mainly improved diabetic complications and exerted an antihyperglycemic effect mediated by increasing insulin sensitivity, but mostly used in combination with the regular antihyperglycemic measurements. There were no significant adverse effects reported in the studies (Xie et al. 2011).

4.5.2.4 Xiaoke Wan

Xiaoke Wan contains *A. membranaceus* root, *R. glutinosa* root, *T. kirilowii* root, *P. montana* root, *Dioscorea opposita* rhizome, *Sc. chinensis* fruit, *Zea mays* stigma, and glibenclamide. It is used to treat type 2 DM. Many clinical reports showed that Xiaoke Wan had similar or better antihyperglycemic effects in diabetic patients compared with glibenclamide. In these reports, more than 80% of type 2 DM patients had significant or moderate improvement in hyperglycemia and other diabetic symptoms. Xiaoke Wan had more improvement in other diabetic symptoms such as thirsty and hungry and complications such as blood lipid and blood fluid parameters than glibenclamide. In addition to stimulation of insulin secretion

mediated by glibenclamide (one of components in Xiaoke Wan), Xiaoke Wan enhanced insulin sensitivity likely mediated by promoting adiponectin secretion in type 2 DM patients. Xiaoke Wan was claimed to be safer than glibenclamide to a certain extent. Overuse should be avoided because this formula contained glibenclamide, which can easily cause hypoglycemic response after overuse (Xie et al. 2011).

4.5.2.5 Jinqi Jiangtang Pian

Jinqi Jiangtang Pian contains *A. membranaceus* root, *Nemipterus virgatus* (Golden thread), and *Lonicera tatarica* flower. Jinqi Jiangtang Pian had a moderate antihyperglycemic effect in mild or moderate type 2 DM patients but had no significant effect in severe type 2 DM patients when it was used alone. Nevertheless, its use combined with positive drug such as glibenclamide had better effects in type 2 DM patients after the treatment than glibenclamide alone. In addition, Jinqi Jiangtang Pian combined with positive drugs (such as metformin, acarbose, or glibenclamide) might have more improvement in diabetic dyslipidemia and the early development of diabetic nephropathy than positive drugs alone. Its antihyperglycemic action was related to improvement of insulin sensitivity by reducing serum lipid, regulating immune functions, enhancing antioxidative systems, and improving microcirculation and β-cell function. The formulation had no significant adverse effects in type 2 DM patients (Xie et al. 2011).

4.5.2.6 Jiangtangjia Pian and Kelening Jiaonang

Jiangtangjia Pian contains *A. membranaceus* root, *P. cirrhifolium* rhizome, *Pseudostellaria heterophylla* root (Falsestarwort), *T. kirilowii* root, and *R. glutinosa*. Jiangtangjia Pian is used to treat type 2 DM patients. In one clinical study (48 cases of type 2 DM patients), Jiangtangjia Pian improved blood glucose control after the treatment combined with anti-diabetic drugs such as sulfonylureas, biguanides, and insulin. Interestingly, in this study, blood glucose was poorly controlled in these patients of type 2 DM by using those anti-diabetic drugs before the use of this formulation. Furthermore, its single use also had an antihyperglycemic effect in 10 newly diagnosed type 2 DM patients.

Herbs in Kelening Jiaonang are similar to Jiangtangjia Pian but might have different oral dosage or prepared process. This formula is used to treat type 2 DM patients. In a clinical report, Kelening Jiaonang significantly lowered blood glucose level in type 2 DM patients combined with regular anti-diabetic drugs after treatment compared with that before treatment. Glibenclamide in combination with Kelening Jiaonang in treatment of type 2 DM patients was more effective and less toxic than its single use. Kelening Jiaonang administration for 1 month significantly improved blood glucose levels in 30 cases of type 2 DM patients who administrated regular anti-diabetic drugs but had poor control. Also, 8 weeks of treatment of Kelening Jiaonang had a significant improvement in blood glucose in those type 2 DM patients with sulfonylurea failure, which indicated that this formulation might improve insulin resistance. Both of these formulations reduced the blood glucose and increased body weight in alloxan-induced diabetic mice, suggesting that these drugs might exert an insulin-like effect. No significant adverse effects were reported of these herbs (Xie et al. 2011).

4.5.2.7 Xiaotangling Jiaonang

Xiaotangling Jiaonang contains *P. ginseng, N. virgatus* (Golden thread), *T. kirilowii* root, *Eucommia ulmoides* bark, *A. membranaceus* root, *S. miltiorrhiza* root (Danshen root), *L. barbarum* fruit, *Astragalus complanatus* seed, *Paeonia albiflora* root, *A. asphodeloides* rhizome, *Sc. chinensis* fruit, and glibenclamide. Xiaotangling Jiaonang is another formula that contained both herb medicines and glibenclamide. It was reported that Xiaotangling Jiaonang had significant antihyperglycemic effect in 30 cases of type 2 DM after treatment compared with that before treatment. Among 44 cases of type 2 DM, 88.6% of patients showed significant and moderate improvement after the herbal formulation treatment, while 75.0% of those patients ($n = 32$) treated with positive control showed the effect. About 98.67% of type 2 DM patients ($n = 150$) treated with Xiaotangling Jiaonang in combination with metformin showed significant or moderate improvement in diabetic symptoms and other

complications (diabetic dyslipidemia and blood fluid parameters) while only 78% of those patients ($n = 50$) treated with metformin alone showed similar effects. In addition, this herbal medicine effectively improved blood glucose control in 66.7% of diabetic patients ($n = 24$) with secondary failure of sulfanylurea. Xiaotangling Jiaonang treatment also increased insulin sensitivity index in type 2 DM patients ($n = 47$) compared with glibenclamide ($n = 35$), which indicated that treatment of this formulation could improve insulin resistance in these patients. Antihyperglycemic mechanisms of Xiaotangling Jiaonang are related to improvement in insulin sensitivity in type 2 DM patients (Xie et al. 2011).

4.5.2.8 Shenqi Jiangtang Keli

Shenqi Jiangtang Keli contains ginsenosides from ginseng stem and leaf, *A. membranaceus* root, *R. glutinosa* root, *L. barbarum* fruit, *T. aestivum, T. kirilowii* root, *Ophiopogon japonicas* tuber, *D. opposita* rhizome, *Sc. chinensis* fruit, *Rubus chingii* fruit (palm leaf raspberry), and *Alisma orientalis* rhizome (*Alisma plantago-aquatica*). Shenqi Jiangtang Keli is clinically used in type 2 DM patients. In a clinical study, 82.85% of type 2 DM patients ($n = 35$) showed appreciable effects after the treatment. Shenqi Jiangtang Keli significantly enhanced the antihyperglycemic effect of metformin in 30 cases of type 2 DM patients. Shenqi Jiangtang Keli alone had significant anti-diabetic effect in 235 cases of type 2 DM patients compared with diet or exercise-controlled controls. But most of the patients were diagnosed as slight or mild cases. The polyherbal formulation mainly improved the diabetic syndromes and even exerted an antihyperglycemic effect in type 2 DM patients with secondary failure to sulfonylureas. Anti-diabetic mechanisms of Shenqi Jiangtang Keli are related to improvement in sensitivity and restore functions of pancreatic islets in type 2 DM patients. The formulation had no significant adverse effects (Xie et al. 2011).

4.5.2.9 Other Formulation in Chinese Traditional Medicine

Other important polyherbal formulations approved by Chinese Food and Drug administration include Ganlou Xiaoke Keli, Jiantang Jiaonang, Jiangtangshu Jiaonang, Jiangtangning Jiaonang, Jiangtang Wan, Kangji Xiaoke Pian, Qizhi Jiangtang Jiaonang, Shenqi Jiangtang Keli, Shenhua Xiaoke Cha, Tangniaoling Pian, Tangle Pian, Tangniaole Jiaonang, Xiaokeling Pian, Xiaokeping Pian, Xiaokean Jiaonang, Xiaoke Jiangtang Pian, Yuquan Pian, Yuye Xiaoke Chongji, Yangyin Jiangtang Pian, Yijin Jiangtang Jiaonang, Yusanxiao Jiaonang, and Zhenqi Jiangtang Jiaonang (Xie et al. 2011). In addition to these, other Chinese polyherbal formulations in use are more than 50. These are used to treat DM and its complications, to a large extent, along with other treatments (Flaws et al. 2002).

4.6 Problems Associated with the Existing Polyherbal Formulations Including Ayurvedic Formulations

Although the existing formulations are not developed rationally, if efficacy and safety are satisfactory they are useful in the treatment of DM. But there are problems associated with the formulations. The phytochemical constituents of raw plant materials may vary due to different geographical locations, climatic conditions, environmental hazards, and so on. Besides, soil nutrition and ecological conditions, including microbial attack and insect attack, could change the efficacy and safety of the herbal drug. This is particularly true when the plant products are collected from the wild. In some cases diurnal variations (time of collecting the plant material) and the stage of maturities of the plant parts give variations in efficacy and/or safety. Different ecotypes and genotypes are known to occur in some plant species. It is not easy to standardize the finished herbal product for a reproducible quality. Thus, batch-to-batch variations in raw plant material could result in variations in efficacy and safety.

The variations can be overcome to a large extent when the plants are grown under specific growth conditions. There is a need to develop agrotechnology for plants currently collected from the wild considering the medicinal quality. Such an agrotechnology was not developed for most of the medicinal plants. Adulterations, substitutions, contamination, and shortcuts in manufacturing are not uncommon in the

Ayurvedic and other formulations available in the market. There is a misconception that Ayurvedic and other natural product formulations are always safe. Detailed toxicity evaluations and controlled clinical studies are lacking to a large extent. In some cases, good clinical practices, as applicable to the conventional modern medicine, are not followed in the case of Ayurvedic and traditional herbal medicines (Parasuraman et al. 2014). Many Ayurvedic formulations may contain added toxic mercury and lead. Although it is claimed that the purification/detoxification process will remove the toxicity, there is no solid experimental proof for the same (Parasuraman et al. 2014). In the case of medicines for diabetes, long-term toxicity evaluation is essential and toxic materials should not be included in the formulations.

Another point is the presence of too many ingredients in one formulation. For example, the polyherbal formulation Diabecon is prepared from about 24 plant species. It is possible that a few important plants in the formulation could be sufficient. No experimental proof is there to justify the presence of all these plant products in one formulation. Such a huge amount of phytochemicals may give immunological problems. There are needs to subject such polyherbal formulations to scientific rationale and detailed safety and efficacy evaluations. Consumption of numerous medicinal plants containing preparations for prolonged period may induce adverse immune responses and other cumulative adverse effects of certain phytochemicals. It is possible that in certain cases, a few ingredients may provide better effects than a formulation/medicine containing many ingredients.

4.7 Combination Medicines with Pure (Chemical Entity) Phytochemicals

Some of the limitations of crude plant preparations mentioned earlier can be overcome if combination drugs are developed using a few isolated active principles. Active principles with known mechanisms of action and safety can be carefully picked up as detailed above under development of rational polyherbal formulations (Section 4.4). Such preparations are likely to be extremely safe with excellent efficacy and could eventually cure certain types of type 2 DM. However, such combination medicines developed in light of modern medical sciences could be more expensive compared to crude polyherbal formulations or phytomedicines.

4.8 Conclusion

DM is a complex metabolic disease with many target molecules and cells for drug action. A combination of several bioactive phytochemicals acting on different targets involved in the complex metabolic disease, at low concentrations can exert greater ameliorative effects than high concentrations of a chemical entity drug acting on a major target molecule. The efficacy and safety margin could be more favorable in type 2 DM treatment with rationally formulated polyherbal medicines. Although polyherbal formulations are used to treat DM from ancient times onward, scientific studies on them are limited. However, available pharmacological and clinical evaluations of polyherbal formulations and combination therapies are promising. Low concentrations of different active principles can correct the metabolic syndrome. A polyherbal formulation or combination medicine could turn out to be a safer and effective medicine for DM. Use of nutraceuticals present in edible plant parts can further reinforce the safety aspect in the long run. If polyherbal preparations are developed, considering mechanisms of actions of individual ingredients and the combination, and drug interactions if any, will have the potentiality even to cure certain types of type 2 DM. A carefully developed rational combination of active molecules (crude polyherbal preparations prepared with standardized extracts/fractions or mixture of pure chemical entity active principles) could prove to be the best solution to combat DM. Several mechanisms of action involved are known in the therapy of DM with plant products. When most of the appropriate pathways are activated simultaneously by the combined action of reasonably low levels of several active principles, the anti-DM effects could reach the maximum level with the least or without adverse side effects. Future research should give more emphasis on the development of therapy with multiactive principles in a rational and scientifically defined manner. Possibly, due to the superior action of even the crude traditional combination therapy, new single chemical entity botanical product drugs are not emerging in the case of DM.

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5

Methods to Assess Anti-Diabetes Mellitus Activity of Plants

5.1 Introduction

Even today, the majority of the world population uses plant-based products (herbal formulations, decoctions, powders, etc.) to treat diabetes mellitus (DM). But, scientific studies have not established in most of the cases the safety and efficacy of traditionally used plant-based medicines. It is true that varying levels of pharmacological (reverse pharmacological) studies have been carried out on experimental animals to determine their usefulness as anti-DM therapeutic agents. However, these studies are insufficient to a large extent. One of the hindrances in the studies on traditional anti-DM plants and plant-based products is the nonavailability of expertise and appropriate inexpensive animal experimental models and *in vitro* assay systems in most of the laboratories, particularly, in the developing and underdeveloped countries. Although many animal models and *in vitro* systems are available, most of the scientific studies on anti-DM medicinal plants were carried out using alloxan-induced as well as streptozotocin-induced diabetic rats and mice. Some of the *in vivo* anti-DM models are overlapping between type 1 and type 2 DM; type 2 DM itself is a heterogeneous disease. In the reverse pharmacological studies on existing herbal drugs and in the development of new plant product-based drugs, evaluation of efficacy in appropriate *in vivo* animal models may be followed by *in vitro* mechanism of action studies and, if suitable, clinical studies. Agents that show anti-DM effect in animals are not necessarily effective in humans and vice versa. Similarly, agents that show anti-DM effects in *in vitro* assays are not necessarily effective in *in vivo* and vice versa. This could be due to the differences in the absorption, metabolism, and elimination of compounds. Studies on experimental animals and human clinical studies are essential to determine the safety and efficacy of herbal medicines. *In vitro* assays, by virtue of their more rapid output, lower cost, and need for less material, are ideal means of following the active components during a fractionation and isolation process (Soumyanath and Srijayanta 2005). To facilitate systematic study in this direction, the available important *in vivo* animal experimental models and *in vitro* assays and clinical methods are briefly described in this chapter with appropriate references for details.

5.2 Animal Models of DM

DM is induced in several species of experimental animals by pharmacological, surgical, or genetic manipulations. Most of the experiments on diabetes are carried out using rats and mice, although some studies are still performed in larger animals. Currently, the mouse model is one of the most used due to its small size, the availability of over 200 well-characterized inbred strains, and the ability to delete or overexpress specific genes through knockout and transgenic technologies (Masiello 2006; Rees and Alcolado 2005).

5.2.1 Chemical-Induced Models

The majority of animal experiments carried out to determine anti-DM activity of plants used toxic chemical-induced diabetic models. Streptozotocin and alloxan are by far the most frequently used drugs to induce DM and these models have been useful for the study of multiple aspects of the disease. Both drugs

exert their diabetogenic action when they are administered intravenously (i.v.), intraperitoneally (i.p.), or subcutaneously. Due to the similarity of alloxan and streptozotocin to glucose, glucose can compete with these chemicals and thus fasting animals tend to be more susceptible to alloxan and streptozotocin (King 2012). The dose of these agents required for inducing DM depends on the animal species, route of administration, and nutritional status of the animals. According to the administered dose of streptozotocin, duration of the administration, and developmental stages of animals used, syndromes similar to type 1 or type 2 DM can be induced (Arulmozhi et al. 2004; Frode and Medeiros 2008).

5.2.1.1 Alloxan-Induced DM

Alloxan is an oxygenated pyrimidine derivative. It is present as alloxan hydrate in aqueous solution. The cytotoxic action of alloxan is mediated by reactive oxygen species. Alloxan and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide with a simultaneous massive increase in cytosolic calcium concentration, which causes destruction of pancreatic β-cells. The range of the diabetogenic dose of alloxan is quite narrow and even light overdosing may be generally toxic and may cause the loss of many animals. This loss is likely to stem from kidney tubular cell necrotic toxicity. The most frequently used intravenous dose of alloxan in rats is 65 mg/kg, but when it is administered i.p. or subcutaneously its effective dose must be higher than 150 mg/kg. In mice, doses vary from 100 to 200 mg/kg i.v. In general, experimental protocols recommend that administration of alloxan must be done in the fasting period (8–12 h) followed by addition of glucose solution to avoid hypoglycemia. The destruction of pancreatic β-cells by alloxan is associated with a huge release of insulin, which makes animals susceptible to severe hypoglycemia that may be lethal. It is also reported that fasted animals are more susceptible to alloxan effects and increased blood glucose in fed animals provides partial protection. Alloxan is unstable in solution and, therefore, fresh preparations should be used (Frode and Medeiros 2008). Alloxan has been used to induce type 1 DM in rabbits (100–150 mg/kg, i.v.) and dogs (50–700 mg/kg, i.v.) also (Eddouks et al. 2012). Although alloxan-induced diabetes is generally considered as type 1 DM, the degree of β-cell destruction by alloxan may differ for a given dose and route of administration depending on nutritional and physiological state of the animals. Thus, the diabetic condition developed is rarely a typical type 1 DM with complete or almost complete β-cell destruction and negligible insulin production. Blood insulin levels and histological studies of islets of pancreas for insulin positive cells are needed to confirm the complete destruction of β-cells. Insulin content of pancreas can also be measured. However, alloxan diabetic animals are not resistant to insulin action. Furthermore, automatic regeneration of β-cells can occur. Therefore, sufficient number of alloxan-control animals should be used in experiments.

5.2.1.2 Streptozotocin-Induced DM

Streptozotocin (streptozocin) is a naturally occurring nitrosourea; it is a 2-deoxy glucose derivative of the carcinogen N-methyl-N-nitrosourea. Streptozotocin is produced by bacteria, *Streptomyces achromogenes*. The cytotoxic action of streptozotocin is also mediated by reactive oxygen species and alkylation of DNA. Streptozotocin enters the pancreatic β-cell via the glucose transporter 2 (GLUT2). Streptozotocin induces activation of poly adenosine diphosphate ribosylation, nitric oxide release, nicotinamide adenine dinucleotide^{+} (NAD^{+}) depletion, and reduction in adenosine triphosphate (ATP) production. Thus, streptozotocin indirectly destroys pancreatic β-cells by necrosis. In adult rats, 60 mg/kg (i.v.) is the most common dose of streptozotocin to induce insulin-dependent diabetes (Patel et al. 2006), but higher doses are also used. Streptozotocin is also efficacious after intraperitoneal administration of a similar or higher dose, but single doses below 40 mg/kg may be ineffective. In general, rats are considered diabetic if tail blood glucose concentrations in fed animals are greater than 200–300 mg/dL, 2 days after streptozotocin injection (Frode and Medeiros 2008).

The potential problem with streptozotocin is that its toxic effects are not restricted to pancreatic β-cells since it may cause renal injury (Valentovic et al. 2006), oxidative stress, inflammation, and endothelial dysfunction. The destruction of pancreatic β-cells by alloxan or streptozotocin is associated with a huge release of insulin, which makes animals susceptible to severe hypoglycemia. Thus, following treatment with

streptozotocin animals are fed with glucose solution (5%) for 12–24 h; afterward, an increase of glucose levels is observed in comparison to control animals due to insulin deficiency (Frode and Medeiros 2008).

In general, experimental protocols recommend that administration of streptozotocin must be done in the fasting period (8–12 h) followed by addition of glucose solution to avoid hypoglycemia. Besides rats, mice and dogs, other animal species such as rabbits, pigs, and monkeys have been used to induce diabetes by these protocols, but rabbits and pigs are more resistant to streptozotocin (Rees and Alcolado 2005). In general, the majority of published studies using these models of diabetes induced by chemical drugs report the amount of reduction of blood glucose following acute or chronic treatment with a specific natural product. Comparative studies are carried out with diabetic animal groups treated with known anti-diabetic drugs, but results do not permit to further explore the mechanism of action of the studied natural products (Frode and Medeiros 2008).

5.2.1.2.1 Streptozotocin-Induced Type 1 DM

In adult mice, streptozotocin given in multiple low doses (40 mg/kg, i.v. for 5 days) induces insulin-dependent diabetes that is quite similar to the autoimmune forms (islet inflammation and β-cell death) of type 1 diabetes (Rees and Alcolado 2005). In contrast, a single dose between 60 and 100 mg/kg of streptozotocin administered systemically to rats and mice can also cause insulin-dependent diabetes, but it lacks the autoimmune profile (Frode and Medeiros 2008).

Streptozotocin is used to induce type 1 DM in numerous species including hamster, shrews, rabbits, dogs, pigs, and primates. Severe insulin-dependent DM has been produced in the musk shrew by a single high-dose (100 mg/kg) intraperitoneal injection of streptozotocin. Type 1 DM can be induced in New Zealand rabbits by single intravenous injection of 65 mg/kg streptozotocin. Type 1 DM can be induced and maintained in vervet monkeys (*Chlorocebus aethiops*) with a single dose of intravenous administration of 45 or 55 mg/kg streptozotocin (Eddouks et al. 2012; Singh and Pathak 2015).

5.2.1.2.2 Streptozotocin-Induced Type 2 DM

Type 2 nonobese DM can be induced in rats by either intravenous (tail vein) or intraperitoneal treatment with streptozotocin to neonatal rats. Single dose of streptozotocin to rats in the first day of life (100 mg/kg, i.p.) or on day 2, 3, or 5 (120 mg/kg, i.p.) induces type 2 DM. At 8–10 weeks of age and thereafter, rats neonatally treated with streptozotocin manifest mild basal hyperglycemia, impaired response to the glucose tolerance test, and loss of pancreatic β-cell sensitivity to glucose. It has been observed that streptozotocin at first abolished the pancreatic β-cell response to glucose, but a temporary return of responsiveness then appears which is followed by its permanent loss. The neonatal streptozotocin model (with alterations in dose and day of streptozotocin injection) exhibits various stages of type 2 DM such as impaired glucose tolerance and mild, moderate, and severe glycemia. The β-cells in neonatal streptozotocin-diabetic rats bear a resemblance to insulin secretory characteristic found in patients with type 2 DM. Thus, the neonatal streptozotocin model can be considered as one of the animal models of type 2 DM (Arulmozhi et al. 2004; Frode and Medeiros 2008; Singh and Pathak 2015; Mythili et al. 2004).

A slow infusion of streptozotocin (130 mg/kg) in pigs on a low-fat diet induces the characteristic metabolic abnormalities of type 2 DM and it was found to be sensitive to oral metformin therapy. Insulin resistance in streptozotocin-diabetic pigs is most likely secondary to hyperglycemia and/or hyperlipidemia (Koopmans et al. 2006).

5.2.1.2.3 Streptozotocin–Nicotinamide–Induced Type 2 DM

In this model, nicotinamide is administered to provide partial protection from streptozotocin toxicity to β-cells (Masiello et al. 1998). This model appears closer to type 2 DM than other available animal models with regard to insulin responsiveness to glucose and sulfonylureas. Among the various dosages of nicotinamide tested in 3-month-old Wistar rats (100–350 mg/kg), the dosage of 230 mg/kg, given i.p. 15 min before streptozotocin administration (65 mg/kg i.v.) yielded a maximum of animals with moderate and stable nonfasting hyperglycemia (8.6 mM vs. 6.6 mM in controls) and 40% preservation of pancreatic insulin stores. Four to 9 weeks after inducing DM, in the isolated perfused pancreas of the DM rats, insulin response to glucose elevation was clearly present, although significantly reduced with respect to controls. Moreover, the insulin response to tolbutamide was similar to that observed

in normal pancreases. In rats administered streptozotocin plus nicotinamide, intravenous glucose tolerance tests revealed clear abnormalities in glucose tolerance and insulin responsiveness, which were interestingly reversed by tolbutamide administration (40 mg/kg, i.v.). The authors concluded that this novel noninsulin-dependent DM syndrome with reduced pancreatic insulin stores is similar to human type 2 DM in that it has a significant response to glucose (although abnormal in kinetics) and preserved sensitivity to tolbutamide; this model is useful for pharmacological investigations of new insulinotropic agents (Masiello et al. 1998). This model is in considerable use to test the anti-DM activity of botanical products. In one study, type 2 DM was induced by a single intraperitoneal injection of 60 mg/kg streptozotocin (Sigma Aldrich, Germany) followed by intraperitoneal administration of nicotinamide (Ranbaxy Chemicals Ltd, Mumbai, India) 120 mg/kg, 15 min afterward. Streptozotocin was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal saline. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h, and then on day 7 after injection. The threshold value of fasting plasma glucose to diagnose diabetes was taken as >6.88 mM (Shirwaikar et al. 2006).

5.2.1.2.4 High-Fat-Diet- and Streptozotocin-Induced Type 2 DM

Type 2 DM with insulin resistance and hyperglycemia was induced in rats by feeding high-fat diet and administering a normal dose of streptozotocin. In this method, male Sprague–Dawley rats (about 7 weeks old) were fed normal chow (12% of calories as fat) or high-fat diet (40% of calories as fat) for 2 weeks and then injected with streptozotocin (50 mg/kg, i.v.). Before streptozotocin injection, fat-fed rats had similar glucose concentrations to chow-fed rats, but significantly higher insulin, free fatty acid, and triglyceride concentrations. Plasma insulin concentrations in response to oral glucose (2 g/kg) were increased twofold by fat feeding and adipocyte glucose clearance under maximal insulin stimulation was significantly reduced suggesting that fat feeding induced insulin resistance. Streptozotocin injection increased blood glucose, insulin, and lipids in fat-fed rats compared with chow-fed streptozotocin-injected rats. Fat-fed streptozotocin-administered rats were not insulin deficient compared with normal chow-fed rats, but had hyperglycemia and somewhat higher insulin response to an oral glucose challenge. In addition, insulin-stimulated adipocyte glucose clearance was reduced in fat-fed streptozotocin-injected rats compared with both chow-fed and chow-fed streptozotocin-administered rats. Fat-fed streptozotocin-challenged rats were sensitive to the glucose-lowering effects of metformin and troglitazone (Reed et al. 2000).

5.2.1.2.5 High-Fat-Diet- and Low-Dose Streptozotocin-Induced Type 2 DM

In another study, type 2 DM was developed by feeding 4-month-old Sprague–Dawley rats with high-fat diet (30% of calories as fat) and injecting with a low dose (15 mg/kg) of streptozotocin after high-fat diet for 2 months. The body weight of rats in the group of rats given 15 mg/kg streptozotocin after high-fat diet for 8 weeks increased significantly more than that in the group of rats given 50 mg/kg streptozotocin (the model of type 1 diabetes) (595 vs. 352 g). Fasting blood glucose levels for high-fat diet and 15 mg/kg streptozotocin group were 16.9 mmol/L versus 5.2 mmol/L in normal control and 5.6 mmol/L in rats given high-fat diet only. The islet morphology (as examined by immunocytochemistry) in the high-fat and low streptozotocin group was affected; quantitative analysis showed that the islet insulin content was higher than that with type 1 DM. The authors concluded that the new rat model of type 2 diabetes established with conjunctive treatment of low dose of streptozotocin and high-fat diet was characterized by hyperglycemia, hyperlipidemia, and light impairment in insulin secretion accompanied by insulin resistance, which resembles the clinical manifestation of type 2 diabetes. Such a model, easily attainable and inexpensive, would help further elucidation of the underlying mechanisms of diabetes (Zhang et al. 2003).

In another study, type 2 DM rats were produced by intraperitonial administration of 35 mg/kg of streptozotocin to high-fat fed (58% of calories as fat) rats (Srinivasan et al. 2005). In this study, male Sprague–Dawley rats (160–180 g) were fed with normal pellet diet (12% calories as fat) or high-fat diet for a period of 2 weeks. The high-fat-fed rats exhibited significant increase in body weight, basal plasma glucose, plasma insulin, triglycerides, and total cholesterol levels compared to normal diet-fed control rats. Besides, the high-fat-fed rats showed significant reduction in glucose disappearance rate on intravenous glucose tolerance test. Hyperinsulinemia together with reduced glucose disappearance rate suggested that the feeding of high-fat-diet-induced insulin resistance in rats. After 2 weeks of dietary manipulation, the rats from control and high-fat-diet-fed groups were injected i.p. with streptozotocin

(35 mg/kg). Insulin-resistant high-fat-fed rats developed clear hyperglycemia upon streptozotocin injection that caused only mild elevation in plasma glucose in normal-diet-fed rats. Though there was significant reduction in insulin level after streptozotocin injection in high-fat-fed rats, the reduction observed was only to a level that was comparable with normal-diet-fed control rats. In addition, the levels of triglycerides and total cholesterol were further increased after streptozotocin treatment in high-fat-fed rats. In contrast, streptozotocin (35 mg/kg, i.p.) failed to significantly alter insulin, triglyceride, and total cholesterol levels in normal-diet-fed rats. Thus, these high-fat-diet fed streptozotocin-treated rats simulate natural disease progression and metabolic characteristics typical of individuals at increased risk of developing type 2 diabetes because of insulin resistance and obesity. Furthermore, the high-fat-diet-fed streptozotocin-treated rats were found to be sensitive for glucose-lowering effects of insulin-sensitizing (pioglitazone) as well as insulinotropic (glipizide) agents. Thus, the combination of high-fat-diet-fed and low-dose streptozotocin (i.p.)-treated rat serves as an alternative animal model for type 2 diabetes (Srinivasan et al. 2005).

5.2.1.3 Goldthioglucose-Induced DM

Obese type 2 diabetic mice can be induced by intraperitonial injection of goldthioglucose at doses ranging from 150 to 350 mg/kg. The mouse gradually develops obesity, hyperinsulinemia, and insulin resistance over a period of 16–20 weeks after goldthioglucose injection. This compound is transported in particular to the cells of ventro-medial hypothalamus and causes necrotic lesions, which subsequently leads to the development of hyperphagia and obesity. The treatment also increases body lipids, synthesis of triglycerides in the liver, and secretion of triglycerides; it increases adipose tissue lipogenesis and decreases glucose metabolism in muscle. These abnormalities are qualitatively similar to genetically obese mice (*ob/ob*). In addition, these diabetic mice exhibit many molecular defects in insulin signal transduction pathways (Singh and Pathak 2015).

5.2.1.4 Other Chemical-Induced DM

High fat or fructose and glucocorticopids induce type 2 DM in rats. Diets massively enriched with fats or fructose and the administration of glucocorticoids result in type 2 (noninsulin-dependent) diabetes in rats (Day and Bailey 2005).

Atypical antipsychotic drugs like clozapine and olanzapine induced type 2 DM in animals. Patients with schizophrenia are known to suffer from diabetes more often than the general population. Clozapine and olanzapine had a rapid potent effect on insulin sensitivity by lowering the glucose infusion rate and increasing hepatic glucose production in animals tested using hyperinsulinemic–euglycemic and hyperglycemic clamp procedures. Furthermore, these drugs decreased peripheral glucose utilization and impaired β-cell function as reflected by a decrease in insulin secretion. Thus, certain antipsychotic medications exert an immediate impact on metabolic parameters (Singh and Pathak 2015).

There are some other toxic chemicals known to cause DM in animals. For example, dithizone injection (50–200 mg/kg) produced initial hyperglycemia after 2 h and normoglycemia after 8 h and then hyperglycemia after 24–72 h. Another study described the effect of sirolimus on cyclosporine-induced pancreatic islet damage in rats. Sirolimus is diabetogenic and aggravates cyclosporine A-induced pancreatic islet dysfunction (Singh and Pathak 2015). However, these models are not well characterized and their usefulness in anti-DM activity screening has not been established.

5.2.2 Surgical Models of DM

Another technique used to induce type 1 DM is the complete removal of the pancreas. A few researchers have used this model in the last few years to explore effects of natural products using animal species such as rats, pigs, dogs, and primates (Choi et al. 2004a; Masiello 2006; Rees and Alcolado 2005). Limitations to this technique include (1) high level of technical expertise and adequate surgical room environment, (2) high risk of animal infection, (3) adequate postoperative analgesia and antibiotic administration, (4) supplementation with pancreatic enzymes to prevent malabsorption, and (5) loss of pancreatic counter

regulatory response to hypoglycemia. More recently, partial pancreatectomy has been used, but more than 80% surgical removal of pancreas in rats is required to obtain mild to moderate hyperglycemia. In this case, small additional surgical removal can result in significant hypoinsulinemia (Frode and Medeiros 2008; Masiello 2006). The relative glucose uptake in various tissues of 90% pancreatectomized rats could be studied by using either hyperglycemic or euglycemic hyperinsulinemic clamp methodologies. This experimental design permits to evaluate if the compound has some effect upon both resistance to and secretion of insulin (Choi et al. 2004b).

5.2.3 Spontaneous or Genetically Derived DM

Animal strains that develop spontaneous DM permit the evaluation of the effect of a natural product in an animal without the interference of side effects induced by chemical drugs like alloxan and streptozotocin reported above. Similar to the human condition, these strains display complex and heterogeneous characteristics of DM. In some of spontaneous models, insulin resistance predominates in association with obesity, dyslipidemia, and hypertension, which enables to study some events that are observed in human type 2 DM. Some obese strains like *ob/ob* mouse may maintain euglycemia due to a robust and persistent compensatory pancreatic β-cell response, matching the insulin resistance with hyperinsulinemia. On the other hand, the db/db mouse rapidly develops hyperglycemia since their pancreatic β-cells are unable to maintain the high levels of insulin secretion required throughout life. Food intake is important in determining the severity of the diabetic phenotype and restriction of energy intake reduces both the obesity and hyperglycemia seen in this strain of mice. An example of nonobese type 2 DM is the spontaneously diabetic Goto–Kakizaki (GK) rat (Chen and Wang 2005). Genetic defects and environmental factors contribute to the development of type 2 DM animal models. Many of these defects and contributing factors have been identified (Day and Bailey 2005). Most of the important models are given below.

5.2.3.1 Obese Models of Type 2 DM

Some of the commonly used spontaneous mutation or genetically derived obese models of type 2 diabetes are the following.

5.2.3.1.1 $Lep^{ob/ob}$ Mouse (ob/ob Mouse)

This is a monogenic model of obesity and type 2 diabetes in mice ($Lep^{ob/ob}$ mouse or ob/ob mouse). A spontaneous mutation discovered in an outbred colony was bred into C57BL/6 mice. The mutated protein was identified as leptin. The weight increase starts at 2 weeks of age and the mice develop hyperinsulinemia by 4 weeks and the blood glucose concentrations continue to rise, peaking at 3–5 months. Other metabolic aberrations include hyperlipidemia, a disturbance in temperature regulation, and lower physical activity. The pancreatic islet volume is markedly increased in these mice. Islets maintain insulin secretion and the β-cell failure is only partial. It is not a true representative of human type 2 DM (King 2012).

5.2.3.1.2 $Lepr^{db/db}$ Mouse (db/db Mouse)

This model is due to an autosomal recessive mutation in the leptin receptor. These mice ($Lepr^{db/db}$ mouse or db/db mouse) are hyperphagic, obese, hyperinsulinemic, and hyperglycemic. Obesity is evident from 3 to 4 weeks of age with hyperinsulinemia becoming apparent around 2 weeks of age and hyperglycemia developing in 4–8 weeks (King 2012).

5.2.3.1.3 Zucker Diabetic Fatty Rats

The Zucker Diabetic Fatty rats (ZDF rats) were discovered after a cross of Merck M-strain and Sherman rats. They have a mutated leptin receptor that induces hyperphagia and the rats become obese at 4 weeks of age with hyperinsulinemia, hyperglycemia, and hypertension. They also have impaired glucose tolerance (Srinivasan and Ramarao 2007). A mutation in this strain led to the derivation of a substrain with a diabetogenic phenotype. These rats are less obese than the ZDF rats, but have severe insulin resistance, which they are unable to compensate for due to increased apoptosis levels in the β-cells. These rats

show hyperinsulinemia at around 8 weeks of age followed by decreased insulin levels and diabetic complications (King 2012). In males, DM usually develops in 8–10 weeks, but females do not develop overt DM (Srinivasan and Ramarao 2007).

5.2.3.1.4 New Zealand Obese Mice

The New Zealand Obese mice model (NZO mice, polygenic model) was created by selective breeding. It is hyperphagic and obese, which may be a consequence of leptin resistance. They are resistant to peripheral leptin administration, but sensitive to centrally administered leptin indicating a defect in leptin transport across the blood–brain barrier. NZO mice are also hyperinsulinemic, which stems from hepatic insulin resistance from an early age, which seems to result from impaired regulation of liver fructose-1,6-bisphosphatase. They show elevated levels of blood glucose and impaired glucose tolerance, which worsens with age. Islets are hyperplastic and hypertrophic at 3–6 months of age, but β-cell loss occurs at later time points (King 2012).

5.2.3.1.5 Kuo Kundo Mice

This is a polygenic model of obesity. These mice are mildly obese with high levels of leptin. This strain is derived from wild-derived ddY mice in Japan. They develop severe hyperinsulinemia and demonstrate insulin resistance in both muscle and adipose tissue; the islets are hypertrophic and degranulated. Furthermore, this strain shows diabetic nephropathy. A derivative of this strain is the Kuo Kundo mice (KK-A^Y) mice, which were created by introducing the yellow obese A^Y gene in the KK strain. This mouse develops maturity obesity and has more severe hyperinsulinemia and more prominent changes in the pancreatic islets. This is due to the ectopic expression of the agouti protein antagonizing the melanocortin receptor 4 in the hypothalamus (King 2012).

5.2.3.1.6 Otsuka Long-Evans Tokushima Fat Rat

Otsuka Long-Evans Tokushima Fat (OLETF) rat was derived from a spontaneously diabetic rat discovered in an outbred colony of Long Evans Rats. Selective breeding led to the OLETF strain that has mild obesity and hyperglycemia after 18 weeks. Diabetes is inherited by the males. The pancreatic islets undergo cellular infiltration (6–20 weeks of age), hyperplasia (20–40 weeks), and finally islets become fibrotic. These rats also exhibit renal complications (King 2012).

5.2.3.1.7 TallyHo/Jng Mice

TallyHo/Jng mice are a naturally occurring model of obesity and type 2 diabetes, derived from selective breeding of mice that spontaneously developed hyperglycemia and hyperinsulinemia in an outbred colony of Theiler Original mice. In these mice, adiposity and lipid levels were increased. Hyperglycemia is limited to male mice, which develops in 10–14 weeks. The pancreatic islets are hypertrophied and degranulated and hyperinsulinemia is evident. This model has not been completely characterized for diabetic complications (King 2012).

5.2.3.1.8 NoncNZO10/LtJ Mice

NoncNZO10/LtJ mice were created by combining independent diabetic risk-conferring quantitative trait loci from two unrelated strains of NZO mice with nonobese, nondiabetic mice. These mice develop liver and skeletal muscle insulin resistance at 8 weeks of age and chronic hyperglycemia from about 12 weeks. Islet mass initially increases and subsequently β-cell loss occurs. Diabetic nephropathy has been observed in some males aged about 1 year and this model is used for diabetic wound healing also (King 2012).

5.2.3.1.9 Tsumara Suzuki Obese Diabetic Mice

By selective breeding of obese male mice of ddY strain, an inbred stain with obesity and increase in urinary glucose named Tsumara Suzuki Obese Diabetic (TSOD) mice was developed. TSOD mouse is of polygenic origin and characterized by polydipsia and polyurea at about 2 months of age, only in male mice, followed by hyperglycemia and hyperinsulinemia. Following these symptoms, obesity gradually developed until about 12 months old. Severe hypertrophy of pancreatic islets was observed

due to proliferation and swelling of β-cells. It has been shown that TSOD mice are almost similar to type 2 DM in humans. It is considered as a useful model for the pathogenic study of diabetic complications (Singh and Pathak 2015).

5.2.3.1.10 Obese Rhesus Monkey (Macaca mulata)

Obese rhesus monkey is an excellent nonrodent model of type 2 obese DM. This monkey develops obesity, hyperinsulinemia, and insulin resistance when maintained on *ad libitum* laboratory diet, which gradually progresses to necrosis of β-cells, severe fall in insulin levels, and overt hyperglycemia over a period of several years. Unlike small rodent models, the final secretion loss is associated with deposition of amylin/amyloid in β-cells and the development of complications similar to human type 2 DM. Pioglitazone has been demonstrated to improve insulin resistance in the obese rhesus monkeys (Singh and Pathak 2015).

Spontaneous models of impaired glucose tolerance that do not usually develop overt diabetes include aging laboratory rats and mice, Zucker fatty rat, nonobese, and noninsulin-dependent diabetic mouse, Bureau of Home Economics rat, Yucatane miniature swine, and so on (Day and Bailey 2005).

5.2.3.2 Nonobese Models of Type 2 DM

Not all type 2 diabetic patients are obese. So there is a need to use lean animal models of type 2 DM also. These include models that have β-cell insufficiency, which ultimately leads to overt type 2 DM in humans. (Neonatal streptozotocin-diabetic rats described in Section 5.2.1.2.2 and streptozotocin nicotenamide induced type 2 DM described in Section 5.2.1.2.3 are also nonobese type 2 diabetic models.)

5.2.3.2.1 Goto–Kakizaki Rats

GK rats were created by repetitive breeding of Wistar rats with the poorest glucose tolerance. This led to the development of a lean model of type 2 DM with glucose intolerance and defective glucose-induced insulin secretion. The development of insulin resistance does not seem to be the main initiator of hyperglycemia in this model; the defective glucose metabolism is considered to be due to aberrant β-cell mass and/or function. However, islet morphology and metabolism seem to differ between different colonies of these rats. The hyperglycemia seems to result from insulin secretory defects. These rats have been used to study β-cell dysfunction in type 2 DM, diabetic complications, and so on (King 2012).

Other nonobese type 2 DM models include Cohen diabetic rat, Torri rat, nonobese C57BL16 (Akitta) mutant mouse, and ASL/Lt mouse (Eddouks et al. 2012).

5.2.3.3 Autoimmune Model of Type 1 DM

The commonly used autoimmune model of type 1 DM includes the NOD mouse (nonobese diabetic mouse), Biobreeding rat (BB rat), and Lewis rats with a defined MHC haplotype (LEW.1AR1/Ztm.iddm) rat. One great advantage of these models is that they can also be used as a model of atherosclerosis, which represents the long-term complication of DM and tested against several natural products (Wu and Huan 2007).

5.2.3.3.1 NOD Mice

The NOD mouse is widely used to test natural products. NOD mice develop insulitis in 3–4 weeks of age. At this stage, the pancreatic islets are predominately infiltrated with CD^{4+} and CD^{8+} lymphocytes. This model typically presents hyperglycemia between 12 and 30 weeks of age. Diabetes is more prevalent in the females compared to males. When these mice become overtly diabetic, they rapidly lose weight and require insulin treatment. Development of DM in the NOD mice is negatively associated with microbial exposure. Therefore, the mice should be kept in specific pathogen-free conditions. The NOD mouse is often used in intervention studies in attempts to prevent or delay the onset of autoimmune disease. This model does represent many aspects of the human disease (King 2012).

5.2.3.3.2 Biobreeding Rats

BB or BB-DP (diabetes-prone BB) rat is an inbred laboratory strain that spontaneously develops autoimmune type 1 DM. These rats usually develop diabetes just after puberty; hyperglycemia occurs normally around 12 weeks of age and have similar incidence in males and females. In this model, the diabetic phenotype is quite severe and the rats require insulin therapy for survival. Unlike NOD mice, these animals are lymphopenic with a severe reduction in CD^{4+} and CD^{8+} T cells. Lymphopenia is not a characteristic of type 1 DM in humans. However, the model has been available in elucidating more about the genetics of type 1 DM. Besides, BB rats have been used in intervention studies and studies of diabetic neuropathy (King 2012).

5.2.3.3.3 LEW.1AR1/Ztm.iddm Rat

This is another model of spontaneous insulin-dependent DM rat. This rat model arose spontaneously in a colony of congenic LEW.1AR1. These rats exhibit insulitis and overt diabetes manifests at around 8–9 weeks. The incidence of diabetes is approximately 60% with equal incidence in both genders. The relatively short prediabetic period in these animals allows for effective analysis of different stages of the immune cell infiltration. It also survives well after the onset of overt diabetes and thus can be used to study diabetic complications (King 2012).

5.2.3.3.4 AKITA Mice

This is a genetically induced insulin-dependent diabetes. This was derived in Akita, Japan, from a C57BL/6NS1c mouse with a spontaneous mutation in the insulin 2 gene preventing correct processing of proinsulin. This causes an overload of misfolded proteins and subsequent endoplasmic reticulum (ER) stress. This results in severe insulin-dependent diabetes starting from 3 to 4 weeks of age. Untreated homozygotes rarely survive longer than 12 weeks. It has also been used as a model of type 1 diabetic macrovascular disease and neuropathy. In addition, this model is used to study alleviators of ER stress in the islets and in this respect it shows some of the pathology of type 2 DM also (King 2012).

Other prone strains to type 1 DM include New Zealand white rabbit, Kreesbond dog, Chinese hamster, and Celebes black ape. However, they have not been used in studies to evaluate natural products to treat diabetes, except in preclinical trials of exenatide (incretin analog) (Rees and Alcolado 2005).

5.2.3.4 Genetically Engineered DM

In this case, rodents may be produced to express a gene transferred from another species (transgenic) or inactivate or remove an existing gene (knockout), which is thought to play a key part in glucose metabolism. Although significant advances in this field have arisen in recent years, especially with the advent of transgenic mice, there have been no or extremely limited studies carried out on natural products using these models. Certainly, the high costs restrict their study in sophisticated protocols that explore mechanisms of potential therapeutic agents that either stimulate pancreatic β-cell growth or inhibit pancreatic β-cell death (Frode and Medeiros 2008). Genetically engineered mice that show a sustained period of noninsulin-dependent diabetes include insulin receptor knockout in liver (IR–/– liver), insulin receptor substrate-2 knockout (IRS-22−/−), GLUT4 heterozygous knockout (GLUT4+/−), hepatic nuclear factor-1 knockout (HNF-1α−/−), and so on (Day and Bailey 2005). Genetically engineered mice have been created to allow ablation of β-cells in adult mice. Regeneration after ablation of β-cells can be studied using these models. These models include doxycycline-induced expression of diphtheria toxin in β-cells and diphtheria toxin receptor-rat insulin promoter (RIP) mice. In the later model, the β-cells have been genetically modified to express the diphtheria toxin receptor under the insulin promoter. Thus, diphtheria toxin can be administered and will selectively ablate the insulin-producing cells as mouse cells do not normally express the diphtheria toxin receptor. When the toxin is withdrawn, the β-cells regenerate over a period to some extent and the effect of candidate natural products on the regeneration can be studied (King 2012). In addition, knockout and transgenic mice have become a powerful tool in elucidating the influence of specific genes in glucose metabolism and the pathogenesis of DM.

5.2.3.4.1 Human Islet Amyloid Polypeptide Mice

A characteristic of type 2 DM in humans is the formation of amyloid within the islet tissue, which derives from amyloid polypeptide (IAPP). Rodent IAPP is not amyloidogenic. However, transgenic mice have been created to express human IAPP under the insulin promoter that can form amyloid within the islets. It has been demonstrated that increasing the expression of hIAPP increases β-cell toxicity. Adaptation of β-cell to increased insulin demand is restricted in this model (King 2012).

5.2.4 Diet/Nutrition-Induced Type 2 DM

5.2.4.1 C57/BL6J Mouse

A type 2 DM model was developed by simply feeding high-fat feed to nonobese, nondiabetic C57BL/6J mouse strain. It is characterized by marked obesity, hyperinsulinemia, insulin resistance, and glucose intolerance. In addition, they exhibit marked fasting as well as basal hyperglycemia. These mice develop severe obesity and diabetes if weaned onto high-fat diets. In these mouse, the severity of DM is a direct function of obesity; diabetes is completely reversible by reducing dietary fat. These mice when treated with inhibitor of dipeptidyl peptidase-4 (DPP4) exhibited normal glucose tolerance in association with augmented insulin secretion (Singh and Pathak 2015).

5.2.4.2 Other Diet-Induced Rodent Models

Desert gerbil (*Psammomys obesus*) and Nile grass rat (*Arvicanthis niloticus*) tend to develop obesity and diabetes in captivity due to the availability of plenty of food. Desert gerbils are not hyperphagic but when high-energy nutrition is made available with limited physical activity, obesity, hyperinsulinemia, and subsequently diabetes develop. Researchers have used these animals in studies that aim to prevent nutritionally induced DM. Nile grass rat spontaneously develops obesity, dyslipidemia, and hyperglycemia by 1 year of age when kept on normal chow diet in captivity. They show other signs of DM and metabolic syndrome such as reduced β-cell mass, atherosclerosis, and liver steatosis (King 2012). Other/nutrition/diet-induced obese diabetic animals include Sand rat and Spiny mouse (Eddouks et al. 2012).

5.2.5 Other Animal Models of DM

5.2.5.1 Virus-Induced Model of DM

Epidemiological studies suggest the involvement of viral infections in the pathogenesis of type 1 DM in humans. Several animal models have used viruses to initiate β-cell destruction. The destruction can be either due to direct infection of β-cells or initiation of an autoimmune response against β-cells. Viruses used to induce diabetes in animals include coxsackie virus, encephalomyocarditis virus, and Kilham rat virus. In the BB diabetes-resistant rat, infection with a parvovirus induces islet destruction via upregulation of the toll-like receptor 9-signaling pathway. However, the virus-induced model can be complicated as the outcome is dependent on replication levels of the virus as well as timing of the infection (King 2012; Singh and Pathak 2015).

5.2.5.2 Intrauterine Growth Retardation–Induced Diabetic Rats

A method to induce diabetes in adult rats is to mimic the unfavorable intrauterine environment, which in humans leads to low birth weight and is supposed to confer high risk for the development of diabetes in adult age. This model known as intrauterine growth retardation by uteroplacental insufficiency in the rat is based on the belief that uterine malnutrition may also increase the risk of diabetes among offspring in later life. This has been demonstrated by several means, including bilateral uterine artery ligation at 19 days of gestation in rats. The diabetogenic effects of manipulating the intrauterine environment are probably mediated by a permanent programming of the developing offspring. It is of interest to note that the increased risk of diabetes continues into subsequent generations, which in turn suggests that changes

also affect the germ cell line. Animal models with increased pancreatic β-cell apoptosis have also been developed (Frode and Medeiros 2008).

5.2.5.3 Models for Diabetic Complications

Microvascular (retinopathy and nephropathy) and neuropathic disorders that typically develop with chronic diabetic hyperglycemia in human diabetes are uncommon in common rodent models of diabetes. This probably reflects the relatively short life span of rodents compared with the protracted period of hyperglycemia required for development of these complications. Nevertheless, ageing diabetic rodents, particularly those with severe hyperglycemia, sometimes exhibit thickening of glomerular capillary basement membranes and increased loss of urinary albumin. Cataracts and impaired conduction by peripheral nerves are also evident in some models, but classical proliferative retinopathy and autonomic neuropathy have not been observed. A useful model of the insulin-resistance syndrome is the spontaneously hypertensive rat. This carries the *cp* (corpulent) mutation of the leptin receptor and, in conjunction with a genetic susceptibility for hypertension, produces a syndrome of obesity and insulin resistance. Some strains also develop hyperlipidemia, noninsulin-dependent diabetes, atherosclerosis, and ischemic heart disease (Day and Bailey 2005). Some of the models mentioned in the Section 5.2.3 can also be used for diabetic complication studies. For example, LEW.lARl/Ztm.iddm rat (type 1 DM) survives well after the onset of overt DM and this can be used to study the complications of DM. TSOD mice are almost similar to type 2 DM in humans and are considered as useful for the pathogenic study of diabetic complications. NoncNZO10/LtJ mice are used for diabetic wound healing and nephropathy studies.

5.2.6 Assessment of Anti-DM Activity Using Animal Models

At least one *in vivo* experimental study should be carried out in a suitable animal model using the herbal preparation in the way it is used in traditional medicine. Different parts of plant (fresh and dried) have to be compared to select the best plant part. In most of the studies available in the literature, water or alcohol extract was used to test the anti-DM properties; in some cases, the studies were carried out after defatting the plant materials with ether. It is observed that the defatting procedure could result in the loss of the active principles in certain cases. Active principles soluble in nonpolar solvents such a petroleum ether and n-hexane are also present in certain plants. Therefore, different extracts including nonpolar solvent extracts have to be screened to select the best extract.

The guidelines that apply to preclinical testing of a new chemical entity drugs do not necessarily apply to a traditional medicinal plant treatment. For example, the part of the plant (e.g., leaf or root) may be a normal dietary ingredient traditionally consumed as a raw or cooked ingredient of diet. The same edible part of the plant may also be used as an unrefined extract (e.g., simple decoction or infusion) to control DM. If the purpose of testing is to assess claimed anti-diabetic efficacy of the plant as a normal dietary adjunct, a comprehensive program of tests designed for a new chemical entity would not be appropriate. If it is proposed to consume inordinately large quantities of an unrefined extract, chronic toxicity assessments are indicated. Standard preclinical tests should be anticipated for a highly refined extract or novel isolated principle if this is proposed for clinical investigation and possible therapeutic use as a conventional medicine.

5.2.6.1 Selection of an Appropriate Animal Model

Although toxicity tests are customarily undertaken in normal, nondiabetic animals, efficacy studies are most usefully undertaken in models that most closely represent the clinical target population. The importance of the progressive loss of pancreatic β-cell reduction in the course of type 2 DM has been the focus of therapeutic targets in the development of novel and potential drugs acting by enhancing pancreatic β-cell growth and/or survival (Masiello 2006).

The heterogeneity of human types of DM and the lack of exact replicas among nonprimate animals often require efficacy studies in more than one model after establishment of anti-DM activity in preliminary screenings. Accounts of the traditional use of anti-diabetic plants in type 1 or type 2 diabetic

patients provide an indication of the type of model (e.g., insulin dependent or noninsulin dependent) that might be suitable for initial investigation of hypoglycemic activity (Day and Bailey 2015). In type 2 DM, the mechanisms underlying the hyperglycemia should be considered and whether this is relevant to the study of selected natural products. For example, it should be noted that not all animal models of DM and strains develop DM complications. To study DM complications, accordingly a suitable model should be selected. Many animal models have a gender bias that does not exist in humans. The exact mechanisms of gender bias have not been elucidated; it could be the differences in the hormones. This aspect should be considered while selecting the models and animals (males and females).

Experimentally induced models of insulin-dependent diabetes are often not completely devoid of endogenous insulin. This is an important consideration when claims of an insulin substitute are being investigated. To test the efficacy of anti-diabetic plants using streptozotocin-induced or alloxan-induced diabetes in rodents, a convenient procedure is to commence plant therapy within a few days of streptozotocin/alloxan administration before hyperglycemia becomes severe. Efficacy can then be judged by a slower progression and less severe hyperglycemia. If the study is continued until a parallel placebo (untreated) group develops ketoacidosis and requires insulin, this suggests anti-diabetic activity in an insulin-dependent state. However, it is possible that the therapeutic intervention has prevented complete β-cell destruction. This can be seen if insulin concentrations are measured and animals survive when the intervention is discontinued. Because some natural regeneration of islets can occur from islet remnants, long-term survival cannot be exclusively attributed to the therapeutic intervention (Day and Bailey 2015).

An alternative protocol to test efficacy in an insulin-dependent state is to introduce plant therapy to spontaneously or experimentally induced models that have already developed severe hyperglycemia and are controlled by exogenous insulin injections. When plant treatment is introduced and the dosage titrated up, evidence of reduced hyperglycemia or a reduction of insulin dosage without deterioration of glycemic control can be used as indices of efficacy.

Human type 2 diabetes arises through the combined impact of varying levels of insulin resistance and β-cell dysfunction. Therefore, a model designed to test efficacy in type 2 DM should exhibit both of these pathogenic features. Therapies that ameliorate obesity and dyslipidemia offer secondary benefits to improve glycemic control in obese patients; therefore, models that incorporate these features can often yield additional relevant information. Thus, the diabetic db/db mouse and male ZDF rat provide very useful models for type 2 DM. It is noteworthy that a plant treatment may have no efficacy if the model in which it is tested lacks the particular pathogenic feature (e.g., insulin resistance, β-cell dysfunction, obesity, dyslipidemia) against which the treatment exerts its main effect. It may be necessary to conduct studies in at least a few relevant animal models to establish efficacy as well as to get insights into mechanisms of action (Day and Bailey 2015).

5.2.6.1.1 Pharmacological Assessment of End Points

Pharmacological assessment of anti-DM activity of botanical products will be determined through measuring different biochemical parameters. This includes evaluating the serum glucose, serum insulin, glycosylated hemoglobin, total cholesterol, triglyceride, serum urea, serum creatinine, and markers for liver function (plasma alanine transaminase, plasma aspartate amino transferase, and alkaline phosphatase). The anti-diabetic activity will be further confirmed through histopathological evaluation of pancreatic sections and insulin content in pancreas.

Serum glucose is the most important biochemical parameter for the evaluation of the anti-DM activity. This can be measured using the glucose oxidase method, which is based upon the oxidation of glucose to gluconic acid and hydrogen peroxide in the presence of glucose oxidase. Then, in the presence of peroxidase, hydrogen peroxide combines with 4-aminophenazone and phenol to form a pink-colored quinoneimine dye. Its intensity is subsequently measured at 546 nm and is directly proportional to the glucose concentration present in the specimen (Barham and Trinder 1972). Serum insulin is also one of the most decisive parameters in the estimation of hypoglycemic activity. It is evaluated using the radioimmunoassay kit, which is a double-antibody method. Insulin in the sample competes with a fixed amount of ^{125}I-labeled insulin for specific antibody's binding sites. Then, addition of a second antibody causes an effective separation of bound and free insulin followed by centrifugation and finally decantation. The radioactivity in the pellet is subsequently measured, and it is inversely proportional to the

quantity of insulin present in the sample. This test is effective in the determination of insulin levels in the bloodstream and is also useful in the evaluation of pancreatic β-cell activity (Hales and Randle 1963). Glycosylated hemoglobin is also an important parameter to be assessed. It gives an indication of the blood-glucose level over the past period (usually 3 months). It is estimated by lysis of the blood specimen followed by exposure to protease digestion. Amino acids, including glycated valines from the β-chains of hemoglobin, are successfully released. These acids act as a substrate for recombinant fructosyl valine oxidase enzyme, released by *Escherichia coli*, which specifically cleaves N-terminal valines thus, producing hydrogen peroxide. The latter is then evaluated using a horseradish peroxidase catalyzed reaction together with a suitable chromagen. For total hemoglobin estimation, it is performed through the conversion of all the specimen hemoglobin derivatives to hematin using an alkaline method. The blood specimens are then subjected to lysis with a consequent hemoglobin release. The same lysate undergoes two parallel tests; the first determines the glycated hemoglobin content, while the second test evaluates total specimen hemoglobin content. Finally, HbA1c concentration is expressed as a ratio of glycated hemoglobin to total hemoglobin (Wolf et al. 1984).

5.2.7 Nonmammalian Animal Models

5.2.7.1 Zebrafish Model of DM

The zebrafish is a small freshwater fish that was developed as an animal model in the 1980s for the study of developmental biology. In contrast to rodents, zebrafish embryos are optically transparent and zebrafish development is external that permits direct observation of embryonic development. In living zebrafish larvae, pancreatic cells can be visualized. Zebrafish larva is shown in Figure 5.1a. The zebrafish is a good model for screening of anti-DM natural products. The development of zebrafish-based anti-DM compound screening is based on the marked similarities in glucose homeostasis with mammals. It has recently been demonstrated that anti-diabetic natural compounds can be identified in zebrafish using activity-guided fractionation of crude plant extracts. Furthermore, the development of fluorescent-tagged glucose bioprobes has allowed the screening of natural product-based modulators of glucose homeostasis in zebrafish.

Diabetes can be induced in zebrafish by simply adding glucose to the fish water. Besides, zebrafish are inexpensive and easier to handle compared to mammalian models. This model requires less time for screening for anti-DM compounds and less amount of test compound is required relative to mammalian *in vivo* models. It has been demonstrated that hypoglycemia inducing drugs, which function via PEPCK (phosphoenoyl pyruvate carboxy kinase 3) inhibition could be detected using zebrafish larvae, which are amenable for 96-well plate format screening. Fluorescence imaging of whole zebrafish is possible for glucose uptake analysis. Furthermore, diabetes-related gene-based screening is also possible. Since the zebrafish has marked similarities in glucose homeostasis with mammals, this fish can be used to study pancreatic β-cell neogenesis, quantitative analysis of glucose homeostasis, and diabetic complications. Transgenic zebrafish lines that monitor and allow the quantification of cell proliferation by using the fluorescent ubiquitylation-based cell cycle indicator technology were developed; furthermore, transgenic zebrafish were developed to study insulin resistance. Studies using this unique *in vivo* fish model, already, led to the identification of β-cell differentiation and proliferation effects of drugs (Tsuji et al. 2014). Recently, this interesting zebrafish model in the study of Anti-Diabetes natural products has been updated in an excellent review (Tabassum et al. 2015).

5.2.7.2 Silkworm Model of DM/Hyperglycemia

The silkworm (Figure 5.1b) is the larva or caterpillar of the domesticated silkmoth, *Bombyx mori*. Sugar levels in the silkworm hemolymph (blood of silkworm) increased within 1 h after intake of a high-glucose diet, and that the administration of human insulin decreased elevated hemolymph sugar levels in silkworms. Thus, it appears that silkworms may be useful to screen agents from plants that act like insulin. However, in this hyperglycemic silkworm model, administration of pioglitazone or metformin, drugs used clinically for the treatment of type 2 diabetes, had no effect (Matsumoto et al. 2011). The same

(a) (b)

FIGURE 5.1 Nonmammalian models for screening anti-diabetes mellitus activity. (a) Zebrafish larva (30 h postfertilization; photo courtesy of Prof. Lalitha Ramakrishnan) and (b) silkworm.

others have established a silkworm model of type 2 diabetes for the evaluation of anti-diabetic drugs such as pioglitazone and metformin. Silkworms fed a high-glucose diet for more than 18 h exhibited a hyperlipidemic phenotype. In these hyperlipidemic silkworms, phosphorylation of C-Jun N-terminal kinase (JNK), a stress-responsive protein kinase, was enhanced in the fat body, an organ that functionally resembles the mammalian liver and adipose tissue. Fat bodies isolated from hyperlipidemic silkworms exhibited decreased sensitivity to human insulin. The hyperlipidemic silkworms have impaired glucose tolerance, characterized by high fasting hemolymph sugar levels and higher hemolymph sugar levels in a glucose tolerance test. Administration of pioglitazone or metformin improved the glucose tolerance of the hyperlipidemic silkworms. These findings suggest that the hyperlipidemic silkworms are useful for evaluating the hypoglycemic activities of candidate drugs against type 2 diabetes (Matsumoto et al. 2015). This may be useful as an inexpensive model for initial screening of botanical products. However, more studies are required to establish the reliability of this method.

5.3 *In Vitro* Methods

Anti-diabetic agents in current use as well as herbal drugs can affect several pathways of glucose metabolism such as insulin secretion, insulin sensitivity, glucose absorption, and so on. Incretins and transcription factors such as peroxisome proliferator–activated receptor-gamma (PPAR-γ) are valuable targets of modern therapy. Insulin receptor, GLUT, however, has not been yet the focus of anti-diabetic therapy. Plant products also positively influence these targets (see Chapter 3). *In vitro* methods involved in these studies serve as complementary tools to understand the mechanisms of action of selected plant extract or isolated compounds and to explore findings obtained in *in vivo* models.

5.3.1 Stimulation of Insulin Secretion

A number of *in vitro* models have been developed for studying the pancreatic secretion of insulin. These include the perfused pancreas, intact isolated islets, purified β-cells, and insulin-secreting cell lines. Insulin released is measured by radioimmunoassay (using ^{125}I-labeled insulin) or enzyme-linked immunoassay (Ruitton-Uglienco 1981). Perfused pancreas, isolated islets, and purified β-cells are all prepared from freshly sacrificed animals (usually rats or mice). Isolation of the islets of Langerhans involves collagenase digestion and purification from exocrine tissues of pancreas. Islet isolation from rodents yields a maximum of several hundreds of islets (Poitout et al. 1996; Soumyanath and Srijayanta 2005).

5.3.1.1 Isolated Islet Cells

Several *in vitro* assays are available to study details of insulin secretion. It is known that insulin secretion occurs when pancreatic β-cells utilize glucose to generate ATP from adenosine diphosphate (ADP). The resulting increase in cytoplasmic ATP/ADP ratio closes ATP-sensitive potassium channels, causing depolarization of the plasma membrane, which activates voltage-dependent calcium channels. This results in elevation of the intracellular calcium concentration, which triggers insulin secretion. In type 2 diabetes, pancreatic β-cells exhibit atypical ion channel activity and an abnormal pattern of insulin secretion (Affourtit and Brand 2006). These pathways can be studied with isolated pancreatic β-cells from control and diabetic rat or mouse; isolated β-cells can be obtained by collagenase digestion technique, followed by adequate separation and transfer to appropriate culture medium (Frode and Medeiros 2008).

Although a significant number of islets can be obtained from pancreata of large animals, isolation and purification techniques are time-consuming and require technical expertise. The techniques to purify primary β-cells are complicated and require special techniques such as fluorescence-activated cells sorting to differentiate between β-cells and other cells of the islets of Langerhans (Poitout et al. 1996). In addition, primary β-cells do not proliferate in culture and are difficult to maintain for a long period of time without special techniques. These factors limit the use of intact islets or primary β-cells in rapid throughput experiments (Soumyanath and Srijayanta 2005).

5.3.1.2 Insulin Secreting Cell Lines

Transformed cell lines in culture conditions are used to study mechanisms of both insulin secretion and β-cell dysfunction. A number of insulin-secreting cell lines have been developed in an attempt to retain the characteristic features of β-cells. The cell lines are transformed using different techniques such as irradiation, viral tranformation, and transgenic technology (Poitout et al. 1996). They are likely to show variations from primary β-cells in terms of their behavior and responsiveness to insulin secretagogues (Persaud 1999; Poitout et al. 1996). The most widely used β-cell lines are rat insulinoma induced by x-ray irradiation (RINm5F), hamster islet cells transformed with SV40 (HIT-T15), β cell tumor cells (β-TC), C57BL/6 mouse insulinoma cell line (MIN6), insulinoma cell line (INS-1), and BRIN-BD11 cells (Poitout et al. 1996). Their application in the natural products area is increasing. The advantage of cell lines is that they can be used in rapid-throughput experiments and are much less labor-intensive and easy to culture than the use of isolated islets or β-cells. This, therefore, minimizes the number of animals used in an experiment. However, because these cells are a transformation of pancreatic β-cells, some characteristic features of β-cells may not be faithfully represented by the cell lines (Persaud 1999).

While measuring insulin secretion in islets *in vitro* or cell lines certain practical factors need to be considered. Any increase in the permeability of cell membranes (e.g., by contact with saponins) or damage to cell membrane will result in a release of insulin by nonspecific mechanisms. Another factor to consider is that glucose, which can be present in polar plant extracts, can act as a stimulant to insulin secretion. It is important to remove glucose from extracts before testing them (Soumyanath and Srijayanta 2005).

5.3.2 Stimulation of β-Cell Proliferation

Proliferative effect of drugs including herbal extracts can be studied in cell lines. For example, to test for a proliferative effect of *Vaccinium angustifolium* extracts on β-cells, extracts were applied to replicating (nongrowth arrested) β-TC cells and incorporation of ^{3}H-thymidine was evaluated. Cells were seeded in 24-well plates at a density of 1.0×10^{5} cells/well and incubated in growth medium for 24 h. Incubation was continued for another 48 h in growth medium while one group was treated with tetracycline (1 μg/mL) to arrest growth. Replicating cells were then incubated for 24 h in the presence or absence of extracts. A measure of 1 μCi/mL of methyl ^{3}H-thymidine was added to medium over the last 6 h of treatment. Cells were then rinsed three times in phosphate-buffered saline (PBS) and lysed with 0.1 M NaOH for 30 min and scraped. The lysate was added to 1 mL of liquid scintillation cocktail and incorporated radioactivity was measured in a scintillation counter. Four replicates were performed for each experimental condition. Average counts from tetracycline-treated (growth-arrested) wells were considered as nonspecific

incorporation and were subtracted from all other measures (Martineau et al. 2006). Proliferative effects can also be studied by counting actual number of cells or measuring DNA content.

5.3.3 Glucose Uptake and Insulin Action

Insulin resistance either at the adipocyte or skeletal muscle levels contribute to hyperglycemia. Adipocytes from different sites of the body may have different biological or pathological effects. Pathways related to insulin resistance may be studied in cell lines of adipocytes such as murine 3T3-L1 cells and rat L6 muscle engineered to overexpress GLUT4. These cell types may be used as tools to evaluate the effects of natural products upon glucose uptake (Frode and Medeiros 2008).

5.3.3.1 Alternative Glucose Substrate for In Vitro *Uptake Studies*

The radiolabeled substrate D-2-deoxy-[^{3}H] glucose is commonly used for studies on glucose uptake into muscle, fat, or liver. A nonradioactive fluorescent derivative of 2-deoxy-glucose, 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose, could be used as an alternative (Ball et al. 2002). This compound demonstrates a favorable uptake profile into cardiomyocytes, including sensitivity to insulin (Soumyanath and Srijayanta 2005).

5.3.3.2 Insulin Action in Liver

The liver is a key organ in the regulation of plasma glucose levels. Insulin mediates several activities in the liver via signaling pathways that help to lower plasma glucose levels (including glucose uptake by activating glucokinase enzyme, glucose breakdown by activating glycolytic enzymes, and glycogen synthesis by activating glycogen synthase). Concurrently, glycogenolysis and gluconeogenesis are inhibited. Glucagon has opposing effects on most of these insulin-mediated actions. In the fasted state glucose for systemic use is released from the liver (but not from muscle) by glycogenolysis and by hepatic and renal gluconeogenesis. This process is stimulated by low-insulin and high-glucagon levels. Thus, insulinomimetics, insulin-sensitizing agents, and glucagon antagonists would be of therapeutic use against hyperglycemia in diabetes. The enzymes involved in gluconeogenesis and glycogenolysis that could form suitable targets for anti-diabetic medicines include glycogen phosphorylase, glycogen synthase kinase 3, glucose-6-phosphatase, fructose-1,6-bisphosphatase, and PEPCK (Kurukulasuriya et al. 2003). Glucokinase is an important insulin-sensitive enzyme that phosphorylates glucose as it enters the hepatocyte and produces glucose-6-phosphate, a substrate for glycogenesis and glycolysis. The effect of natural products on insulin-mimetic and insulin-sensitizing activity can be distinguished by examining the effect of test substances (extract or isolated molecules) in the presence or absence of insulin and comparing its effects to those of insulin alone in the test model. Systems developed thus far mostly use tissues taken from rodents. Perfused liver, liver slices or homogenates, hepatocyte suspensions, hepatocyte monolayer cultures, hepatocytes in coculture with epithelial cells, periportal and perivenous hepatocyte suspensions or cultures are used to study the effect of drugs on liver *in vitro* (Soumyanath and Srijayanta 2005).

The use of crude liver preparations such as slices or homogenates is always hampered by limitations of substrate and oxygen diffusion (Agius 1987). The perfused liver is the system most closely representing physiological conditions. However, the use of perfused liver is limited by short-term viability and limited availability of tissues from a single preparation. Its use has, therefore, been replaced with isolated primary hepatocytes maintained in suspension or culture. Viable parenchymal hepatocytes were separated using a two-step collagenase perfusion method (Berry and Friend 1969). Although these cells have been widely used over a number of years to study glucose handling, their disadvantage is that they are in a catabolic state of protein and glycogen turnover and have short-term viability (Agius 1987). However, isolated hepatocytes can recover from the catabolic state and can be maintained for several days for long-term studies in monolayer culture. This system has been widely used in a number of studies on the direct action of drugs on liver cells *in vitro*. The drawback of monolayer culture of hepatocytes is that the cells tend gradually to lose some characteristic functions of the liver (e.g., loss of glycogen content, albumin production, gluconeogenesis, and ketogenesis) during culture (Soumyanath and Srijayanta 2005).

The most frequently measured parameter of insulin's effects on the liver is glycogen synthesis. A number of methods have been developed to measure glycogen production in hepatocytes. These differ in terms of the techniques used to extract glycogen from the cells and the methods used to quantify the extracted glycogen. Cells are first solubilized or disrupted to release glycogen, using strong alkali, perchloric acid, sonication, or freeze–thawing. Glycogen is then precipitated using 66% ethanol (Soumyanath and Srijayanta 2005). One method of quantifying the precipitated glycogen is to measure the amount of radiolabeled glucose incorporated from the original incubation medium. D-[U-^{14}C]-glucose can be used; however, if tritiated glucose is preferred, it is important that D-[3-^{3}H]-glucose and not D-[6-^{3}H]-glucose be used because the hydrogen in position 6 could be partially lost during conversion of glucose to glycogen by indirect pathways. A colorimetric method can also be used to quantify glycogen in which glucose is liberated from glycogen using the enzyme β-amyloglucosidase (Vu et al. 1998). The glucose liberated is measured using enzymes such as glucokinase/glucose-6-phosphate dehydrogenase or glucose oxidase (Bergmeyer and Bernt 1963). Glucose released into the medium is usually measured using a glucose oxidase method following centrifugation of the suspension. An alternative to the addition of test compounds to hepatocytes is to measure the activity of various relevant enzymes *in vitro* in hepatic tissue obtained from animals treated with the plant extract *in vivo*. Key enzymes of glucose metabolism including glucokinase can be measured using standard methods reported in the literature or available from commercial enzyme suppliers.

Hepatoma cell lines from the rat (e.g., FTO-2B and H4IIE) and humans (HepG2 and Hep3B) have been established as an alternative to the use of primary hepatocytes. They have been widely used to investigate the effect of conventional anti-diabetic drugs on liver metabolism. Transfected cell lines have been developed from FTO-2B and H4IIE cells (FTOGK and H4GK, respectively), which express glucokinase. These new cells are able to take up glucose more efficiently and accumulate high levels of glycogen (Soumyanath and Srijayanta 2005).

5.3.3.3 Insulin Action in Muscle

The uptake and utilization of glucose into muscle is, to a large extent, under the influence of insulin. GLUT4 transporter is translocated to the cell surface in response to insulin. The details of the methodology used to study the uptake of glucose into muscle cells are given elsewhere (Gray and Flatt 1998b). Glucose uptake is followed using D-2-deoxy-[^{3}H] glucose and glucose oxidation by conversion of D-[U-^{14}C] glucose to labeled carbon dioxide (trapped in NaOH-saturated filter paper). Following incubation with D-[U-^{14}C]-glucose, glycogen is precipitated with 95% ethanol and examined for ^{14}C content following hydrolysis and resolubilization. Rat hemidiaphragm is also used to study glucose uptake and glycogen synthesis (Soumyanath and Srijayanta 2005). A rat skeletal muscle cell line, L6, could be used for the study of anti-diabetic agents. Cells are obtained as myoblasts that are induced by adjusting the medium to differentiate into an alignment stage and then into fused myotubes. Glucose transport (measured using ^{3}H-2-deoxyglucose) is most sensitive to insulin in the myotubes, corresponding to an increase in muscle/fat-specific GLUT4 transporters. GLUT1 transporters decreased during muscle cell differentiation. Glucose consumption and transport in L6 myotubes were sensitive to a thiazolidinedione anti-diabetic drug, which showed additive effects to insulin (Arakawa et al. 1998).

5.3.3.4 Insulin Action in Adipose Tissue

Adipocytes are sensitive to insulin; insulin causes glucose uptake and its incorporation into fat as glycerol and inhibits the hydrolysis (lipolysis) of triglycerides. Glucose uptake into adipocytes is mediated by GLUT4 transporters. Adipocytes are present in various parts of the body where fat is stored. However, primary adipocytes for experimental work are usually isolated from the epididymal adipose tissue (fat pads) of aged rats. Glucose uptake and oxidation, lipogenesis, and inhibition of lipolysis (breakdown of lipids) are three effects of insulin that can be observed in this tissue as described elsewhere (Edens et al. 2002). Lipolysis was measured using an enzymatic fluorescence method to assay glycerol in the cell culture medium.

The mouse-derived 3T3-L1 fibroblast cell line provides an alternative to the use of freshly isolated primary adipocytes. The cells are commercially available in preadipocyte form and can be induced to differentiate into adipocytes by the inclusion of a glucocorticoid, insulin, and an agent that elevates intracellular cyclic adenosine monophosphate (cAMP) (e.g., isobutylmethylxanthine) in the culture medium. The differentiation process, as well as glucose uptake, lipogenesis, and inhibition of lipolysis in differentiated cells could be assessed using this cell line (Soumyanath and Srijayanta 2005).

The use of an alternative commercially available rat preadipocyte cell line in which differentiation to adipocytes can be induced by dexamethasone and insulin was reported. The differentiated cells were used to evaluate the effects of *Salacia reticulata* and some of its isolated components on lipolysis by measuring the triglyceride content of the cells (Yoshikawa et al. 2002).

The insertion of GLUT4 cDNA (GLUT4myc) into 3T3-L1 adipocytes was achieved (Kanai et al. 1993). These cells are used to study insulin-induced translocation of GLUT4 transporters to the cell surface. Similarly transfected Chinese hamster ovary fibroblasts are also in use to study drug-induced translocation of GLUT4 (Kamei et al. 2002; Kanai et al. 1993).

5.3.3.5 Phosphorylation and Dephosphorylation Kinetics of Insulin Receptor and Insulin Receptor Substrates

Rat embryo fibroblasts (Rat-1) overexpressing the human insulin receptor isoform A are grown in Dulbecco's modified Eagle's/F12 mix medium supplemented with 200 nM methotrexate and 10% fetal calf serum (FCS) in six-well culture plates and subsequently incubated for 18 h in Dulbecco's modified Eagle's/F12 mix medium without FCS. For phosphorylation kinetic studies, cells are incubated with insulin or insulin derivatives or plant extracts or isolated molecules for various time periods (0–120 min). Subsequently, the cells are rinsed once with ice-cold buffered saline and solubilized in lysis buffer (50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid [HEPES], 150 mM NaCl, 1.5 mM $MgCl_2$, 1 mM ethylene glycol tetraacetic acid [EGTA], 15 mM $Na_4P_2O_7$, 100 mM NaF, 10% v/v glycerol, 1% v/v Triton X-100, trypsin, aprotinin, 1 mM phenylmethylsulfonyl fluoride [PMSF], 1 mM Na_3VO_4, pH 7.5). For the dephosphorylation kinetics, the cells are incubated with insulin or the test preparations for 3 min and dephosphorylation of the insulin receptor is initiated by dilution of the ligand. The monolayers are then kept for various time periods at 37°C. After washing with ice-cold buffered saline, cells are solubilized in lysis buffer. After centrifugation (10 min at 16,000 g), the supernatants are collected and diluted as described and the proteins are separated by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (Thorat et al. 2012).

5.3.4 Adipocyte Differentiation

3T3-L1 preadipocytes are used to assay the effects of drugs on adipocyte differentiation as described (Martineau et al. 2006). For example, 3T3-L1 preadipocytes differentiating in the presence of *V. angustifolium* extracts were assessed for accelerated differentiation over nontreated cells by measuring the accumulation of triglycerides at the end of the treatment period as is often done to determine PPAR-γ agonist activity. 3T3-L1 preadipocytes were grown in 24-well plates. One day after attaining confluence, proliferation medium was replaced with differentiation medium containing 250 μM 3-isobutylmethyl xanthine, 1 μM dexamethasone, and 670 nM insulin with either vehicle (dimethyl sulfoxide or DMSO) alone, extract in vehicle, or positive control in vehicle. This medium was changed after 24 h. After 48 h, medium was replaced with differentiation medium containing only insulin with or without plant extracts or controls. This medium was changed every 24 h. Rosiglitazone (10 μM), a PPAR-γ agonist of the thiazolidinedione family, was used as a positive control, while vehicle in proliferation medium was used as a negative control. Experiments were terminated after the first visual detection of intracellular lipid droplets by phase-contrast microscopy in vehicle-treated cells, typically by day 5 or 6 of the incubation period. At this time, micrographs were taken of live cells with a 40× objective. Intracellular lipids in live cells were then stained with AdipoRed fluorescent reagent (Cambrex Bio Science, Walkersville, MD), a Nile red derivative, as per manufacturer's protocol. Briefly, cells were washed in PBS (8.1 mM Na_2HPO_4, 1.47 mM KH_2PO_4, 137 mM NaCl, 2.68 mM KCl, pH 7.4), then 1 mL of PBS was added to each well

followed by 30 μL of reagent. After a 15-min incubation at ambient temperature, fluorescence was measured with a plate reader using a 485-nm excitation filter and a 572-nm emission filter. Four replicates were performed for each condition. The mean value obtained from the negative control condition was considered as background and subtracted from all other readings.

5.3.5 Glucagon Receptor Antagonists

Gluconeogenesis increases in type 2 diabetes and this is the primary contributor to fasting hyperglycemia and can be stimulated by the hormone glucagon (Kurukulasuriya et al. 2003). The process can be inhibited using glucagon receptor antagonists or inhibitors of specific enzymes in the gluconeogenic pathway such as PEPCK (Kurukulasuriya et al. 2003). Although initial studies focused on peptide analogs as antagonists, nonpeptidic antagonists have been reported, suggesting that some plant secondary metabolites may possess this activity. Screening methods for glucagon antagonists include measuring the displacement of ^{125}I-glucagon from binding sites in rat liver preparations or in Chinese hamster ovary cells and baby hamster kidney cells transfected with the human glucagon receptor (Azizeh et al. 1996; Connel 1999).

A method measuring the inhibition of glucagon-stimulated adenylate cyclase activity in rat hepatocyte or liver membranes has also been described (Azizeh et al. 1996). The advantage of this assay is that it detects compounds with glucagon antagonistic activity rather than mere binding to the receptor. Fenugreek extracts decreased the amount of glycogen phosphorylase-a activity only in hepatocytes stimulated with glucagon and not in unstimulated cells (Al-Habori et al. 2001). Some natural products with glucagon antagonist activity include a sugar-based material isolated from an African medicinal plant by the British company Phytopharm (Soumyanath and Srijayanta 2005).

5.3.6 PPAR-γ Ligand Activity Screening

PPARs are ligand-activated nuclear receptors. Three PPAR subtypes have been identified: α, β (also called δ and NUC1), and γ. PPAR-γ is the most widely studied PPAR and exists in two protein isoforms (γ1 and γ2) due to use of an alternative promoter and alternative splicing. Ligands for PPAR-γ include fatty acids, arachidonic acid metabolites such as 15-deoxy-D12,14-PGJ_2, as well as the thiazolidinedione class of compounds that include pioglitazone and rosiglitazone. Thiazolidinediones are potent, selective PPAR-γ agonists that lower the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia found in type 2 diabetic subjects and are presently used as oral anti-diabetic drugs. The use of these synthetic ligands has increased the understanding of PPAR-γs mechanism of activation and subsequent biological effects. Drug candidates may be identified by screening natural products for PPAR-γ ligand activity (Clark 2002; Kersten et al. 2000; Usui et al. 2005).

Fluorescence polarization-based single-step assay for screening PPAR-γ ligands has been developed. In this assay, a ligand of PPAR-γ is conjugated to fluorescein and is used as the displacement probe. Ligands, agonists, and antagonists of PPAR-γ will displace the fluorescent probe leading to a decrease in fluorescent probe. The PPAR-γ ligand screening assay kits are available (Cayman's PPAR-γ ligand screening assay kit). The assay has been validated using known agonists/ligands of PPAR-γ (arachidonic acid, rosiglitazone, troglitazone, etc.) with IC_{50} values ranging from nanomolar to millimolar concentrations.

5.3.7 Glucagon-Like Protein-1 Levels

Glucagon-like protein (GLP-1) has become a key biomarker in the treatment of type 2 diabetes. The main actions of GLP-1 are stimulation of insulin secretion and inhibition of glucagon secretion and food intake. The active forms are rapidly degraded *in vivo* into inactive forms by the enzyme, DPP-4. GLP-1 is secreted by L-cells of intestine. The mouse L-cell model was generated from a large bowel tumor in mice carrying a proglucagon/simian virus 40 large T-antigen transgene, whereas human NCI-H716 L cells were derived from a poorly differentiated adenocarcinoma of the cecum. Fetal rat intestinal cell cultures are a heterogeneous primary L-cell model, cultured from fetal intestines collected from term pregnant Wistar rats. All three cell models release GLP-1 appropriately in response to a variety of known

secretagogues, making them ideal models to study GLP-1 secretion from the L cell. Furthermore, the mouse L-cell model also releases cholecystokinin, whereas fetal rat intestinal cell cultures have been shown to secrete peptide YY and somatostatin, albeit at levels insufficient to alter L-cell secretion (Lim et al. 2009). Insulin resistance was induced by a 24-h pretreatment with media containing 10^{-7} M insulin. After pretreatment, cells were washed for 3 × 40 min with media containing 1% bovine serum albumin before addition of test agents for 2 h (Lim et al. 2009). Studies demonstrated that similar conditions are sufficient to decrease insulin action in adipocytes and myotubes.

To study insulin-like growth factor-I (IGF-I) secretion, cells were washed with Hanks' balanced salt solution and treated with insulin, insulin-like growth factor-I (IGF-I) (Long R3 IGF-1; Novozymes GroPep, Adelaide, Australia), glucose-dependent insulinotrophic polypeptide (GIP) (10^{-6} M; Bachem Inc., Torrance, CA-positive control), or phorbol 12-myristate 13-acetate (PMA; 10^{-6} m, positive control; Sigma-Aldrich, St. Louis, MO), and treatments were prepared. Some cells were also pretreated with the pharmacological inhibitors, LY294002 or PD98059, each at 50 μM for 15 min. After the 2-h treatment, peptides in supernatants or cell extracts were collected by reversed-phase extraction.

Total GLP-1 was assayed in cell and medium samples by radio-immuno assay with a GLP-1 antiserum (Affinity Research Products, Nottingham, UK) that targets the carboxy terminus of GLP-$1^{7–36NH2}$. Secretion was expressed as the total amount of GLP-1 in the medium, normalized to the total cell content of GLP-1 (media plus cells) and expressed as a percent of control (Lim et al. 2009).

5.3.7.1 Dipeptidyl Peptidase-4 Inhibitor Screening

DPP4 inhibitors have emerged as a new class of oral anti-diabetic agents. These inhibitors promote glucose homeostasis by inhibiting the degradation of glucose-dependent insulinotropic polypeptide and GLP-1 by DPP4. GLP-1 extends the action of insulin while suppressing the release of glucagon (Ghate and Jain 2013). DPP4 Inhibitor Screening Assay Kits are commercially available from many sources. The kit provides a convenient fluorescence-based method for screening DPP4 inhibitors. The assay uses the fluorogenic substrate, Gly-Pro-Aminomethylcoumarin (AMC), to measure DPP4 activity. Cleavage of the peptide bond by DPP releases the free AMC group, resulting in fluorescence that can be analyzed using an excitation wavelength of 350–360 nm and an emission wavelength of 450–465 nm (Ghate and Jain 2013).

5.3.8 Inhibition of Carbohydrate Digestion

The main sources of glucose in the diet are starch, sucrose, and lactose. Starch is initially broken down to oligosaccharides by the enzyme α-amylase present in saliva and pancreatic juice. The pancreatic α-amylase released into the small intestine is several times more powerful than the salivary enzyme, and contact with these enzymes results in almost total conversion of starch to the disaccharide maltose and other very small glucose oligomers before it leaves the duodenum. α-Glucosidase is a collective term referring to membrane-bound enzymes of the small intestinal villi involved in the breakdown of α-linkages of oligosaccharides and disaccharides into glucose. These enzymes include maltase, isomaltase, sucrase, lactase, trehalase, and α-dextrinase.

The final products of carbohydrate digestion are the monosaccharides glucose, fructose, and galactose. Normally, monosaccharides released by digestion are rapidly absorbed in the first half of the small intestine. However, in the presence of the inhibitors, digestion occurs throughout the small intestine, resulting in slower absorption of monosaccharides and blunting of the postprandial glucose rise. A search for compounds that can inhibit α-amylases or intestinal α-glucosidases is, therefore, regarded as one of the therapeutic approaches for developing novel anti-diabetic agents. Acarbose is an example of a drug used in diabetic therapy that acts by this mechanism (Soumyanath and Srijayanta 2005).

5.3.8.1 α-Amylase Assay

Salivary and pancreatic α-amylases are available commercially. Assay of α-amylases activity involves incubating the enzyme with starch as substrate, resulting in the release of the reducing disaccharide maltose (Bernfeld 1955). Maltose is quantified by the addition of 3,5-dinitrosalicylic acid, which is reduced to

3-amino-5-nitrosalicylic acid, a reddish product detectable at 540 nm. Maltose is quantified by reference to a standard curve. In the presence of an α-amylase inhibitor, the amount of maltose released will be reduced. On a practical note, the natural presence of reducing sugars in plant extracts under investigation can result in artificially high absorbance readings. Their contribution should be evaluated by including suitable controls (starch plus plant extract, but no enzyme). Methods may also be used to remove these sugars prior to testing (Soumyanath and Srijayanta 2005).

5.3.8.2 α-Glucosidase Assay

The inhibitory effect of plant extracts on α-glucosidases activity is assessed *in vitro* by determining a decrease in the amount of glucose liberated from molecules of substrate after incubation with the enzyme assay mixture. Glucose can be determined colorimetrically using the glucose oxidase method. Alpha-glucosidase enzyme used in these studies can be prepared from rat small intestine brush border membrane or obtained from commercial source. Rat intestinal acetone powder is also available commercially and α-glucosidases can be partially purified and used in free solution or immobilized onto a gel support to mimic their membrane-bound state *in vivo.* For faster analysis, a continuous method for enzyme assay has been developed (Matsumoto et al. 2003) in which immobilized α-glucosidase is coupled to an immobilized glucose oxidase reactor using a multichannel stopped flow system (Soumyanath and Srijayanta 2005).

5.3.9 Inhibition of Glucose Absorption from the Intestine

An excellent description for *in vitro* method to study glucose absorption from intestine is provided in a review (Soumyanath and Srijayanta 2005). *In vitro* systems used to study intestinal glucose absorption include models prepared from whole small intestine and those prepared from isolated cells or cellular components. Everted segments or everted sacs of small intestine are used for studying intestinal absorption. These are prepared from whole small intestine everted onto a glass rod with the mucosal surface exposed in the bathing solution. The substance whose absorption is to be studied is added to the bathing solution along with potential modifiers of absorption. The amount absorbed into the sacs is quantified by means of radiolabeled substrate, colorimetric methods, or high-performance liquid chromatography. The inverted gut has been used to study the effect of anti-diabetic plant extracts. The major drawback of the everted gut model is related to the short-term viability (maximum viability 3 h) of the tissues. Additionally, this system alone cannot provide conclusive information on the mechanism by which absorption is reduced. A simple model measuring glucose diffusion through a semipermeable membrane to investigate mechanical effects of plant extracts on glucose absorption has been developed (Gallagher et al. 2003). Isolated membrane preparations from enterocytes have been developed to study mechanisms of absorption at the glucose transporter level. These models include brush border membrane vesicles prepared from apical membrane and vesicles prepared from basolateral membrane. Knowledge of intestinal amino acid and sugar transport have greatly expanded owing to these models. Glucose transport into brush border membrane vesicles is by the sodium-dependent glucose transporter (SGLT1), whereas that into basolateral membrane vesicles is due to GLUT2 transporters (Thorens 1996). Evidence from rat models suggests that expression of both of these transporters is raised in the diabetic state (Burant et al. 1994). Effects on these two transport systems can be studied separately and uncomplicated by glucose metabolism using these apical membrane vesicles and basolateral membrane vesicles. Vesicles are incubated with ^{3}H-D-glucose and are rapidly filtered through a cellulose acetate/nitrate membrane after set time intervals over a period of about 1 min. The vesicles are retained on the filter and glucose transported into them can be quantified by counting the radioactivity. The time points are used to construct a glucose uptake profile and the inhibition at peak uptake can be measured. The brush border membrane vesicles model has been used to study the effects on intestinal glucose absorption of extracts of fenugreek, *Momordica charantia,* and soya phytochemical and for general screening of plant extracts. Green tea polyphenols have also been shown to inhibit SGLT1 in brush border membrane vesicles (Soumyanath and Srijayanta 2005).

Techniques to culture mature enterocyte monolayers as cell culture models for drug absorption have been extensively developed in an attempt to overcome the problems of rapid degradation of animal tissues and the variations due to differences between species and animals that usually occur when intestinal

tissues and isolated membrane preparations are used. However, the attempt has met with little success. It has been reported that, when intestinal epithelial cells were cultured as a monolayer, they underwent transformation to a cell type different from the initial cells (Soumyanath and Srijayanta 2005).

To date, studies on intestinal absorption have exploited cells derived from human colon carcinoma cells (e.g., Caco-2, HT-29, SW 116, LS 174T, SW 480). Among these, the Caco-2 cell line is the most widely used for intestinal transport and function studies. Despite its colonic origin, Caco-2 cells have been reported to undergo spontaneous enterocytic differentiation in culture. The cells have been reported to have morphological (polarized and columnar cells and the presence of microvilli) and biochemical properties (the distribution of brush border enzymes) that are much more intestinal than colonic. Caco-2 cells have been used to study the transport of various substances, including natural products such as flavonoids.

HT-29 cells that also originate from colon cell lines have been reported to have a lower degree of enterocytic differentiation compared to Caco-2 cells. However, HT-29-H cells, a subclone of HT-29, can secrete mucin molecules and produce a mucus gel layer similar to that present on the human intestinal epithelium. This layer is thought to be a rate-limiting barrier to absorption of molecules across the intestine and absorption studies using these cells may therefore be similar to the *in vivo* situation (Soumyanath and Srijayanta 2005).

5.3.10 Inhibition of Aldose Reductase Activity

Aldose reductase is a critical enzyme in the polyol pathway that plays an important role in DM. Neutrophil aldose reductase activity was increased in patients with type 1 diabetes with complications. In type 2 diabetes, patients with complications also had higher aldose reductase activity than those without complications. Inhibition of the activity of this enzyme can prevent cataract in diabetic patients' lenses. Plant products are tested for their activity against aldose reductase present in the lens. A spectrophotometric assay has been developed for the measurement of aldose reductase. The enzyme activity was measured by monitoring the change in absorbance at 340 nm and 30°C, which accompanies the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) catalyzed by aldose reductase 2.

Normally, the lenses of rats are isolated and homogenized for 30 s in a tube containing 10 mM sodium phosphate and 2-mercaptoethanol (pH 7) at 0°C. In one study, the incubation mixture contained 0.4 M $(NH_4)2SO_4$ in 0.1 M HEPES buffer (pH 7), 10 mM DL-glycerol as substrate, and 0.12 mM NADPH as coenzyme in a total volume of 1 mL. The supernatant of homogenate of lenses, centrifuged at 17,300 g for 10 min (200 μL), is added to the quartz cuvette containing the incubation mixture. Decreases in absorbance at 340 nm were recorded after 15 min in a spectrophotometer. One unit of activity is the activity of the enzyme that can produce 1 μmol NADP+ from NADPH in 1 min (Goodarzi et al. 2006).

In another study, the assay mixture contained 2.4 mL phosphate buffer 0.067 M (pH: 6.2), 100 μL NADPH 0.104 mM, 300 μL enzyme preparation, 100 μL test extract of final concentration 50 μg/mL, and 100 μL DL-glyceraldehyde (10 mM) to start the reaction, in a final volume 1.1 mL. The reaction was monitored for 5 min. Each crude extract was assayed in triplicate. A reference blank containing all the above reagents except DL-glyceraldehyde was used to correct the nonenzymatic oxidation of NADPH. Data are normally presented as % inhibition (Termentzi et al. 2008; Zaher et al. 2002). Different concentrations of test extract should be used to determine the dose response.

5.3.11 Activity and Expression of AMP-Activated Protein Kinase

AMP-activated protein kinase (AMPK), a highly conserved heterotrimeric protein, plays a key role in energy homeostasis. Ghrelin is shown to stimulate hypothalamic AMPK activity and inhibit liver and adipose tissue AMPK activity. The effects of ghrelin on AMPK activity can be studied using an elegant kinase assay, which involves immunoprecipitating AMPK protein from the tissue of interest followed by quantifying its enzymatic activity using radiolabeled ATP in the presence of a suitable substrate. As a surrogate marker of AMPK activity, AMPK Thr (172) phosphorylation can be measured by Western blotting. Information about the AMPK pathway can also be gained by studying the mRNA expression of various AMPK subunits and by western blotting for phosphorylated acetyl-CoA carboxylase, a key AMPK target. These methods have been widely used and published for investigating the effects

of ghrelin on AMPK activity (Lim et al. 2012). These methods can also be used to study the effect of botanicals on the enzyme and many studies have been reported (see Chapter 3).

5.3.12 Interfering Phytochemicals in the *In Vitro* Assays

Three groups of plant constituents that may cause interference in diabetes-related *in vitro* bioassays are sugars, saponins, and polyphenols. Polar extracts of plant material can contain significant concentrations of sugars such as glucose, fructose, and galactose. These compounds can interfere with many of the anti-DM related bioassays, particularly those that measure glucose uptake. These sugars could dilute the radiolabeled glucose used in the assay, which would result in low counts that give the impression of decreased uptake. Furthermore, this glucose could increase the glucose concentration in the *in vitro* assay medium, resulting in the stimulation of certain glucose-sensitive processes such as insulin secretion from pancreatic β-cells. The α-amylase starch breakdown inhibition assay is also prone to interference from plant-derived reducing sugars. It is important to examine polar plant extracts for the presence of glucose and other monosaccharides. This can be done using simple laboratory spot tests for reducing sugars, such as the standard Fehling's solution test or dinitrosalicylic acid reduction. The sugars present can be identified and semiquantified using thin-layer chromatography. Gas or high-performance liquid chromatography can be used for more accurate quantitation. Sugars in an extract can be removed by dialysis through a semipermeable membrane or by size exclusion chromatography through an appropriate gel column such as Sephadex G-10 (Houghton and Raman 1998). However, in this process other small molecules of interest may be lost in the process (Soumyanath and Srijayanta 2005).

Saponins have the property of disrupting cell membranes. If they are present in significant quantities in plant extracts, they may have detrimental effects in cell-based *in vitro* assays. Furthermore, they may overshadow a true mechanism-based effect of an extract in these cell systems. Cell membrane disruption by saponins can be investigated using the trypan blue exclusion method or by measuring lactate dehydrogenase (LDH) release. It is recommended that dose–response studies be performed in parallel for the desired biological effect and cell damage in order to determine the extent to which they coincide. Aqueous extracts containing saponins also form stable froths when shaken in a test tube. Polyphenolic compounds, which are ubiquitous in nature, bind easily to proteins and often give rise to false positives or negatives in bioassays. Polyphenols can be removed from an extract by a variety of methods (Wall et al. 1996).

5.3.13 Solubilizing Plant Extracts for *In Vitro* Studies

Almost all the *in vitro* bioassays in use utilize an aqueous environment. It is essential that plant extracts dissolve completely in the *in vitro* medium and this may present difficulties when dealing with nonpolar extracts. Some options are to predissolve the extract at high concentration in a minimum quantity of water-soluble organic solvent such as ethanol, methanol, or DMSO. The solution is then added to the bioassay medium in a volume so that the concentration of solvent is not detrimental to the assay. This nontoxic safe concentration must be determined by prior experimentation. For example, a number of cell-based assays are able to tolerate up to 3% DMSO. Care should be taken that precipitation does not occur when the concentrated extract solution is added to the aqueous medium. An alternative is to use a surfactant solubilizing agent such as one from the Tween series (Soumyanath and Srijayanta 2005). Effect of Tween on the system also has to be considered.

5.4 Clinical Evaluation

Since herbal anti-DM drugs are in use in traditional medicine from ancient times, these therapies do not have an established procedure for clinical evaluation of efficacy and safety. What is needed is reverse pharmacological studies to establish their safety and efficacy in light of modern medical sciences. Conventional drugs follow a sequential process, starting with a new bioactive chemical entity isolated from a plant. Preclinical pharmacological studies include mechanism of action, efficacy and safety, pharmacokinetics, and toxicity studies in experimental animals and *in vitro* assays. If preclinical

studies show promising efficacy, safety permission should be obtained from the appropriate regulatory authorities to begin clinical trials. Application is then made for clinical testing as an investigational new drug. Clinical tests start cautiously in a small group of healthy volunteers (phase 1) followed by small trials in patients (phase 2). If an agent is appropriately efficacious without any toxicity, extensive trials are performed in larger groups of patients (phase 3). With satisfactory indices of efficacy and safety, a new drug application is made to market the agent as a therapeutic agent (medicine).

If a discrete compound is isolated from a traditional plant treatment, it enters the conventional testing processes. However, unrefined extracts and whole-plant therapies that are already in use are not subjected to phase 1 through phase 4 clinical trials because their use predates current legislation and they are without any recorded or known toxicity. Many commercial anti-diabetic plant therapies involving formulations of edible anti-DM plant parts are made available as dietary adjuncts, supplements, or other "over the counter" (OTC) categories that do not carry specific medicinal claims. Such nutraceutical preparations can also be made privately by practitioners and patients outside conventional pharmaceutical legislation.

The requirements for evaluation of conventional medicines are described in detail by regulatory agencies such as the US Food and Drug Administration (FDA) (https://www.fda.gov) and the European Agency for the Evaluation of Medicinal Products (http://www.endora.org/emea.html). It is not entirely clear how to interpret these requirements for herbal preparations, although in principle all medicines should conform to the same general standards. In this regard, substantial variability exists between countries (Day and Bailey 2005). Established traditional systems of medicines such as Ayurveda have separate regulatory authorities in India.

Most of the published clinical studies on the efficacy of anti-diabetic plant materials have not been undertaken to comply with licensing requirements for registration purposes. They commonly involve unblinded protocols with small numbers of patients; the diabetic status is often poorly defined and many studies last for less than 6 months. The end points of these studies are typically standard measures of glycemic control and an oral glucose tolerance test. The majority of studies measured the levels of glycated hemoglobin (HbA1c) and/or fructosamine as longer-term indices of glycemic control. Relatively few studies with plant extracts have measured insulin concentrations and complex procedures to investigate mode of action such as the euglycemic–hyperinsulinemic clamp technique and the minimal-model intravenous glucose tolerance test have rarely been undertaken (Day and Bailey 2005).

5.4.1 Phase 1 Clinical Trial

A step-by-step approach is usually followed in the development of new herbal medicine; however, such an approach may not be required to validate the safety and efficacy of an already existing herbal medicine. Phase 1 trials for a new compound or a new formulation are generally carried out with a small number of healthy volunteers or patients suffering from DM (WHO 1993).

Most clinical studies to assess the efficacy of traditional anti-DM plants, by nature of their use in traditional medicine, are not the first exposure in humans (equivalent to phase 1). However, newly isolated principles from plants that have shown anti-diabetic activity in preclinical studies and been granted investigational new drug status will be treated as first exposure in humans. Chemical entities isolated from edible plant parts (nutraceuticals) may not require phase 1 trial; the study may be limited to dose fixation, efficacy evaluation, and long-term effects.

In the case of nonnutraceuticals compounds, an initial dose-ranging study is required, probably using an acute single-dose design starting at about 1/100 of the no-effect dose in the most sensitive animal species studied during preclinical experimentation. The duration of repeat-dose studies with slowly acting agents and the parameters to be monitored are subject to clinical discretion, but blood glucose will be closely followed, together with vital signs and standard blood chemistry. Stepwise dose escalation studies are then undertaken, and it is often not practical to measure pharmacokinetics at the same time. It must be appreciated that anti-diabetic principles do not necessarily show basal blood glucose-lowering activity in normal (nondiabetic) individuals and may not show a significant effect on a glucose tolerance test or meal tolerance test. Therefore, higher doses are best examined on a few patients before proceeding to larger groups, and other pharmacodynamic parameters may be more instructive for determination of the upper dose level (Day and Bailey 2005).

5.4.2 Phase 2 Clinical Trials

Phase 2 studies are done on a limited number of patients to determine clinical efficacy and to further confirm safety. Such studies are usually designed as randomized, double-blind, controlled studies, where an existing alternative treatment or a placebo is given to the control or placebo group. It is often difficult to blind the use of raw plants and unrefined extracts with a distinctive taste or smell, and patients who participate in the studies are often already familiar with the material under investigation. Recruitment to initial trials of this nature is customarily restricted to mild to moderate type 2 patients, although adjunctive therapy with insulin can be studied using different protocols.

Diet and mild exercise controlled type 2 DM patients with unsatisfactory but stable glycemic control (e.g., HbA1c in the range 7.5–10%; fasting plasma glucose in the range 7.5–13 mmol/L) are usually included if they have no complications and the functions of vital organs such as liver, kidney, and heart are normal. When patients have previously received anti-diabetic drug therapy, a short (e.g., 2 weeks) washout period may suffice, but this can create interpretation difficulties for chronic studies using HbA1c as an end point.

After a brief pretreatment period, a randomized, blinded, placebo-controlled design is usually acceptable for acute and short-term studies. However, chronic studies may now be encouraged to adopt an active treatment arm as control using a recognized conventional agent because an extended period of poor control without active treatment is not considered acceptable. But, this can be done strictly monitoring blood glucose levels, provided the herbal drug has a very good reputation among patients who used the therapy. If possible, at least three doses of the test agent are included in the design. In chronic studies, the daily dosage will be titrated up at weekly (or, exceptionally, monthly) intervals in accordance with the level of glycemic control. This can be based on fasting plasma glucose and patient self-monitoring of blood glucose until a preset level of control (e.g., fasting plasma glucose < 6 mmol/L) is achieved. In chronic studies, HbA1c is now the preferred end point measure of efficacy, although a selection of other indices of metabolic control can be included as end points, and end points other than HbA1c will be required for short-term studies. The most commonly used parameters are 24-h glucose profile and tests of insulin secretion, insulin sensitivity. In addition lipid profiles, oxidative stress, liver function, kidney function, and so on, are to be determined. Safety monitoring throughout all studies should be as thorough as possible (Day and Bailey 2005).

5.4.3 Phase 3 and 4 Clinical Trials

In phase 3 studies, a larger group of patients is usually included and the study is conducted at several centers using a randomized double-blind design to validate preliminary evidence of efficacy obtained in phase 2 studies. Normally, such studies are conducted under conditions that are as close as possible to the anticipated conditions of normal use (WHO 1993). Isolated and chemically characterized compounds from plants and synthetic analogs investigated as potential new anti-diabetic therapies would be expected to require the same phase 3 evaluation as that for conventional medicinal agents. However, in several situations, the design and management of large-scale trials would differ for individual natural chemicals, (nutraceuticals, in particular) mixtures of these chemicals, or unrefined plant materials.

One such situation would be that in which the proposed usage is not primarily based on a medicinal claim and use will be recommended in quantities that are not exceptionally beyond those anticipated during normal dietary consumption of the material. Dietary supplement status would be a potential positioning of such material. Nevertheless, some evidence of efficacy to match with the claims made on the packaging should be provided, and satisfactory evidence of safety should be established. Large-scale trials to provide this information are difficult to organize in a blinded manner with unrefined materials. The boundaries between a natural health product and a medicine are often unclear. Categorization is somewhat arbitrary and may reflect the claims made on the packaging and the recommended dosage rather than the testing procedure (Day and Bailey 2005).

The sponsors and the recruited patients should comply with revised versions of the 1964 Declaration of Helsinki or appropriate alternatives (Stockhausen 2000) for compounds to be evaluated in phase 3 trials. All trials should also comply with local ethical committee requirements and other criteria defined by regulatory agencies of concerned countries.

The preferred design and organization of trials for regulatory purposes can vary between regulatory agencies, and consultation with the agency is always advisable.

For anti-diabetic agents, trials are likely to last 4–12 months (6 months on average) and calculations will be used to determine numbers required based on the predefined end points. Type 2 diabetic patients recruited for these trials are customarily inadequately controlled by diet alone and without significant complications. Subgroups comprising patients with particular characteristics (e.g., young or elderly patients and patients with clearly defined accompanying conditions such as hepatic or renal insufficiency) may be included with appropriate clinical discretion.

A typical trial will be fully randomized, double blinded, and placebo controlled, or it will include arms with conventional comparator agents (the latter is increasingly preferred given the known risks of poor glycemic control). Most large trials are multicenter and often multinational and therefore dictate a detailed unambiguous protocol with predetermined instructions for all reasonably anticipated events.

Independent safety monitoring is usually included in these trials. It is usually cost-effective to include more than one dosage form of the test agent, although most designs will titrate up the dosage until a particular level of glycemic control is achieved (e.g., fasting plasma glucose < 6 mmol/L). Because diabetic patients are often receiving other medications, it is important to minimize and keep full account of changes to any medications and other conditions that could influence diabetic control. Frequent monitoring of blood glucose, plasma lipids, liver function, kidney function, blood pressure, and general well-being are customarily incorporated into phase 3 trials. Patient self-monitoring of blood glucose is valuable for drug titration, and laboratory measurements of fasting plasma glucose and HbA1c are used for main assessments. The primary end point is usually based on HbA1c, with supplementary information from a glucose tolerance test or meal tolerance test. Secondary end points will include other metabolic indices and standard clinical parameters. Comprehensive recordings of adverse events will include symptoms of hypoglycemia and adverse effects on the functions of vital organs.

To finalize the labeling and gain approval for marketing, the risk–benefit analysis must be favorable for the patient groups involved. This is interpreted in somewhat different ways by different agencies, but the underlying principles are consistent. For an anti-diabetic agent wherein long-term use is envisaged, safety is paramount. Efficacy of the new agent is preferably better than or comparable to existing agents. If a new agent offers one or more novel modes of action or other benefits that can be used to advantage when existing agents are contraindicated or no longer effective, efficacy may be interpreted more liberally. Likewise, it is advantageous if a new agent that works through different mechanisms can be used in an additive or synergistic capacity with existing agents.

Trials that recruit patients already receiving active oral therapy may incorporate a prior washout period, although this creates similar problems of interpretation as discussed for phase 2 trials.

Alternatively, patients can be switched to the test agent and/or receive the test agent as additive therapy while the placebo arm continues to receive the original therapy alone. Trials with insulin-treated patients raise special difficulties and very rigorous glucose monitoring is essential. Introduction and titration of the test agent may require adjustment to the insulin dosage, which can be used as a measure of efficacy. Extensive trials equivalent to phase 3 regulatory trials have not been reported for raw anti-diabetic plant materials or unrefined extracts (Day and Bailey 2005).

In the conventional medicine, phase 4 clinical studies are performed after dosage form is available for general use. The main purpose of such studies is to detect toxic events that are not detected earlier (WHO 1993).

5.4.4 Ethical Issues

Traditional herbal medicines, including anti-DM medicines, originated in ancient times and as expected these medicines have not been studied scientifically regarding mechanisms of actions, active principles involved, combined action of active principles present in the medicine, and long-term safety evaluation. Even controlled clinical studies to establish the efficacy of these medicines are lacking in most cases; the shelf lives of such herbal drugs are also not established in light of modern science. A present-day rational mind cannot accept such medicines with confidence.

Although it is generally believed that plant drugs are not toxic, it is known that many plant products cause toxicities such as neurotoxicity, reproductive toxicity, and liver toxicity. A well-known example is the presence of hepatotoxic pyrrolizidine alkaloids in certain traditional medicinal plants. Many plants from the Boraginaceae, Compositae, and Leguminosae families contain well over 100 hepatotoxic pyrrolizidine alkaloids. For example, water extracts of some anti-diabetic *Momordica* species used in traditional medicine to treat DM have been reported to cause hepatic portal inflammation and testicular lesions. Therefore, detailed toxicity studies are required for herbal drugs that have not been tested for toxicity previously. Furthermore, some herbal practitioners do not reveal the components of their medicines; it is not possible to make an objective assessment of potential safety hazards and the regulatory agents should not allow such medicines to be used.

Some patients will consult with conventional and traditional medicine practitioners and may take conventional and traditional medicines at the same time. Because traditional medicines are often taken without consultation, it should be appreciated that interactions between these medicines can occur. For example, the blood glucose-lowering effects of *M. charantia* fruit are additive to that of currently used sulfonylurea drugs and can precipitate episodes of hypoglycemia. Some plants still carry a mystique that may owe more to reputation and placebo effect than medicinal benefit (Day and Bailey 2005).

Now, traditional medicine has moved to a second stage known as evidence-based complementary and alternative medicines. Here, herbal drugs and the raw materials used for the drug preparation are subjected to studies for scientific evidence for their efficacy and safety. Traditional medicines are embodiments of human experience, traditional human wisdom, and belief over different periods in the evolutionary history of humans. Such herbal traditional drugs are studied with the help of modern experimental tools and current yardsticks for safety and efficacy. New knowledge and new herbal medicines are emerging from such studies.

We have to look for the third and ultimate stage for traditional herbal medicines. This is the integration phase of time-tested herbal medicines and conventional pharmacological therapies. Here, a mixture of phytochemicals or standardized extracts is rationally combined on the platform of traditional knowledge and developed in the light of modern science to provide modern standards of safety and efficacy. Thus, the ultimate destination is the fine integration of conventional pure chemical entity medicine and rejuvenated traditional herbal medicine/phytomedicines.

With regard to intellectual property rights, herbal medical information, whether derived from native peoples or herbal practitioners, could be worthy of patentable status if it can be justified by appropriate criteria (Day and Bailey 1988).

5.5 Conclusion

In this chapter, an attempt has been made to present almost all of the available methods to study anti-DM activities of plant products (crude preparations, extracts, isolated compounds, etc.) to facilitate research leading to anti-DM medicine development with standards of safety and efficacy. *In vitro* studies, among other things, provide insights into the mechanisms of action. In the case of traditional anti-DM plants, it is better to perform various *in vitro* mechanism studies after confirming anti-DM activity *in vivo*, at least, in one animal model. Each *in vitro* method may facilitate to screen large number of plants that work through a particular mechanism only. However, it should be remembered that in the case of DM diverse mechanisms can control the disease and one plant, in many cases, acts through more than one mechanism. The *in vivo* animal studies using short-term, chemical-induced models such as streptozotocin-induced type 2 DM in rodents may not be sufficient in view of the fact that these models are not true representatives of human type 2 DM and the existence of metabolic differences in different species. Therefore, at least, after the successful initial screening of candidate herbal drugs/natural products, a few more relevant animal models including, at least, one nonrodent species may be used; males and females should be included at least in one model. Pitfalls and limitations in each *in vivo* model should be adequately considered. If the active principles are not known, it is practically not possible to perform fuller pharmacokinetic studies in animal models. Therefore, activity-guided isolation of at least the major active principle or principles are needed even in the case of crude extract therapy. Herbal

drugs in traditional use without any known toxicity need not require animal toxicity studies such as LD_{50} determination; an acute toxicity study with a few reasonably high doses, higher than therapeutic doses, is sufficient. Availability of reliable and inexpensive animal models will facilitate preclinical evaluation in experimental animals that will in turn facilitate clinical trials. One of the major gap area remains to be filled and this includes long-term animal experiments and follow-up controlled clinical trials on herbal drugs including polyherbal formulations/phytochemical combinations. Polyherbal nutraceuticals and nontoxic herbal combinations should also be subjected to preclinical and clinical studies to determine their degree of efficacy, interaction with other drugs, and so on. They are very promising even to cure certain types of type 2 DM.

6

Sustainable Utilization of Anti-Diabetes Mellitus Plants

6.1 Introduction

The success of phytomedine or herbal drug development is linked to the production of good quality plants as per requirement. For using plant-based conventional natural product drugs also, the availability of uniform high-quality plant raw materials as and when needed is very crucial. When a plant is found very promising in the preliminary screening, target plant collection in bulk quantity may be a problem in certain cases due to limited availability of plant biomass, scattered distribution, inconsistent efficacy, and so on.

For diabetes mellitus (DM), more than 1,000 plants have been reported with varying levels of anti-diabetes mellitus (anti-DM) properties. Of these, more than 100 plants (about 130) are very promising plants with anti-DM properties (Subramoniam 2016). Most of the promising plants are provided in Table 6.1. Some plants with anti-DM properties are rare and threatened and are collected from the wild for medicinal purposes; such plants need conservation as well as propagation for sustainable utilization. Most of the important edible anti-DM plants are cultivated for human consumption as food and spice. A list of these plants is presented in Table 6.2. Possibly, cultivation conditions could influence medicinal value. For most of the anti-DM plants, appropriate agrotechniques have not been developed keeping in view the anti-DM properties of the plants. In this chapter, an attempt has been made to present the state of important anti-DM plants in terms of their availability, consistency in quality, and strategies and approaches for the supply of high-quality anti-DM plants for sustainable utilization for human welfare. Information on micropropagation studies and measures to be taken for conservation are also provided to facilitate further research and actions required in this direction.

6.2 *In Vitro* Propagation of Plants through Tissue Culture

Plant tissue culture is the process of growing plant cell, tissue, and organ in an artificially prepared nutrient medium, semisolid or liquid under aseptic conditions. It is based on the principle of totipotency—the ability of a plant cell to develop into whole new plant. Plant tissue culture has a crucial role in conservation and sustainable utilization of plant species. In the conventional cultivation, there are many plants that do not flower and produce viable seeds under certain climatic conditions or have long periods of growth and multiplication. Species which are difficult to regenerate in sufficient numbers by the conventional methods are saved from extinction by biotechnological intervention including tissue culture propagation, production of large-scale uniform planting material through *in vitro* tissue culture for introduction in the field, and long-term cryopreservation. Further, medicinally important biomass can also be obtained through tissue culture. Tissue culture of selected clones with high medicinal value is particularly very important for plant species that show a lot of variability in the content of desired active principles. Plant tissue culture technique allows mass multiplication and propagation under aseptic conditions. It is not dependent on the season for the availability of plant material. Tissue culture technique allows obtaining a large number of plants from a limited source available using minimum space and less time (Sharma and Vashistha 2015). The advantages of *in vitro* micropropagation of plants include high rate of multiplication, availability of plant material as per requirement (independent of regional and

TABLE 6.1

Most of the Very Important Anti-Diabetes Mellitus (Anti-DM) Plants[a]

No.	Botanical Name	Common Name	Family	Parts Used
1.	*Abelmoschus esculentus* (L.) Moench	Lady's finger, ochra	Malvaceae	Fruits
2.	*Abroma augusta* L.	Flame of the forest, Devil's cotton	Fabaceae	Leaves
3.	*Acacia catechu* Willd.	Catechu, cutch tree	Fabaceae	Leaves
4.	*Aegle marmelos* (L.) Correa	Bael, stone apple, holy fruit tree	Rutaceae	Leaves
5.	*Ajuga iva* L.	Herb ivy, musky bugle	Lamiaceae	Whole plant
6.	*Allium cepa* L.	Onion	Lilliaceae	Bulbs
7.	*Allium sativum* L.	Garlic	Alliaceae or Lilliaceae	Bulbs
8.	*Aloe vera* (L.) Burm. f.	Aloe	Aloaceae	Leaves
9.	*Alstonia scholaris* L.	Devil tree	Apocynaceae	Barks, leaves
10.	*Anacardium occidentale* L.	Cashew nut tree	Anacardiaceae	Stem barks, nuts (kernel)
11.	*Anemarrhena asphodeloides* Bunge	Zhi Mu (Chinese)	Lilliaceae	Rhizomes
12.	*Annona muricata* L.	Soursop, Paw-Paw	Annonaceae	Leaves
13.	*Areca catechu* L.	Betel nut palm	Arecaceae	Nuts
14.	*Artemisia dracunculus* L.	Tarragon, dragon herb	Asteraceae	Leaves
15.	*Artemisia herba-alba* Asso	Wormwood	Asteraceae	Aerial parts
16.	*Asparagus racemosus* Willd.	Shatavari, satavar	Liliaceae	Roots
17.	*Azadirachta indica* A. Juss.	Neem tree	Meliaceae	Leaves, seeds, etc.
18.	*Bauhinia forficata* Link	Pata de vaca, casco de vaca, orchid tree, cow paw	Fabaceae	Leaves
19.	*Bauhinia variegata* L.	The mountain ebony	Fabaceae	Leaves
20.	*Berberis aristata* DC.	Indian barberry, tree turmeric	Berberidaceae	Stem barks
21.	*Berberis vulgaris* L.	Barberry	Berberidaceae	Roots, stem barks
22.	*Bidens pilosa* L.	Spanish needles, devil's needle	Asteraceae	All parts
23.	*Bixa orellana* L.	Achiote, chiot, annatto tree	Bixaceae	Seeds
24.	*Boerhaavia diffusa* L.	Hohweed, horse purslane	Nyctaginaceae	Leaves
25.	*Bougainvillea spectabilis* Willd.	Bougainvillea. bouganvila	Nyctaginaceae	Stem barks, root barks
26.	*Brassica juncea* Czern. & Coss.	Indian mustard	Brassicaceae	Leaves and seeds
27.	*Caesalpinia bonbuc* (L.) Roxb.	Nata karanja, prickly shrub	Caesalpiniaceae	Seeds
28.	*Cannabis sativa* L.	Marijuana	Cannabaceae	Flowers
29.	*Casearia esculenta* Roxb.	Carilla fruit	Flacourtiaceae	Roots
30.	*Cassia auriculata* L.	Tanner's *Cassia*	Cesalpinaceae	Flowers, leaves
31.	*Cassia fistula* L.	Indian laburnum, purging fistula	Cesalpinaceae	Leaves
32.	*Cassia kleinii* W. & A.	Nela tangedu, mullilla thottalvadi	Fabaceae	Leaves
33.	*Cassia occidentalis* L. or *Senna occidentalis* (L.) Link.	Coffee senna, fetid cassia	Leguminosae	Leaves, aerial parts
34.	*Catharanthus rosus* (L.) G. Don f.	Madagascar rosy periwinkle	Apocynaceae	Leaves

(*Continued*)

TABLE 6.1 (*Continued*)

Most of the Very Important Anti-Diabetes Mellitus (Anti-DM) Plants[a]

No.	Botanical Name	Common Name	Family	Parts Used
35.	*Cinnamomum cassia* (Nees & T. Nees) J. Presl.	Cinnamon, Chinese cinnamon	Lauraceae	Inner barks (spice)
36.	*Cinnamomum verum* J.S. Presl.	Cylon cinnamom, true cinnamom	Lauraceae	Inner barks (common spice)
37.	*Citrullus colocynthis* (L.) Schrad.	Bitter cucumber, bitter apple	Cucurbitaceae	Seeds and fruits
38.	*Citrullus lanatus* (Thunb.) Matsumara & Makai	Watermelon	Cucurbitaceae	Fruits (rind of the fruit is anti-DM)
39.	*Clerodendron phlomidis* Linn.f.	Wind killer, clerodendrum	Verbenaceae	Leaves
40.	*Coccinia indica* Wight & Arn.	Scarlet vine, ivy gourd	Cucurbitaceae	Unripe fruits (vegetable)
41.	*Coffea arabica* L.	Coffee, Arabica coffee	Rubiaceae	Coffee beans
42.	*Coriandrum sativum* L.	*Coriander*	Apiaceae	Seeds, aerial parts of young plants, etc
43.	*Costus pictus* D. Don.	Cana agria or Cana de jabali (in Mexico)	Zingiberaceae/ Costaceae	Leaves
44.	*Costus speciosus* (Koenig) Sm.	Spiral flag	Zingiberaceae/ Costaceae	Leaves, rhizomes
45.	*Cucumis sativus* L.	Cucumber	Cucurbitaceae	Fruits, seeds
46.	*Cuminum cyminum* L.	Cumin, huminum	Apiaceae/ Umbelliferae	Seeds (condiment)
47.	*Curcuma longa* L.	Turmeric	Zingiberaceae	Rhizomes
48.	*Cyamopsis tetragonoloba* (L.) Taub.	Cluster beans	Fabaceae	Beans (vegetable)
49.	*Dioscorea bulbifera* L. and related spp.	Air potato, potato yam	Dioscoriaceae	Tuberous
50.	*Elephantopus scaber* L.	Elephant foot, dila-dila	Compositae	Leaves, whole plant
51.	*Enicostema hyssopifolium* (Willd.) Verd. = *Enicostemma littorale* Blume	Nahi, vellarugu	Gentianacea	Leaves, whole plant
52.	*Eriobotrya japonica* Lindl.	Loquat, logat	Rosaceae	Leaves
53.	*Euclea undulata* Thunb.	Guarrie, khoi	Ebenaceae	Stems, roots
54.	*Ficus benghalensis* L.	Banyan tree	Moraceae	Stem barks
55.	*Ficus carica* L.	Edible fig, common fig	Moraceae	Fruits
56.	*Ficus racemosa* L.	Cluster fig	Moraceae	Fruits
57.	*Fraxinus excelsior* L.	Common ash, English ash	Oleaceae	Seeds
58.	*Ginkgo biloba* L.	Ginkgo, maidenhair tree, kew tree	Ginkgoaceae	Leaves
59.	*Glycyrrhiza uralensis* Fisch.	Chinese licorice, licorice	Fabaceae	Roots
60.	*Gongronema latifolium* Benth.	Akan-asante, aborode-aborode (West Africa)	Asclepiadaceae/ Periplocaceae	Leaves, barks, resins
61.	*Gymnema sylvestre* R. Br.	Periploca of the wood	Asclepiadaceae	Leaves
62.	*Helicteres isora* Linn.	Indian screw tree	Sterculiacease	Roots
63.	*Hemidesmus indicus* (L.) R. Br.	Indian sarsaparilla	Asclepiadaceae	Roots
64.	*Hemionitus arifolia* (Burm.) Moore	Heart fern	Hemionitidaceae	Whole plant
65.	*Hintonia latiflora* (Sesse & Moc.) Bullock.	Colpalchi	Rubiaceae	Stem barks
66.	*Hunteria umbellata* K.Schum. Hallier f.	Demouain	Apocynaceae	Seeds

(*Continued*)

TABLE 6.1 (*Continued*)

Most of the Very Important Anti-Diabetes Mellitus (Anti-DM) Plants[a]

No.	Botanical Name	Common Name	Family	Parts Used
67.	*Ipomoea batatas* L.	Sweet potato, patate douce	Convolvulaceae	Tuberous roots
68.	*Lagerstroemia speciosa* (L.) Pers	Banaba	Lathraceae	Leaves
69.	*Lepidium sativum* L.	Garden cress	Brassicaceae	Fresh or dried seeds
70.	*Lupinus mutabilis* Sweet	Hanchcoly, white lupin	Fabaceae	Edible seeds
71.	*Mangifera indica* L.	Mango tree	Anacardiaceae	Leaves, seed kernels, mango peel
72.	*Melothria mederaspatana* (L.) Cogn.	Madras pea pumpkin	Cucurbitaceae	Leaves (vegetable)
73.	*Momordica charantia* L.	Bitter melon, bitter gourd	Cucurbitaceae	Unripe fruits (vegetable)
74.	*Morus alba* L.	White mulberry	Moraceae	Roots, leaves
75.	*Murraya koenigii* (Linn.) Spreng.	Curry leaf, kari patta	Rutaceae	Leaves
76.	*Nelumbo nucifera* Gaertn	Sacred lotus	Nymphaeaceae	Rhizomes
77.	*Ocimum sanctum* Linn.	Holy basil, tulasi	Lamiacea	Leaves, roots
78.	*Olea europaea* L.	Olive	Oleaceae	Leaves
79.	*Opuntia streptacantha* Lemaire	Prickly pear cactus, nopal[b]	Cactaceae	Cladodes (stem)
80.	*Panax ginseng* L.	Asian ginseng	Araliaceae	Berries, roots
81.	*Panax quinquefolius* L.	American ginseng	Araliaceae	Berries, roots
82.	*Peganum harmala* L.	Esfand, wild rue	Zygophyllaceae	Seeds
83.	*Phyllanthus amarus* Schum & Thonn.	Harracane weed, gale-o-wind	Phyllanthaceae	Whole plant
84.	*Phyllanthus emblica* L.	Indian gooseberry, amala	Euphorbiaceae	Fruits
85.	*Pongamia pinnata* (L.) Pierre	Indian beech, pongam	Leguminosae	All parts
86.	*Prunella vulgaris* L.	Lance self-heal, mountain self-heal	Labiatae	Spikes
87.	*Prunus amygdalus* Batsch	Almond	Rosaceae	Nuts
88.	*Psidium guajava* L.	Guava	Myrtaceae	Fruit juice
89.	*Pterocarpus marsupium* Roxb.	Indian kino tree	Fabaceae	Barks
90.	*Punica granatum* L.	Pomegranate	Lythraceae	Seeds, fruits
91.	*Salacia oblonga* Wall. ex Wight. & Arn.	Folk chundan, ponkoranti	Celastraceae	Stems, roots, leaves
92.	*Salvia officinalis* L.	Garden sage, true sage	Lamiaceae	Leaves
93.	*Scoparia dulcis* L.	Sweet broom weed	Scrophuilariaceae	Seeds, leaves, whole plant
94.	*Semicarpus anacardium* L.F.	Ballatak or bhilwa	Anacardiaceae	Fruits, seeds, nuts
95.	*Silybium marianum* (L.) Gaertn	Holy thistle, milk thistle	Asteraceae	Aerial parts
96.	*Smallanthus sonchifolius* (Poepp & Endl.) H. Robinson	Yacon	Asteraceae	Tuberous
97.	*Stereospermum teteragonum* DC.	Yellow snake tree, trumpet flower tree	Bignoniaceae	Roots
98.	*Stevia rebaudiana* (Bert.) Bertoni	Stevia, sweet leaf, sweet herb of Paraguay	Asteraceae	Leaves
99.	*Syzygium cumini* (L.) Skeels.	Black berry, black plum	Myrtaceae	Fruits
100.	*Syzygium malaccense* (L) Merr. & Perr	Wax jambu, Malay-apple, rose apple	Myrtaceae	Barks, leaves, roots
101.	*Tamarindus indica* L.	Tamarind tree	Fabaceae	Seeds, fruit pulps
102.	*Tectona grandis* L.	Teak	Lamiaceae	Leaves

(*Continued*)

TABLE 6.1 (*Continued*)

Most of the Very Important Anti-Diabetes Mellitus (Anti-DM) Plants[a]

No.	Botanical Name	Common Name	Family	Parts Used
103.	*Tephrosia purpuria* (L.) Pers	Sarboka, sharapunkha	Fabaceae	Seeds, roots
104.	*Terminalia chebula* Retz	Ink-nut tree	Combretaceae	Fruits and nuts
105.	*Tinospora cordifolia* (Willd.) Miers. ex Hook. f. & Thoms.	Guduchi	Menispermaceae	Whole plant
106.	*Trigonella foenum-graecum* L.	Fenugreek	Leguminosae	Seeds, leaves
107.	*Vaccinium angustifolium* Ait.	Low bush blue berry	Ericaceae	Fruits
108.	*Zingiber officinale* Rosc.	Ginger	Zingiberaceae	Rhizomes
109.	*Ziziphus jujube* Mill.	Ilanthai pazham	Rhamnaceae	Leaves
110.	*Ziziphus spina-christi* (L.) Willd	Christ's thorn jujube	Rhamnaceae	Leaves

[a] *Source:* Subramoniam, A. *Plants with Anti-Diabetes Mellitus Properties*, CRC Press, Boca Raton, FL, 2016. With permission.

[b] "Nopal" is used to refer *Opuntia* sp.

TABLE 6.2

Important Anti-Diabetes Mellitus (Anti-DM) Plants Cultivated in Large Scales for Human Consumption as Food or Spice[a]

No.	Botanical Name	Common Name	Family	Edible Part with Anti-Diabetes Activity
1.	*Abelmoschus esculentus* (L.) Moench	Lady's finger, ochra	Malvaceae	Fruits
2.	*Allium cepa* L.	Onion	Lilliaceae	Bulbs
3.	*Allium sativum* L.	Garlic	Alliaceae or Lilliaceae	Bulbs
4.	*Anacardium occidentale* L.	Cashew nut tree	Anacardiaceae	Nuts (kernel)
5.	*Artemisia dracunculus* L.	Tarragon, dragon herb	Asteraceae	Leaves
6.	*Bidens pilosa* L.	Spanish needles, beggar's ticks	Asteraceae	Leaves
7.	*Brassica juncea* Czern. & Coss.	Indian mustard	Brassicaceae	Leaves and seeds
8.	*Cinnamomum cassia* (Nees & T. Nees) J. Presl.	Cinnamon, Chinese cinnamon	Lauraceae	Inner barks (common spice)
9.	*Cinnamomum verum* J.S. Presl.	Cylon cinnamom, true cinnamom	Lauraceae	Inner barks (common spice)
10.	*Citrullus lanatus* (Thunb.) Matsumara & Makai	Watermelon	Cucurbitaceae	Fruits (rind of the fruit)
11.	*Coccinia indica* Wight & Arn.	Scarlet vine, ivy gourd	Cucurbitaceae	Unripe fruits (vegetable)
12.	*Coffea arabica* L.	Coffee, Arabica coffee	Rubiaceae	Coffee beans
13.	*Coriandrum sativum* L.	Coriander	Apiaceae	Seeds and aerial parts of young plant
14.	*Cucumis sativus* L.	Cucumber	Cucurbitaceae	Fruits including seeds (vegetable)
15.	*Cuminum cyminum* L.	Cumin, huminum	Apiaceae/ Umbelliferae	Seeds (condiment)
16.	*Curcuma longa* L.	Turmeric	Zingiberaceae	Rhizomes
17.	*Cyamopsis tetragonoloba* (L.) Taub.	Cluster beans	Fabaceae	Beans (vegetable)
18.	*Dioscorea bulbifera* L.	Air potato, potato yam	Dioscoriaceae	Tuberous
19.	*Ficus carica* L.	Edible fig, common fig	Moraceae	Fruits
20.	*Fraxinus excelsior* L.	Common ash, English ash	Oleaceae	Seeds

(*Continued*)

TABLE 6.2 (*Continued*)

Important Anti-Diabetes Mellitus (Anti-DM) Plants Cultivated in Large Scales for Human Consumption as Food or Spice[a]

No.	Botanical Name	Common Name	Family	Edible Part with Anti-Diabetes Activity
22.	*Ipomoea batatas* L.	Sweet potato, patate douce,	Convolvulaceae	Tuberous roots
23.	*Lepidium sativum* L.	Garden cress	Brassicaceae	Fresh or dried seeds, pods[b]
24.	*Lupinus mutabilis* Sweet	Hanchcoly, white lupin	Fabaceae	Seeds
25.	*Mangifera indica* L.	Mango tree	Anacardiaceae	Seed kernels and mango peels
26.	*Melothria maderaspatana* (L.) Cogn.	Madras pea pumpkin	Cucurbitaceae	Leaves (vegetable)
27.	*Momordica charantia* L.	Bitter melon, bitter gourd	Cucurbitaceae	Unripe fruits (vegetable)
28.	*Murraya koenigii* (L.) Spreng.	Curry leaf, kari patta	Rutaceae	Leaves (spice)
29.	*Opuntia streptacantha* Lemaire	Prickly pear cactus, nopal[c]	Cactaceae	Cladodes (stem)
30.	*Phyllanthus emblica* L.	Indian gooseberry, amala	Euphorbiaceae	Fruits
31.	*Prunus amygdalus* Batsch	Almond, suphala	Rosaceae	Nuts
32.	*Psidium guajava* L.	Guava	Myrtaceae	Fruit juice and fruits
33.	*Punica granatum* L.	Pomegranate	Lythraceae	Seeds, fruits
34.	*Salvia officinalis* L.	Garden sage, true sage	Lamiaceae	Leaves
35.	*Smallanthus sonchifolius* (Poepp & Endl.) H. Robinson	Yacon	Asteraceae	Tuberous
36.	*Stevia rebaudiana* (Bert.) Bertoni	Stevia, sweet leaf, sweet herb of Paraguay	Asteraceae	Leaves
37.	*Syzygium cumini* (L.) Skeels.	Black berry, black plum	Myrtaceae	Fruits
38.	*Tamarindus indica* L.	Tamarind tree	Fabaceae	Seeds, fruit pulps
39.	*Terminalia chebula* Retz	Ink-nut tree	Combretaceae	Fruits and nuts
40.	*Trigonella foenum-graecum* L.	Fenugreek	Leguminosae	Seeds, leaves
41.	*Vaccinium angustifolium* Ait.	Low bush blue berry	Ericaceae	Fruits
42.	*Zingiber officinale* Rosc.	Ginger	Zingiberaceae	Rhizomes

[a] *Source:* Subramoniam, A. *Plants with Anti-diabetes Mellitus Properties*, CRC Press, Boca Raton, FL, 2016. With permission.

[b] Anti-DM activity of edible leaves remains to be studied.

[c] Used generally to refer *Opuntia* sp.

seasonal variations), production of clones with desired characteristics, and bulk production of almost uniform plantlets for planting in the field.

The basic tissue culture techniques involve several steps starting from explants. Explant is a piece of tissue from the plant used to initiate tissue culture. It may be in the form of shoot tips, nodes, internodes, leaf tissues, petioles, root tips, anther, embryo, and so on. But explants from actively growing region of the plant, having the meristematic tissues of young plants, at the beginning of the growing season generally give best results. Microbial contamination of plant tissue culture is a common problem. Therefore, the maintenance of aseptic conditions is essential for successful *in vitro* propagation. Explants are generally cleaned with distilled water and sterilized. The agents used for sterilization include mercuric chloride, ethyl alcohol, antibiotic and liquid bleach. Two or more of these agents are used following specific procedures. The nutrient medium is normally sterilized using an autoclave at 121°C temperature and 15 psi pressure for 20 min.

Culture media contain vital nutrients and elements for *in vitro* growth of plant tissues. A number of basic nutrient media are used for *in vitro* culture works. Generally Murashige and Skoog (MS) medium with 3% (w/v) sucrose and 0.8% (w/v) agar is used for most of *in vitro* culture studies; for woody plants, normally woody plant medium (WPM) is used. Appropriate nutrient medium may have to be standardized for the *in vitro* propagation of different plant species (Mathew and Philip 2000; Sharma and Vashistha 2015). Growth hormones regulate various physiological and morphological processes in plants and are also known as plant growth regulators (PGRs). These regulators are synthesized by plants; the synthetic regulators are also used. PGRs can also be added to cultures for improving plant growth and differentiation and influencing metabolite syntheses. Among the growth regulators, cytokinins and auxins are of special importance in plant tissue culture. Generally, cytokinins such as benzylaminopurine (BAP), kinetin, thidiazuron, zeatin, and 2-isopentenyladenine (2-ip) as well as auxins such as indole-3-acetic acid (IAA), indole-3-butyric acid (IBA), α-naphthyl acetic acid (NAA), and 2,4-dichlorophenoxy acetic acid (2,4-D) are used in different concentrations and ratios for *in vitro* regeneration and propagation studies. Cytokines are normally used for the induction of organogenesis and a large number of buds. Depending on chemical structure and concentration, auxins inhibit cell division, stimulate callous or root formation. Besides auxins and cytokins, gibberellins, a group of compounds that stimulate cell division and elongation, are also used. The most commonly used gibberellins is gibberellic acid.

The plant propagation under *in vitro* condition is exposed to a unique set of growth conditions such as low light, high humidity, and poor gaseous exchange, which may support rapid growth and multiplication. The cultures are generally maintained at approximately 25°C under a 16 h photoperiod in cool white fluorescent tubes. There are many types of tissue culture techniques available for micropropagation and plant regeneration. The ideal micropropagation conditions may differ between different plant species. The regeneration of explants into complete functional plantlets under *in vitro* tissue culture conditions involves steps such as shoot induction and multiplication, rooting of *in vitro* generated shoots, root elongation and acclimatization of plantlets in soil, or direct somatic embryogenesis and plant development. Indirectly, the explants can dedifferentiate into callus, and somatic embryogenesis from callus cells can occur under suitable conditions.

6.2.1 Shoot Multiplication *In Vitro*

Direct and indirect approaches have been followed to achieve *in vitro* shoot induction and multiplication in plant species. Direct approach follows the proliferation of apical and axillary bud, while indirect approach involves the multiplication of shoots through callus initiation and somatic embryogenesis from callus cells. In apical and axillary bud proliferation, shoot tips (apical bud and nodal explants/axillary bud) are excised and cultured on nutrient medium supplemented with different concentrations of cytokinins individually or in combination with auxins. After few days, shoots formed are subcultured on the same medium for multiplication. The cells of shoot apex and axillary bud are least susceptible to genotypic changes under cultural conditions. The axillary buds have been found to be suitable for micropropagation in several anti-DM plant species such as *Tinospora cordifolia* (Gururaj et al. 2007) and *Asparagus racemosus* (Bopana and Saxena 2008). A number of workers achieved *in vitro* plant multiplication using both apical and axillary bud of many plant species (Sharma and Vashistha 2015).

6.2.2 Callus

Callus is an unorganized mass of loosely arranged parenchymatous cells formed by dedifferentiation of a plant cell. For callus induction, different explants are cultured on nutrient medium supplemented with different concentrations of auxins individually or in combination with cytokinins. Callus developed from the explants on induction medium is separated, cut into small pieces, and transferred to basal medium (BM) supplemented with different concentrations of cytokinins individually for shoot initiation. But, the major problem in using callus culture for shoot multiplication is the genetic instability of the cells. Callus and suspension cultures from nodal and leaf explants of *Gymnema sylvestre,* an important anti-DM plant, were standardized by several investigators to produce anti-DM compounds (Gopi and Vatsala 2006). Recently, a protocol for the regeneration of complete plantlets of *T. cordifolia* from the callus

induced from leaf explants was developed (Sharma and Vashistha 2015). Multiple shoot regeneration through a callus phase has been demonstrated in many plants including anti-DM plants *Helicteres isora* (Shriram et al. 2008) and *Morus alba* (Lee et al. 2011b).

6.2.3 Rooting of *In Vitro* Regenerated Shoots

After *in vitro* regenerated shoots attained a height of 2–3 cm, these are normally excised and planted on half-strength BM supplemented with different concentrations of auxins individually for rooting. For example, in the anti-DM plants, *Pterocarpus santalinus* (Arockiasami et al. 2000) and *T. cordifolia* (Raghu et al. 2006), IAA induced rooting. The promotive effect of IBA on rooting has been reported in many plants including the anti-DM plant, *Pterocarpus marsupium* (Chand and Singh 2004). In the anti-DM plants *Aegle marmelos* (Nayak et al. 2007) and *Emblica officinalis* (Nayak et al. 2010a), low salt medium (half-strength MS medium) was effective in root formation.

6.2.4 Hardening and Acclimatization of Plantlets in Soil

Hardening refers to the preparation of the *in vitro* regenerated plantlets for a natural growth environment. For successful acclimatization to natural field conditions and normal growth, a careful and gradual transfer of *in vitro* regenerated plantlets is necessary. The rooted plantlets are gently pulled out of the medium and washed in running tap water. The plantlets with well-developed roots are transferred to a sterilized soil and sand mixture (1:1) in small plastic pots. To maintain high humidity around the plants, for some initial days the plastic pots are covered with transparent polythene bags with small holes for air circulation. Plants are watered with half- to quarter-strength salt solution of the nutrient medium on alternate days. Then pots are transferred in Polyhouse. Successful acclimatization and field transfer of *in vitro* regenerated plantlets have been achieved in many medicinally important plant species (Sharma and Vashistha 2015). The ultimate success of commercial *in vitro* propagation depends on the ability to transfer plants out of the culture on a large scale and with a high survival rate.

6.2.5 Somatic Embryogenesis

Somatic embryos are those that are formed from the somatic tissue under *in vitro* conditions and resemble the zygotic embryos of intact seeds. The embryos are initiated either directly from the explant or via callus formation; the embryos can grow into seedlings on suitable medium. The development of somatic embryos from zygotic embryos was also achieved in many plants (Rout 2005).

6.2.6 Suspension Culture

Suspension cultures are formed *in vitro* when friable calli are grown on liquid media in a suitable container and constantly agitated to provide suspension of free cells. Conical flasks are used because of their large surface area that helps in maintaining liquid medium and continuous gas exchange. Suspension cultures are of two types: batch and continuous. In batch cultures a portion of initial cell suspension is taken and subcultured on to fresh media at regular intervals. In continuous cultures, fresh medium is added to existing culture, and excessive cell suspensions are removed at regular intervals. Suspension cultures are widely used in a large-scale production of bioactive phytochemicals. Bioreactors such as Chemostat are specially designed instruments to carry out continuous cultures on a large scale (Sidhu 2010).

6.2.7 Protoplast Cultures

Protoplasts are plant cells in which the cell wall has been removed by enzyme digestion or mechanical process. Protoplasts are isolated by dipping plant tissue into hypertonic solution, causing the plasma membrane to shrink away from cell wall. Now, the cell wall can be removed by enzymatic digestion (pectinase and cellulose) or mechanical methods. Successful plant regeneration was achieved by protoplast culture in certain species (Sidhu 2010).

6.2.8 Hairy Root Cultures

A soil bacterium *Agrobacterium rhizogenes* contains root-inducing plasmids (Ri plasmids). This bacteria can infect plant roots and transfer part of the Ri-plasmid to the plant genome. Expression of this plasmid enables the plant cell to proliferate by increasing the rate of cell division and cell elongation to produce the hairy roots. The hairy roots are characterized by high growth rate, genetic stability, and growth in hormone-free media. Appropriate bioreactors can be designed to culture the hairy roots in a large scale for the production of valuable secondary metabolites including active principles (Srivastava and Srivastava 2007).

6.3 Conservation of Medicinal Plants

There are two methods for the conservation of plant genetic resources, namely *in situ* and *ex situ* conservations. Conservation of the plants in their native habitats (where the plants are currently distributed) is known as *in situ* conservation. *Ex situ* conservation involves conservation outside the native habitat of the plants; it is generally used to safeguard populations in danger of destruction, replacement, or disappearance.

6.3.1 *In Situ* Conservation

In situ protection is normally practiced to conserve threatened plants including medicinal and aromatic plants in their natural habitats. Traditional methods of *in situ* conservation include discouraging cutting down the plants and encouraging the local people to plant the plants to be conserved for domestic use, and creation of nature reserves. *In situ* conservation can be practiced in farmers' fields in case of domesticated plants or in natural environments for wild species (Gepts 2006). Specific protected areas can be created to conserve the plants in the forest where the plants normally occur; seedlings and other appropriate planting materials may be planted and conserved and propagated in the protected areas. The *in situ* conservation areas should be made to serve important activities associated with conservation such as providing education and awareness to the public and students on conservation and sustainable utilization of plants. In spite of *in situ* conservation benefits, it is almost impossible to adopt only this approach for conservation due to the disappearance of large wild areas. Germplasm conservation in live gene banks in natural fields poses problems in terms of required land space and labor input during annual or perennial replanting, maintenance, and documentation. Moreover, plants conserved under such natural conditions are exposed to natural disasters, pests, and pathogens in addition to the inconsistent government policies (Tahtamouni et al. 2015). Further, in many cases, *in situ* propagations are not sufficient to meet the demand for plant materials, particularly those with a slow growth rate and limited viable seed production.

6.3.2 *Ex Situ* Conservation of Plants

Ex situ (off-site) conservation stands for the conservation and maintenance of plants outside their natural habitat as samples in the form of whole plants, seeds, pollens, vegetative propagules, and tissue or cell cultures. *Ex situ* conservation involves three methods, namely, field gene banks, seed banks, and *in vitro* gene banks (*in vitro* propagation and storage including cryopreservation). Gene banks (*in vitro* and field gene banks) facilitate conservation for sustainable utilization of plant resources. *Ex situ* conservation methods of plant samples is usually practiced in botanic gardens and national facilities (Paunescu 2009; Ramsay et al. 2000). There are more than 2,204 botanic gardens in the world that secure more than one-third of the world's flowering plants (BGCI 2001). These gardens acts as the repository of collected material, elite material, and endangered material, and also act as a regional repository of collections as a part of the global system; they facilitates the organization of regeneration programs. National cryobank and genetic conservation are available in certain countries. The purpose of the gene bank is to undertake and promote long-term conservation of plant genetic resources. The importance of gene banks has been recognized since long and such gene banks exist in various parts of the world.

6.3.2.1 Field Gene Banks and Seed Banks

Field gene bank (*ex situ* reserves) can be created in areas such as herbal gardens and botanical gardens. The existing herbal gardens and botanical gardens can be linked for sharing knowledge regarding *ex situ* conservation of medicinal plants. Protected *ex situ* reserves should produce and supply planting materials for cultivation. Compared to *in situ* conservation, *ex situ* conservation is able to store larger number of accessions, in a collection, which are ready to be accessed for characterization, evaluation, and distribution in addition to a higher security level that guarantees a safe conservation of large numbers of accessions (Shibli et al. 2006). Land space requirement, labor costs, and trained personnel requirements comprise major limitations for *ex situ* field conservation (Tahtamouni et al. 2015).

Seed banks are efficient and effective method of conservation for orthodox seeds. The seeds are placed in packets and stored in medium-term storage facilities (maintained at 0°C–5°C temp. and 15%–20% relative humidity) as active collections. Most of the material is also kept in long-term storage facilities (held at colder temperatures, –20 to –180°C). The seed samples are expected to remain viable for 20–30 years in medium-term storage and for up to 100 years in long-term storage depending on the species, the initial seed quality, and specificity of storage conditions. Although the most economical means of germplasm storage for seed propagated species is in the form of seeds, this is not always feasible because some crops do not produce viable seeds; some seeds remain viable for a limited duration only and are recalcitrant to storage; seeds of certain species deteriorate rapidly due to seed-borne pathogens; some very heterozygous seeds are not suitable for maintaining true-to-type genotypes. Effective approach to circumvent the above problems may be application of *in vitro* conservation and cryopreservation technology (Kasagana and Karumuri 2011).

6.3.2.2 In Vitro *Conservation (*In Vitro *Gene Banks)*

Ex situ conservation includes *in vitro* conservation, *in vitro* propagation, and reintroduction of *in vitro* propagated planting materials in the field gene bank. *In vitro* culture represents a wide range of techniques including growing plant parts such as shoot tips, meristems, somatic embryos, or embryogenic callus under aseptic conditions (see Section 6.2). Not only *in vitro* culture techniques have facilitated crop improvement and mass propagation, but they have also yielded great achievements in the scale of germplasm conservation (Negash et al. 2001; Shatnawi et al. 2006). *In vitro* conservation is offering a strong and a multipackage of techniques that perform well when other conservation methods are not feasible. When seed conservation may not be feasible, and in case of costly field gene banks, *in vitro* conservation could be used as a complementary conservation approach for genetic diversity. Tissue culture protocols were applied for the conservation of a wide range of medicinal plants including endangered, rare, and threatened plant species and anti-DM plants such as *Ginkgo biloba*, *G. sylvestre*, *T. cordifolia*, and *Salacia oblonga* (Sharma et al. 2010). In many countries, tissue culture techniques are used to conserve and propagate medicinal plants. In Jordan, for example, tissue culture techniques are also utilized to conserve several medicinal plants including the anti-DM plant *Artemisia herba-alba* Asso (Sharaf et al. 2012). Major *in vitro* conservation techniques developed fall under (1) slow growth procedures, where germplasm accessions are kept as sterile plant tissues or plantlets on nutrient gels and (2) cryopreservation, where plant material is stored in liquid nitrogen. Slow growth procedures provide short- and medium-term storage options, while cryopreservation enables long-term storage of the plant material (Kasagana and Karumuri 2011).

6.3.3 Slow Growth Conservation *In Vitro*

Slow growth conservation is a very simple *in vitro* tissue culture technique that permits conservation of plants material for periods ranging from 6 months to 5 years, depending on the species. This technique is based on reducing the growth rates of the tissue cultured plants and increasing the intervals between subcultures. Three basic methods are used in this technique including physical (reduced temperature and light conditions), chemical (using growth retardants such as osmotic agents and abscissic acid and limiting the availability of nutrients such as carbohydrate to suboptimal levels, and may be used in

different combinations. Slow growth conservation of plant germplasm has been widely applied and practiced for the conservation of many medicinal plants including anti-DM plants such as *Ocimum sanctum*, *Phyllanthus amarus*, *A. herba-alba*, and *Cannabis sativa*. However, investigating the influence of slow growth conservation on the chemical profile of the *in vitro* conserved plant material is an important prerequisite for any medicinal or aromatic plant containing natural products of pharmaceutical interest (Lata et al. 2012; Tahtamouni et al. 2015). The advantage of *in vitro* or reduced growth storage includes little space required in growth rooms for maintaining thousands of genotypes and the absence of diseases and pest attack in culture vessels. Furthermore, *in vitro* storage eliminates the need for long and frustrating quarantine procedures during movement and exchange of germplasm (Kasagana and Karumuri 2011).

6.3.4 Cryopreservation

Cryopreservation is defined as the viable freezing of biological material and their subsequent storage at ultra-low temperatures (−196°C) using liquid nitrogen. At this temperature, all forms of cellular divisions and metabolic activities of plant cells are ceased and the plant materials can be stored unaltered for a long period. Cryopreservation is advantageous over most other conservation methods in terms of simplicity and its applicability to a wide range of genotypes (Paunescu 2009). Besides, the cryogenic storage is practiced in a small volume, which excludes contamination risks and minimizes maintenance requirements. Thus, cryopreservation is usually safe and cost-effective for long-term preservation (Tahtamouni et al. 2015).

Cryopreservation involves removal of all freezable water from tissues using physical or osmotic dehydration, followed by ultra-rapid freezing. Removal of freezable water is very important in preventing freezing injury and retaining post-thaw viability. Crystallization during freezing is the main factor affecting survival of cells subjected to cryopreservation. The tendency to form large ice crystals becomes greater during slow warming, and to avoid this thawing should be performed rapidly by placing the cryovials in a water bath at 37–40°C for a few minutes (Tahtamouni et al. 2015).

The procedures used for cryopreservation of plant cells include two-step freezing, vitrification, encapsulation-dehydration, and droplet vitrification. Two-step freezing includes incubation of cells in appropriate concentrations of a mixture of cryoprotectants, which causes moderate dehydration of the cells, followed by a slow freezing step (e.g., 1°C/min down to about −35°C). Vitrification is based on severe dehydration at nonfreezing temperatures by direct exposure to concentrated cryoprotectants (total concentration ranging from 5 to 8 M), followed by rapid freezing. In encapsulation-dehydration procedure, cells are encapsulated in alginate beads, cultured on medium with increased sucrose concentration, air-dried (using the airflow of a flow cabinet, etc.), and transferred to liquid nitrogen. In droplet vitrification technique, the shoot tips were placed in droplets of cryoprotective medium before ultra-cooling (Sakai and Englemann 2007). The shoot tips are plated on aluminum foils and dehydrated with cryoprotectants such as glycerol based-plant vitrification solution 2 (PVS2). Using aluminum foils facilitates the transfer of shoot tips into and out of liquid nitrogen, which can be beneficial during application of PVS2 as slightly longer incubation times can be toxic for shoot tips (Kaczmarczyk et al. 2011). Shoot tips introduced to droplet-vitrification protocol are treated individually with 5–10 μL droplets of PVS2 on a piece of aluminum foil, which is then immersed in liquid nitrogen. While removing from cryopreservation, after warming, the aluminum foils are plunged in liquid medium containing 1.2 M sucrose for 20 min and then placed on recovery medium. The major achievement of this technique is the possibility of obtaining very high cooling/warming rates due to the very small volume of cryoprotective medium wherein the explants are placed (Sakai and Englemann 2007; Tahtamouni et al. 2015).

Besides conservation, cryopreservation aims to maintain the genetic stability of plant material.

Metabolic activities are theoretically ceased when the explant is stored cryogenically and consequently plant material is expected to be true-to-type after rewarming from cryopreservation. Only differentiated tissues, such as shoot tips, are targeted as plant material for cryogenic storage instead of undifferentiated plant material to avoid any genetic alteration. Evaluation of plant genetic uniformity to validate newly established cryopreservation protocols was carried out as some evidence of epigenetic alterations after cryopreservation of *in vitro* derived plant material was noticed (Mikula et al. 2011). Unlike genetic

changes, the original DNA sequence is not altered by epigenetic modifications as these modifications are usually featured with alterations in DNA methylation (Smulders and Klerk 2011). Although these alterations may affect gene transcription, epigenetic modifications are usually temporary and plants might get back to their normal phenotypes relatively easily (Smulders and Klerk 2011). DNA methylation influences plant vigor and morphogenesis and is highly affected by environmental conditions and stress during tissue culture and cryopreservation (Chen et al. 2011c; Tahtamouni et al. 2015).

6.4 Rare, Endangered, and Threatened Anti-DM Plants

Important anti-DM plants such as *S. oblonga* Wall. ex Wight. & Arn., Celastraceae (endangered, regional); *A. marmelos* (L.) Correa, Rutaceae (vulnerable); *Berberis aristata* D.C., Berberidaceae, (critically endangered); *Citrullus colocynthis* (L.) Schrad., Cucurbitaceae (threatened); and *P. marsupium* Roxb., Fabaceae (endangered) need urgent conservation and propagation. Other anti-DM plants that need conservation and propagation include *Aloe perryi* Baker, Liliaceae (vulnerable); *Andrographis paniculata* (Burm. f.) Nees, Acanthaceae (low risk); *Aquilaria sinensis* (Lour.) Gilg, Thymalaeaceae (near endangered); *Aralia chinensis* L. var. *glabrescens* Harms & Rehder, Araliaceae (vulnerable); *Cinnamomum osmophloeum* Kaneh., Lauraceae (threatened); *Cinnamomum tamala* (F. Hamilt.) Nees. & Eberm., Lauraceae (low risk:near-threatened); *Coscinium fenestratum* (Gartn.) Colebr., Menispermaceae (critically endangered, regional); *Dendrobium huoshanense* C.Z.Tang & S.J.Cheng, Orchidaceae (endangered); *Eugenia floccosa* Bedd.(threatened), Myrtaceae; *Garcinia kola* Heckel, Guttiferae (threatened); *Inula helenium* L., Asteraceae (critically endangered); *Picrorhiza kurroa* Royle, Scrophulariaceae (endangered); *Piper longum* L., Piperaceae (near threatened); *P. santalinus* Linn. f., Fabaceae (endangered, global); *Salacia reticulata* Wight, Celastraceae (endangered, regional); and *Terminalia arjuna* Roxb., Combrataceae (low risk, near threatened) (Anis et al. 2005; IUCN 2013; Joshi et al. 2012).

Many of the medicinal plants that are collected from the wild including anti-DM plants are on the decline. For example, the anti-DM plant *Abroma augusta* was found as a regular plant in Sikkim Himalaya during 1980–1990; but the later decade showed reduction of species from the region. Recently, the species is under critical threat of extinction from the region. The study found that factors such as deforestation, loss of traditional knowledge, modernization of society, and dependence on the conventional medicines were responsible for the drastic decrease in the number of the species (Laydong et al. 2012).

Locating breeding populations of important red-listed anti-DM plants and developing a species recovery program based on scientific studies are needed. In deserving cases, biotechnological intervention such as micropropagation and cryopreservation techniques as given below should be employed. Micropropagation studies conducted on rare, endangered, and threatened plants with anti-DM properties are given below (see Section 6.5.1).

6.5 Micropropagation of Anti-DM Medicinal Plants

In the case of important medicinal plants that are not amenable for rapid propagation by the conventional cultivation methods, biotechnological intervention is needed for desired quantity and quality of plant biomass. Biotechnological intervention including *in vitro* propagation is required in some cases such as rare and endangered plants for conservation and sustainable utilization. This may be achieved by developing *in vitro* propagation techniques including *in vitro* tissue/cell culture and production of high-quality seeding materials through *in vitro* techniques.

Micropropagation techniques are useful not only for conservation and *in vitro* propagation, but also to get uniform, high-quality, large-scale planting materials for mass cultivation in the field as well as for the production of elite genotypes for medicinal purposes. Advances in culturing plant cell cultures should provide new means for the commercial processing of even rare plants and the medicinally important phytochemicals provided by these plants. The introduction of transgenic cultures and regulation

of biosynthetic pathways applying molecular biological techniques in tissue culture enables large-scale production of desired phytochemicals. Thus, even in the case of plants that are amenable for propagation by the normal cultivation methods, micropropagation could be used for the production of desired as well as for bulk production of uniform planting material for large-scale cultivation in the field conditions.

In vitro propagation studies were initiated on most of the important anti-DM plants. Many of the important reports on micropropagation techniques of anti-DM medicinal plants including those in IUCN list (IUCN 2013) and anti-DM food crops are summarized below.

6.5.1 Micropropagation on Rare, Endangered, and Threatened Anti-DM Plants

Micropropagation studies carried out on 17 rare, endangered, or threatened (RET) anti-DM plants are given below. There could be more RET plants with anti-DM properties. It appears that RET anti-DM plants such as *A. perryi* Baker, *A. chinensis* L. var. *glabrescens* Harms & Rehder, *C. osmophloeum* Kaneh., *E. floccosa* Bedd (IUCN 2013) were not subjected to sufficient studies to establish micropropagation protocols.

1. *Aegle marmelos* (L.) Correa, Rutaceae (vulnerable), Bael or stone apple, holy fruit tree.

   Aegle marmelos is a multipurpose medicinal tree occurring in moist deciduous forests in India and near temples. *Aegle marmelos* is a very important anti-DM tree (Subramoniam 2016). It is a vulnerable tree species that needs conservation and propagation. There is genetic variability in the quality of fruits; the seeds are prone to insect attack and have short viability. Vegetative propagation through root suckers is possible; only a limited number of propagules are produced by this method. *In vitro* propagation techniques are capable of producing large number of disease-free uniform propagules. A number of workers attempted *in vitro* propagation of different explants with varying success. High-frequency plantlet regeneration was achieved in cotyledonary nodes of *A. marmelos*. Cotyledonary nodes from 1-month-old *in vitro* grown seedlings were cultured on MS medium supplemented with BA (0–8.8 μM), kinetin (0–9.4 μM), and IAA (0–1.14 μM) either alone or in different combinations. The highest regenerative response was observed on medium containing 6.6 μM BA+1.14 μM IAA where approximately 86.6% of the cultures responded with an average shoot numbers of 487.5 per explant in 7 weeks' time. *In vitro* responded shoots were transferred to root induction medium consisting of half-strength MS supplemented with IAA, IBA, or α-naphthalene acetic acid (NAA). Rooting was best in medium supplemented with 14.7 μM IBA. Rooted plantlets were acclimatized and transferred to the field with 80% survival rate (Nayak et al. 2007).

   In another study, a protocol for rapid *in vitro* propagation from nodal explants of *A. marmelos* has been described. High-frequency bud break was induced on MS BM supplemented with 0.5 mg benzyladenine (BA)/L. After 10 days of culture, nodal explants with multiplied buds started callusing with restricted growth and defoliation. The same nodal explants transferred to the same BM supplemented with 0.5 mg BA/L at different concentrations of either kinetin or gibberellic acid or in combination have shown healthy shoots with expanded shoot length. Excised shoots (2–3 cm long with two to three nodes) have shown rhizogenesis when grown on 1/2 MS BM with 2.5 mg/ IBA and 0.5% activated charcoal/L. After excision, in the second passage, the nodal explants also showed bud break when subcultured on MS BM supplemented with 0.5 mg BA/L. These shoots were successfully rooted on the above-mentioned medium (Puhan and Rath 2012).

   Hairy root induction in *A. marmelos* with *A. rhizogenes* was not successful in an attempt (Khatodia and Biswas 2014).

2. *Andrographis paniculata* (Burm. f.) Nees, Acanthaceae (low risk).

   The natural population of this herb is declining. This plant possesses several pharmacological properties including antihepatotoxic activity, anticancer property, antimicrobial activity, and anti-DM effects. The antihyperglycemic and anti-diabetic properties of this plant (alcohol extract) and its active compound andrographolide have been shown in streptozotocin-induced

rats (Yu et al. 2003). Mediation of β-endorphin in andrographolide-induced plasma glucose-lowering action in type 1 diabetes-like animals has been reported (Yu et al. 2008). *Andrographis paniculata* or its active compound andrographolide showed hypoglycemic and hypolipidemic effects in high-fat-fructose-fed rats also (Nugroho et al. 2012). In a recent study, andrographolide significantly decreased the levels of blood glucose and improved islet β-cells in streptozotocin-induced type 2 diabetic rats (Nugroho et al. 2014).

This plant's high demand for andrographolide extraction led to the depletion of its wild populations. The commercial exploitation of this plant is hampered due to its limited availability. The conventional propagation of this plant species is limited to vegetative means that is inadequate and slow in meeting the commercial quantities required. Variability among the seed-derived progenies and scanty and delayed rooting of seedlings curb its propagation through seeds (Kataky and Handique 2010).

High-frequency shoot proliferation via nodal explants of this plant was achieved in full- and half-strength MS medium supplemented with required concentrations of growth regulators. Rooting was achieved in 0.5 mg/L IAA. The regenerated plants were successfully acclimatized and transferred to the field with 98% survival rate (Kataky and Handique 2010). In another study, regeneration of *A. paniculata* was achieved from nodal explants using MS medium and growth regulators. Maximum number of shoots per explant was recorded on MS medium supplemented with BAP (1.0 μM) and kinetin (0.5 μM). All shoots developed roots after transfer to MS medium supplemented with 2.0 μM IBA. The rooted plantlets were successfully established in soil (Dandin et al. 2012). In a recent study, a cost-effective protocol for rapid *in vitro* regeneration of *A. paniculata* has been reported. MS medium supplemented with BAP (0.5 mg/L) alone showed 100% shoot regeneration from nodal segments. Hundred percent rooting was recorded on the medium containing 0.2 mg/L of IBA (Al-Mamum et al. 2015).

3. *Aquilaria sinensis* (Lour.) Gilg, Thymalaeaceae (tended to be endangered).

Aquilaria sinensis is an evergreen broad leave tree of China. It is a valuable and rare medical species with high economic, ecological, and landscaping values. Because of over-logging, wild trees of *A. sinensis* tended to be endangered.

The leaves of *A. sinensis* have been used in folk medicine for the treatment of diabetes in Guangdong Province, China. In a scientific validation, administration of the 95% ethanol extract of *A. sinensis* leaves (600 mg/kg) for 4 weeks resulted in activation of adenosine monophosphate–activated protein kinase (AMPK) and reduction in fasting blood glucose and glycosylated hemoglobin levels in diabetic db/db mice. In addition, the oral glucose tolerance test showed that the extract could remarkably improve insulin resistance. Compared to thiazolinediones, no weight gain was observed after the administration, which is a severe side effect of thiazolinediones. The authors suggest that the extract could be used as an alternative to thiazolinediones in the management of obesity-related diabetes. In another study, methanol and water extracts (1 g/kg), but not hexane extract, lowered the fasting blood glucose levels by 54% and 40%, respectively, in streptozotocin-induced diabetic rats. In an *in vitro* experiment, these extracts (10 μg/mL) enhanced glucose uptake in rat adipocytes (Pranakhon et al. 2011).

A method for tissue culture and rapid propagation of *A. sinensis* was reported. In this method, propagation coefficient of axillary buds was 4.93 in MS BM with 0.05 mg/L BAP. The shoots were rooted by an indirect way and the frequency of rooting was as high as 94.4%. The survival rate of the test tube plantlets was 93.8% in the transplanting (Ye et al. 1997). In another study, a regeneration system of *A. sinensis* by tissue culture techniques was standardized (Yue 2012). Recently, a tissue culture rapid propagation system of *A. sinensis* has been established by taking the stem with buds of *A. sinensis* as the explant and by virtue of the processes of explant sterilization, multiple shoot induction, rooting, acclimatization, and transplanting. The author believes that the tissue culture technique developed has important practical significance on increasing popularization of the good-quality *A. sinensis* variety and the development and utilization of resources (Leong 2015).

4. *Berberis aristata* D.C., Berberidaceae, Indian Barberry (critically endangered).

   Berberis arista is a red-listed critically endangered endemic Himalayan medicinal shrub found in India, Sri Lanka, and elsewhere. This plant is a native to Himalayas at an elevation of 2,000–3,550 m (Ray et al. 2011). This plant species warrants conservation and propagation, probably, due to extensive collection of roots of this plant for berberine. This plant is rich in berberine that exhibits potent anti-DM activity via multiple mechanisms of action (Almasri et al. 2009; Arif et al. 2014; Chen et al. 2010; Yu et al. 2010; see also Chapter 3). The plant also contains β-sitosterol, an anti-DM compound. Several studies have established the promising anti-DM activity of the extracts of stem bark and root of this plant in alloxan-induced diabetic rats (Akhtar et al. 2008; Gupta et al. 2010; Singh and Kakkar 2009; Semwal et al. 2009).

   A study on vegetative propagation of *B. aristata* showed that apical cuttings when treated with 5,000 ppm IBA performed significantly better sprouting (85%) and rooting (50%) in comparison to other treatments. Control, without IBA treatment, had shown no rooting in different cutting portions (Ali et al. 2008). In a recent study, a protocol for hairy root induction in *B. aristata* was established using two different strains of *A. rhizogenes*. This study reported a protocol for hairy root induction that could be useful for the production of berberine, an important anti-DM compound, and may reduce the overharvesting of this endangered species from its natural habitat (Brijwal and Tamta 2015).

5. *Cinnamomum tamala* (F. Hamilt.) Nees. & Eberm., Lauraceae, (low risk—near threatened).

   Cinnamomum tamala is a medium-sized evergreen tree found in North India; it is also found in tropical and subtropical Asia, Australia, and Pacific region. This plant has hypoglycemic and hypolipidemic properties. *Cinnamomum tamala* (95% ethanolic extract) showed some level of blood glucose lowering effect within 2 weeks of treatment in alloxan diabetic rats (Kar et al. 2003). In streptozotocin-induced diabetic rats, the water extract of this plant leaves at a dose of 125 and 250 mg/kg (by mouth [p.o.], daily for 3 weeks) markedly decreased the levels of fasting blood glucose and urine sugar with a concomitant increase in body weight (Chakraborty and Das 2010). *Cinnamomum tamala* oil also showed anti-diabetic, hypolipidemic, and antioxidant activities in streptozotocin-induced diabetic rats (Kumar et al. 2012). The methanol and successive water extract of this plant bark were found to inhibit α-amylase activity (Kumanan et al. 2010).

   Owing to its medicinal value and being an important ingredient of spices, the demand for this plant is increasing. This plant is being exploited from its natural forest habitat illegally and the natural population is rapidly diminishing. The habitat-specific occurrence, poor regeneration status, and short life span of seeds result in the vulnerable status of the species. In a study an attempt has been made to develop an efficient micropropagation method of multiple shoot formation and subsequent rooting through callus culture from various types of explants (Sharma and Nautiyal 2009).

6. *Citrullus colocynthis* (L.) Schrad., Cucurbitaceae (threatened).

   Citrullus colocynthis is a slender stemmed diffuse or creeping monoecious plant with promising anti-DM properties. It is an important medicinal plant collected from the wild. Due to excessive and destructive exploitation of *C. colocynthis*, it is getting depleted fast. It is listed as a threatened species in the Red Data book of Indian plants (Joshi et al. 2012). In Rajasthan, India, since its seeds are collected for oil, it has become a threatened plant in the desert.

   The seeds, fruits, and root water extracts of *C. colocynthis* showed potent anti-DM activity in animal models of DM (Abdel-Hassan et al. 2000; Agarwal et al. 2012; Al-Ghaithi 2004; Nmila et al. 2000). In a clinical trial conducted in 50 type 2 diabetic patients, the fruit of this plant exhibited a beneficial effect on improving the glycemic profile without adverse effects in type 2 diabetic patients (Huseini et al. 2009).

A rapid clonal propagation system has been developed for *C. colocynthis* through *in vitro* culture of mature nodal segments with axillary bud. Maximum number of multiple shoots was obtained on MS medium supplemented with BAP (2.0 mg/L) and NAA (2.0 mg/L). *In vitro* raised elongated shoots from the cluster were excised and transferred on rooting medium fortified with 4.0 mg/L IBA. These rooted shoots were successfully acclimatized in pots containing vermicompost and sterilized soil (1:3). Direct origin of shoot buds from cultured explants was observed. A rapid, reproducible, regenerating protocol for clonal propagation of *C. colocynthis* through mature nodal explant culture has been established (Meena et al. 2007). In another study, a high-frequency and rapid regeneration protocol was developed from shoot tip explants of *C. colocynthis* on MS medium supplemented with BAP (0.5 mg/L) and NAA (0.5 mg/L). The highest number of shoots (23) was obtained on MS medium containing BAP (0.5 mg/L) and NAA (0.5 mg/L). The regenerated shoots were further elongated on same medium. *In vitro* shoots were excised from shoot clumps and transferred to rooting medium containing IBA (4 mg/L) with 0.2% activated charcoal. The rooted plants were hardened in polycups containing sterile soil and vermiculite and finally well established in the field (survival rate was 60%) (Meena et al. 2010; Meena et al. 2014a). In another study by the same authors *in vitro* callus induction and shoot regeneration in this plant has been reported (Meena et al. 2014b).

7. *Coscinium fenestratum* (Gartn.) Colebr., Menispermaceae (critically endangered, regional).

Coscinium fenestratum is a dioecious, large, woody climber indigenous to the Indo-Malayan region. It grows in the wild natural rain forest with humus rich soil having good drainage. The slow growing liana takes 15 years to reach its reproductive stage. But due to its huge demand, it gets chopped down before it is fit to regenerate. Combination of rampant destruction of the forests along with overexploitation for the raw drug market and very slow rate of regeneration has seriously depleted its population in the wild leading to urgency of conservation measures. The thread status of this species has been assessed as critically endangered in South India due to more than 80% decline in the wild population over the last 30 years. This plant has been listed in the red data book of Vietnam. In India and Sri Lanka, this plant has been listed as an endangered species (Tushar et al. 2008).

Coscinium fenestratum is an important medicinal plant that, among other things, contains the anti-DM compound berberine. Ethanol extract of *C. fenestratum* stem significantly reduces the levels of blood glucose in normal and streptozotocin–nicotinamide-induced diabetic rats. In addition, the extract treatment improved body weight, serum lipid profiles, thiobarbituric acid reactive substance levels, glycosylated hemoglobin, and liver glycogen levels in the treated diabetic rats compared to control diabetic rats. Serum insulin levels were not elevated in the animals treated with the extract (Shirwaikar et al. 2005). The anti-DM activity of the ethanol extract of *C. fenestratum* stem was confirmed in alloxan-diabetic rats also. The ethanol extract showed potent antihyperglycemic effect in alloxan-induced diabetic rats. The antihyperglycemic efficacy was comparable to that of glibenclamide (Manoharan et.al. 2011). The water extract of *C. fenestratum* stem also showed antihyperglycemic activity in streptozotocin–nicotinamide-induced type 2 diabetic rats (Shirwaikar et al. 2008). In another study, the crude dichloromethane and ethyl acetate extracts (250 mg/kg, p.o., daily for 4 weeks) of *C. fenestratum* stem showed a strong hypoglycemic effect by lowering the blood glucose levels and increasing the body weight in streptozotocin-induced diabetic rats (Malarvili et al. 2011).

In nature, this species propagates through seeds and vegetative stem cuttings. Vegetative propagation is very slow, and the conventional propagation through seeds and stem cuttings is inadequate to meet the demands of conservation and sustainable utilization. There have been reports on *in vitro* callus induction for determination of berberine content in *C. fenestratum*. *In vitro* propagation of *C. fenestratum* has also been reported. Multiple shoots were formed from epicotyls explants on MS medium supplemented with 1 μM kinetin and 0.25 μM 2,4-D. Repeated subculturing favored the increase in shoot length and the number of shoots per

explants in MS media containing kinetin and 2,4-D. Complete *in vitro* rooting was obtained in half-strength MS medium supplemented with 2.5 μM IBA. The plantlets were successfully transferred to the field after *ex vitro* acclimatization. This protocol has the potential to be used as a tool for large-scale production of planting materials (Senarath 2010). An image of tissue-cultured shoot of *C. fenestratum* is shown in Figure 6.1.

8. *Dendrobium huoshanense* C.Z.Tang & S.J.Cheng, Orchidaceae (endangered).

   Dendrobium huoshanense is an economically important and endangered medicinal orchid with anti-DM activity. In a recent study, *D. huoshanense* polysaccharide exhibited promising hypoglycemic and antioxidant activities in the alloxan diabetic rats (Pan et al. 2014).

   The effects of cytokinins, carbohydrate sources, and cold pretreatment on the conversion of protocorm-like bodies to shoots were investigated for the enhancement of micropropagation of *D. huoshanense*. The results indicate that a suitable cold pretreatment (10°C for 1 week) followed by the use of 20 μM kinetin and 10 g/L maltose in half-strength MS medium would produce a large number of shoots from protocorm-like bodies for plantlet regeneration of *D. huoshanense* (Ping et al. 2009). Recently, a protocol for regenerating and subsequent *in vitro* flowering of *D. huoshanense* was established mainly via indirect protocorm-like body formation. A four-step method was developed to induce successful plant regeneration on half-strength MS medium supplemented with suitable PGRs. The root tip explants were cultured at 1 mg/L 2,4-D + 1 mg/L thidiazuron for 3 months for callus induction. The calli were subcultured with a 1-month interval at 1 mg/L 2,4-D + 1 mg/L thidiazuron for callus proliferation. The calli were cultured at 2 mg/L NAA + 1 mg/L BA for 2 months for protocorm-like body induction. Protocorm-like body was cultured with 0.1 mg/L IBA for 4 months for plantlet conversion. It took at least 6 months to produce well-rooted regenerated plantlets from the initial callus. The 6-month-old rooted plantlets were transferred onto half-strength MS medium for 6 months, and then potted with Sphagnum moss for acclimatization. After 2 months of culture, the survival rate was 100%. The *in vitro* flowers were obtained on the 8-month-old plantlets at 1 mg/L IBA, 5 mg/L IBA, and 0.1 mg/L NAA, but the flowers showed lack of the gynandrium. The abnormity was overcome with 5 mg/L thidiazuron, and subsequently, the capsules formed without artificial pollination. This protocol provides the basis for further studies on large-scale micropropagation (Lee and Che 2014).

9. *Garcinia kola* Heckel, Guttiferae (threatened).

   Garcinia kola is a medium-sized tree growing up to 12 m high in 8 years in moist forest of West and Central Africa. It is used extensively in African traditional medicine.

FIGURE 6.1 Tissue-cultured plantlet (shoot) of *Coscinium fenestratum*. (Photo courtesy of Dr. William Decruse).

This medicinal plant has anti-DM activity too. Oral administration of water extract of *G. kola* seed at a concentration of 200 mg/kg, over a period of 21 days, significantly decreases the levels of blood glucose and increases the activity of superoxide dismutase (Kingsley et al. 2010). Saponin extract from the root of *G. kola* (100, 200, and 400 mg/kg, daily for 7 days) produced a reduction of 36% in blood glucose after the third day of treatment compared to the 31% observed for metformin. A dose of 200 mg/kg of saponin produced a maximum reduction of about 73% after the seventh day of treatment compared to 36% observed for metformin. Thus, the saponin extract from the root of *G. kola* demonstrated a remarkable glucose-lowering activity (Smith et al. 2012). Kolaviron, a bioflavonoid complex isolated from seeds of *G. kola*, possessed significant hypoglycemic effect in alloxan-diabetic rats. Kolaviron also inhibited rat lens aldolase activity *in vitro*. Further, kolaviron showed remarkable protective effects on renal, cardiac, and hepatic tissues of streptozotocin-diabetic rats (Akinmoladun et al. 2014).

In spite of great demand of *G. kola*, its cultivation is not popular because of the difficulty in seed germination. The literature gives contradicting information concerning the germination of *G. kola* seeds. A study has shown variations in seed germination among collections from different places (Kanmegne and Omokolo 2008). Further, the study showed that pregermination treatments had profound effect on the phenology of *G. kola* seed germination. Multiple shoots, multiple roots, and callus formation were induced from seeds soaked in BAP, NAA, and 2,4-D solutions, respectively. Although the rate of germination was higher and the complete dormancy period was lower in seeds treated with NAA than in seeds with other treatments, none of these treatments significantly enhanced germination (Kanmegne and Omokolo 2008). There is a need to develop simple and efficient *in vitro* propagation methods for this plant.

10. *Inula helenium* L., Asteraceae (critically endangered).

    Inula helenium is one of the critically endangered perennial plants found in Europe and East Asia. The root of this plant has been used in traditional medicine against a variety of ailments. Alantolactone from *I. helenium* is reported to lower blood glucose (Marles and Farnsworth 1995). The root culture of this plant was successfully established, but genetic instability, slow growth, and low efficiency of the cell cultures were noted. In a study, hairy root culture of *I. helinium* was established by inoculation of the leaf and stem explants with *A. rhizogenes* strain (AR15834). The growth rate of the hairy roots was tenfold as compared to control root in the same condition (Shirazi et al. 2013).

11. *Picrorhiza kurroa* Royle, Scrophulariaceae (endangered).

    Picrorhiza kurroa is a fast-depleting medicinal plant. It is endemic to India and grows in inner ranges of alpine Himalayas, from Kashmir to Sikkim in India. The plant possesses hepatoprotective, immunomodulatory, anti-DM, and other properties. The anti-diabetic activity of the plant extract has been shown in alloxan diabetic rats (Joy and Kuttan 1999). Administration of water extract of *P. kurrooa* (100 and 200 mg/kg, p.o.) for 14 days to streptozotocin–nicotinamide-induced diabetic rats resulted in significant reduction in the elevated fasting glucose levels; further, the treatment improved oral glucose tolerance and body weight (Husain et al. 2009).

    The natural regeneration of this plant is through rhizomes and seeds; however, their cultivation rate is very poor. The poor propagation coupled with overexploitation has depleted the species from natural habitat. This plant species is now listed as one of the endangered species of India. The conservation of this plant is essential for promoting *ex sito* plantation that requires large-scale planting material. This can be met by *in vitro* propagation. Plant regeneration from *P. kurroa* has been reported using shoot tips. In another study, an efficient and rapid protocol for mass propagation of *P. kurroa* has been developed. The best results were obtained, when nodal explants from natural plants were cultured on MS BM supplemented with 0.25 mg/L 2,4-D, 0.25 mg/L BAP, 0.2 mg/L NAA, and 0.6 mg/L NAA for profuse callusing, shoot induction, indirect, and direct rapid shoot proliferation, respectively. The root induction was also optimized using auxins. The root induction per explant was the maximum in MS BM supplemented with 0.4 mg/L NAA. The rooted plantlets were hardened and successfully acclimatized and

established in soil (Jan et al. 2010). In another study, *in vitro* shoot multiplication was achieved through sprouting of axillary buds using nodal segments and leaf tissue. For shoot regeneration, the hormone combination of kinetin + IBA (2.0 mg/L + 0.50 mg/L) with leaf explant was found superior. Interestingly, the basal MS medium gave 99.9% response (direct proliferation) with nodal explant. The medium supplemented with IBA (1.0 mg/L) was found to be best for rooting of regenerated shoots. The *in vitro* raised plantlets were hardened and successfully established in the glass house conditions (Sharma et al. 2010). Further, in another study, a regeneration protocol was standardized using leaves from shoot cultures raised from *ex vitro* leaves. Maximum regeneration (94%) and higher shoot number were evident in middle portion of the leaf at 2.32 μM of kinetin. Time of exposure to thidiazuron was emphasized as a 15-day interval, which gave the best response in terms of shoot numbers. For shoot multiplication, kinetin at 2.32 μM was optimum. Microshoots with well-developed root system were obtained in MS medium after 4 weeks. Incubation of cultures at 15 °C for 10 days enhanced the survival under greenhouse conditions. In a parallel study, seed progenesis of these micropropagated plants was raised under *ex situ* conditions (Patial et al. 2012).

12. *Piper longum* L., Piperaceae (near threatened).

    Piper longum is a perennial diocious plant with multiple medicinal properties. Fruit of *P. longum* is a valuable spice; it is also used as a therapeutic agent in the treatment of various ailments in ethnomedicine. The major pharmacologically active compound, piperine, has anti-DM and other properties (Kim et al. 2011).

    Ethyl acetate and ethanol extracts of *P. longum* fruits showed antihyperglycemic activity and attenuated oxidative stress in streptozotocin diabetic rats (Kumar et al. 2011). The water extract of *P. longum* root (200 mg/kg) was found to possess significant anti-diabetic activity after 6 h of the treatment in streptozotocin diabetic rats. The administration of the same dose of the extract for 30 days to streptozotocin-induced diabetic rats resulted in a significant decrease in fasting blood glucose levels with the corrections of diabetic dyslipidemia compared to untreated diabetic rats. There was a significant improvement in the activities of liver and renal functional markers in treated diabetic rats compared to untreated diabetic rats indicating the protective role of the water extract of *P. longum* against liver and kidney damages (Nabi et al. 2013).

    Piper longum is a near-threatened plant species. Normal method of propagation of this plant has some problems such as poor seed viability, low percentage of germination, and scanty or delayed rooting. Not much work on tissue culture has been conducted on this plant, except a few reports on regeneration (Padhan 2015). In a report, efficient and rapid tissue culture systems were developed for *P. longum* through shoot tip multiplication. Multiple shoots were induced from shoot tips cultured on agar-based MS medium containing 8.9 μM BA and 4.64 μM kinetin. Adventitious shoot regeneration from leaf segments was achieved on MS containing 3.6–22.19 μM BA along with 3.31–12.4 μM picloram. Shoot differentiation occurred directly from the leaf bases without intermediate callus formation. Maximum shoot buds were obtained on MS medium with 17.76 μM BA and 8.28 μM picloram. Elongated shoots were separated and rooted in MS medium supplemented with 2.46 μM IBA. Plantlets thus developed were established in soil (Soniya and Das 2002).

    In a recent report, *in vitro* clonal propagation of field-grown plants by nodal explants has been shown. The best shoot proliferation was observed in MS medium containing 1 mg/L kinetin and 1.5 mg/L BAP. Callus induction occurred in 1 mg/L BAP + 0.5 mg/L kinetin; and 10–15 days of callus subculture led to initiation of shoot buds. For rooting, the *in vitro* shoots were inoculated to MS medium supplemented with 0.5 mg/L IAA. The regenerated plantlets were successfully established in soil with 90% survival rate (Padhan 2015). An image of tissue-cultured plantlets of *P. longum* is shown in Figure 6.2.

13. *Pterocarpus marsupium* Roxb., Fabaceae, Indian kino tree (endangered).

    Pterocarpus marsupium is an erect deciduous tree. It is distributed in the Western Peninsula of India and Sri Lanka. The native natural stands of *P. marsupium* are fast disappearing.

FIGURE 6.2 Tissue-cultured plantlets of *Piper longum*. (Photo courtesy of Dr. William Decruse.)

The winged fruit of this tree is the only propagating material, but its germination is low (only 30%). Hard fruit coat and less germinability coupled with poor seed viability are responsible for its diminishing population size. *Pterocarpus marsupium* has been overexploited, which in turn has led to its inclusion in the list of endangered plant species (Anis et al. 2005).

The plant possesses several active principles and different mechanisms of anti-DM action. Water extract of the stem bark showed anti-DM activity in alloxan diabetic rats (Vats et al. 2002), and the anti-DM activity resembled that of insulin (Dhanabal et al. 2006). (–) epicatechin from the water extract of stem bark showed anti-diabetic activity in alloxan diabetic rats and its stimulated isolated rat islets (Ahmad et al. 1991; Sheehan et al. 1983). An isoflavone from the methanol extract of the plant upregulated glucose transporter 4 (GLUT-4) and peroxisome proliferator–activated receptor-gamma (PPAR-γ) on L6 myotubes (Anandharajan et al. 2005). Marsupin and pterostilbene (phenolic constituents of heart wood of *P. marsupium*) lowered blood glucose levels of streptozotocin-induced diabetic rats (Manickam et al. 1997).

Development of plantlets of *P. marsupium* through induction of multiple shoots from seedling-derived cotyledonary node explants and their successful rooting and acclimatization have been reported. The direct regeneration of multiple shoots from cotyledonary node explants of this endangered legume tree will ensure the cloning stocks of this valuable tree. Reproducibility and plantlet regeneration will surely lead to the use of this system in afforestation programmes (Anis et al. 2005). In another study, an efficient protocol was developed for micropropagation of *P. marsupium*. Multiple shoots were induced from cotyledonary nodes derived from 18-day-old axenic seedlings on MS medium supplemented with thidiazuron (0.1–10 μM). The highest shoot regeneration frequency (90%) and maximum number (15) of shoots per explant were recorded on MS medium amended with 0.4 μM thidiazuron. Continuous presence of thidiazuron inhibited shoot elongation. Thidiazuron-initiated cultures were transferred to the secondary medium supplemented with 6-benzyladenine (BA) for shoot growth and elongation. Maximum (90%) shoot elongation with an average shoot length of 5.4 cm was observed

at 5 μM BA. To further enhance the number of shoots per explant, mother tissue was repeatedly subcultured on fresh shoot induction medium after each harvest of newly formed shoots. Thus, by adopting this strategy, an average of 44 shoots per explant could be obtained. About 65% of *in vitro* regenerated shoots produced a maximum number (4.4) of roots per shoot by a two-step culture procedure employing pulse treatment and subsequent transfer of treated shoots to a low concentration of IBA (0.2 μM) along with phloroglucinol (3.96 μM). The *in vitro* raised plantlets were successfully acclimatized first under culture room conditions, then to greenhouse with 70% survival rate (Husain et al. 2007).

14. *Pterocarpus santalinus* Linn. f., Fabaceae (endangered, global).

Pterocarpus santalinus, red sandal wood, is one of the endemic and endangered medicinal plant species of India. It is a medium-sized deciduous tree distributed in the Western Peninsula of India.

The anti-DM properties of this plant have been demonstrated in animal models. Oral administration of bark (alcohol extract) of the plant showed antihyperglycemic activity in diabetic rats (Kameswararao et al. 2001). The plant bark exhibited promising anti-diabetic activity in streptozotocin-induced diabetic rats. It reduced the levels of blood glucose and glycosylated hemoglobin and improved insulin and lipid profiles (Kondeti et al. 2010). Anti-diabetic compounds such as β-sitosterol and β-amyrin were reported from this plant.

A protocol has been developed for the *in vitro* propagation of *P. santalinus* using shoot tip explants. Multiple shoots were induced from shoot tip explants derived from 20-day-old *in vivo* germinated seedlings in 1:1 ratio of sand and soil after treating with gibberellic acid. The highest frequency for shoot regeneration (83.3%) with maximum number of shoot buds (11) per explant was obtained on MS medium supplemented with 1.0 mg/L of 6-benzylaminopurine (BAP) along with 0.1 mg/L of thidiazuron after 45 days of culture. A proliferating shoot culture was established by repeatedly subculturing the original shoot tip explants on fresh medium after each harvest of the newly formed shoots. Sixty percent of the shoots produced roots when transferred to rooting medium containing MS salts and 0.1 mg/L IBA after 30 days. About 73% of the *in vitro* raised plantlets were established successfully in earthen pots. Random amplified polymorphic DNA (RAPD) based DNA fingerprinting profiles were generated using shoot tip explants of this species; this fingerprinting confirmed that there was no genetic variability (Balaraju et al. 2011). Another report demonstrated *in vitro* seed regeneration and induction of enhanced shoot multiplication. The generated shoots with developed root system were successfully acclimatized and grown in greenhouse with 85% survival rate (Vipranarayana et al. 2012).

15. *Salacia oblonga* Wall. ex Wight. & Arn., Celastraceae (endangered, regional).

Salacia oblonga is a glabrous shrub or small tree. It is distributed in the hotter pates of Sri Lanka and Western Peninsula of India. It is an endangered medicinal plant whose conservation is urgently needed.

Salacia oblonga is a very important anti-DM plant. *Salacia oblonga* (hot water extract of roots) improved cardiac fibrosis and inhibited postprandial hyperglycemia in obese Zucker rats (Li et al. 2004). Tea prepared from *S. oblonga* suppressed glucose absorption from the intestine (Matsura et al. 2004). The water extract of the plant showed hypoglycemic and antioxidant activity in streptozotocin-induced diabetic rats (Augusti et al. 1995; Krishnakumar et al. 1999). The aqueous methanol extract of the plant inhibited α-glucosidase and aldose reductase and this effect is caused by salacinol and kotalanol, respectively (Matsuda et al. 1999). Water extract of the root showed antihyperlipidemic and antiobesity activities in Zucker diabetic fatty rats (Huang et al. 2006). Besides, *S. oblonga* root extract showed hypoglycemic and antilipid peroxidative activities in diabetic rats (Krishnakumar et al. 1999). The root extract inhibited cardiac fibrosis and cardiac hypertrophy in Zucker diabetic fatty rats; it inhibited the expression of angiotensin II type 1 receptor in heart of the fatty rats (Huang et al. 2008). *Salacia oblonga* (root extract) exhibited anti-diabetes and hypolipidemic activities in streptozotocin-induced

diabetic rats. Serum insulin level increased and plasma HbA1c level decreased in the extract treated diabetic animals compared to untreated diabetic control animals (Bhat et al. 2012). The plant is reported to contain the anti-DM compound mangiferin as well (Matsuda et al. 1999).

A recent study showed an easy, effective, and simple method of conserving genetic identity and producing elite clones of *S. oblonga* through vegetative propagation. Vegetative propagation was achieved using roots, stems with leaves, and stems without leaves in different concentrations of IBA. Explants (stems and stem with leaves) showed a maximum shooting response with 300 ppm IBA and root explant showed a maximum response with 200 ppm IBA (Deepak et al. 2015). There is a need to develop efficient *in vitro* propagation methods for this plant.

16. *Salacia reticulata* Wight, Celastraceae (endangered, regional).

Salacia reticulata is a medicinally important endangered plant. The distribution of *S. reticulata* is restricted to the Eastern India and Sri Lanka. In this species, seed germination takes a long time and percentage of germination is also low.

This plant is used in traditional medicine to control DM. Important anti-DM compounds such as mangiferin, kotalanol, and salacinal have been isolated from root and stem of this plant. Salacinal, kotanol, and polyhydroxylated cyclic 13-membered sulfoxide, potent α-glucosidase inhibitors have been isolated from *S. reticulata* (Nakamura et al. 2010; Ozaki et al. 2008). In a clinical trial, water extract of *S. reticulata* stem (240 mg/day for 6 weeks) decreased fasting levels of blood glucose and HbA1c levels in type 2 diabetic patients. In another study, a reduction in HbA1c levels has been reported in the patients receiving a preparation of *S. reticulata* tea for 3 months (Ghorbani 2013). In another preliminary clinical study, usefulness of *S. reticulata* consumption (2 g/day for 3 months) in the management of type -2 DM has been observed in 30 patients (Radha and Amrithaveni 2009).

Overexploitation for its anti-DM and antioxidant properties has caused it to be an endangered plant species. Propagation of *S. reticulata in vitro* is promising for its conservation. Only one report on *in vivo* propagation of this plant is available. An efficient protocol of axillary but proliferation and direct organogenesis has been developed for this plant. A suitable ecotype with high content of mangiferin was used for the micropropagation studies. Nodal segments were cultured on MS medium supplemented with different growth regulators. The most efficient shoot multiplication was obtained with the supplementation of BA and IAA (3.5 + 0.5 mg/L). Elongation of the microshoots was achieved by subculture every 20 days. The elongated shoots were rooted on half-strength MS supplemented with IBA. Plantlets were successfully established in the soil in 6–8 weeks. The authors belief that this protocol could be successfully applied for the development of high-quality planting material on a large scale (Dhanasri et al. 2013).

17. *Terminalia arjuna* Roxb., Combretaceae (near-threatened).

Terminalia arjuna is one of the economically important multipurpose medicinal tree of tropical and subtropical forests. It is found throughout the tropical and subtropical region of the peninsular India. In has many medicinal properties including, antibacterial, hypolipidemic, antiinflammatory, and anti-DM activities.

Studies have established the anti-DM activity of *T. arjuna*. Oral administration of ethanol extract of bark of *T. arjuna* (250 and 500 mg/kg, daily for 30 days) to alloxan-induced diabetic rats resulted in a significant decrease of blood glucose level and a decrease in the activities of glucose-6-phosphatase, fructose-1,6-disphosphatase, aldolase, and an increase in the activity of phosphoglucoisomerase and hexokinase in tissues (Ragavan and Krishnakumari 2006). In another study, ethanol extract of *T. arjuna* bark (500 mg/kg) showed a significant decrease in blood glucose levels in alloxan-induced diabetic rats. Further, the extract treatment resulted in a significant increase in glycogen content of liver, cardiac muscle, and skeletal muscle in the diabetic rats. Besides, the bark extract reduced adrenaline-induced hyperglycemia and intestinal glucose absorption (Barman and Das 2012). Oral administration of 500 mg/kg of the acetone extract of the bark to fructose–streptozotocin-induced type 2 diabetic rats lowered blood glucose, improved oral glucose tolerance, and decreased the levels of urine glucose and ketone

bodies compared to control diabetic rats. These effects of the extract were comparable to those of glimepiride (Kumar et al. 2013). The leaf extract of *T. arjuna* also demonstrated remarkable antihyperglycemic and antioxidant activities in streptozotocin-induced diabetic rats (Biswas et al. 2011). Compounds with anti-DM activity such as gallic acid, ellagic acid, and luteolin were reported from this plant.

Low percentage of germination and difficulty in rooting restrict the conventional propagation of *T. arjuna*. In a micropropagation study, cotyledon node explants excised from seedling of *T. arjuna* produced multiple shoots when cultured on MS medium supplemented with 0.5 mg/L BAP. About 88% shoots rooted well after 15 h pulse treatment with 1 mg/L IBA in liquid MS medium followed by transfer to modified MS medium without IBA. About 80% of the plantlets were successfully acclimatized and 70% plantlets survived in the field (Pandey and Jaiswal 2002). In a recent study, an efficient micropropagation protocol was developed through axillary shoot proliferation from nodal explants of mature *T. arjuna*. Nodal stem segments collected during the months of April and May gave best response. Maximum *in vitro* shoot proliferation was obtained on modified MS medium supplemented with 8.66 μM BAP + additives (100 mg/L of ascorbic acid, 50 mg/L of citric acid, 50 mg/L of adenine sulfate, and 25 mg/L PVP). Modified MS medium supplemented with 4.44 μM BAP + 0.54 μM NAA + additive was found to be the best for shoot multiplication. *In vitro* regenerated shoots were rooted when pulse-treated with 984 μM IBA for 10 min and transferred to hormone-free half-strength MS medium containing 100 mg/L activated charcoal. *In vitro* propagated plants were transferred to field after hardening and acclimatization procedure (Choudhary et al. 2015).

6.5.2 Micropropagation Studies on Important Anti-DM Plants

Traditional anti-DM plants that are very promising for anti-DM medicine development based on, mainly, pharmacological studies using animal models of DM are given in Table 6.1. Further, it appears that sufficient or no studies were conducted to establish micropropagation protocols on important anti-DM plants such as *Ajuga iva* (L.) Schreb, *Berberis vulgaris* L., *Casearia esculenta* Roxb., *Cassia kleinii* W. & A., *Clerodendron phlomidis* Linn.f., *Euclea undulata* Thunb., *Gongronema latifolium* Benth., *Hemionitus arifolia* (Burm.) Moore, *Hintonia latiflora* (Sesse & Moc.) Bullock., *Hunteria umbellata* K.Schum.Hallier f., and *Sterospermum teteragonum* D.C. Available, *in vitro* propagation studies carried out on very important anti-DM plants are given below. A detailed report on the *in vitro* propagation techniques used for these plants is beyond the scope of this work. Only glimpses of the *in vitro* propagation studies are provided.

1. *Abelmoschus esculentus* (L.) Monech, Malvaceae, lady's finger, okra.

   Abelmoschus esculentus is an important vegetable with anti-DM property. Micropropagation of *A. esculentus* (okra) for disease-free plantlets through meristem culture has been established (Anisuzzaman et al. 2010). In another study, an efficient transformation system for okra and generation of insect-resistant transgenic plants expressing the cry1Ac gene has been demonstrated. This study will accelerate the development of transgenic okra with novel agronomically useful traits (Narendran et al. 2013).

2. *Abroma augusta* L. Fabaceae, flame of the forest, Devil's cotton.

   Abroma augusta is a medicinal plant with a wide variety of reported uses including promising anti-DM activity. It is widely distributed in Asia. Callus cultures were established from shoot tip explants of diploid *A. augusta* on a modified basal MS medium supplemented with either 2 mg/L 2,4-D + 15% (v/v) coconut milk or 4 mg/L 2,4-D + 2 mg/L NAA + 2 mg/L kinetin +1 g/L yeast extract. This micropropagation protocol was characterized by a rapid proliferation of shoots and easy rooting of the microshoots; the plantlets were easily acclimatized to the external environment and normal physiological development (Sarkar et al. 2015).

3. *Acacia catechu* Wild. Fabaceae, Cutch tree or black catechu.

   Acacia catechu tree is widely distributed throughout Central Asia. Indiscriminate felling of *A. catechu* in forests poses a threat to its regeneration and survival. However, micropropagation protocols have been developed for this plant. Shoot apex explants of *A. catechu* were excised from 15-day-old *in vitro* grown seedlings raised from superior seed stocks. Shoot bud induction from explants was observed on MS medium containing various growth regulators. A maximum of 12 shoots was obtained on MS medium supplemented with 1.5 mg/L BAP and 1.5 mg/L kinetin. Well-developed shoots were rooted on low strength MS medium with 3.0 mg/L IAA and sucrose (1.5%). *In vitro* regenerated plantlets of *A. catechu* were transferred to field conditions (Kaur and Kaunt 2000). In another study, multiple shoots were initiated in stem nodes excised from *in vitro* grown seedlings on MS medium supplemented with BA. When shoots were individually subcultured on half-strength MS medium with 14.7 μM IBA, roots developed. Glutamic acid (40 mg/L) could prevent senescence of leaves. These plantlets thrived well in garden soil (Sahni and Gupta 2002). Another study reported *in vitro* regeneration of this plant from callus and mature nodal explants with some modifications in the method. Addition of adenine sulfate, ascorbic acid, and glutamine in the medium resulted in enhanced axillary branching. For rooting of microshoots, the shoots were dipped in IAA solution for 24 h followed by transfer to half-strength MS medium containing activated charcoal. The rooted plants were transferred to soil; 71% survival rate was recorded (Thakur et al. 2002).

4. *Aegle marmelos* (L.) Correa, Rutaceae

   (see Section 6.5.1).

5. *Allium cepa* L. Lilliaceae, onion.

   Allium cepa is an edible bulbous biennial herb cultivated worldwide. Long-term multiplication of *A. cepa* by cyclic shoot regeneration *in vitro* was reported. The apex must be destroyed or injured to obtain axillary buds. This capacity was restricted to the abaxial base of the youngest sheaths. It was deemed necessary to restore plant individuality before further proliferation; this process constituted one cycle. For successive regeneration, each cycle was composed of three steps: shoot proliferation in the presence of a cytokinin, shoot individualization, and plant development in the absence of growth regulators (Kahane et al. 1992). In another study, highest numbers of microshoots were formed by explants containing stem dome plus basal plate on MS medium supplemented with NAA, BAP, kinetin, and sucrose (Kamstaityte and Stanys 2004).

   In vitro plant production by direct organogenesis from immature flower heads is an ideal approach for clonal propagation of *A. cepa*. As per this method, mature onion bulbs are induced to reproductive phase by vernalization and forced to inflorescence initiation. Immature umbels are dissected from bulbs or cut directly when these appear from the pseudostem among the leaves. Disinfected inflorescences are cultivated in B5 medium modified by Dunstan and short (BDS) BM supplemented with 30 g/L sucrose, 0.1 mg/L NAA, 1 mg/L BA, and 8 g/L agar, pH 5.5, under 16 h photoperiod for 35 days. The regenerated shoot clumps are divided and subcultured under the same conditions. For bulbification phase, the individual shoots are cultured in BDS BM containing 90 g/L sucrose, without PGRs, under 16 h photoperiod. Microbulbs can be directly cultivated *ex vitro* without acclimation (Marinangeli 2013). In another study, *in vitro* plantlet regeneration from the basal disc explants of *A. cepa* was demonstrated. For callus induction and regeneration of plantlets, MS medium supplemented with different concentrations and combinations of growth regulators was used. Maximum callus induction was observed in genotype HUruta in medium supplemented with 1 mg/L 2,4-D. Regenerated plants were obtained via somatic embryogenesis and organogenesis. The survival rate of transferred regenerated plantlets was more than 60% (Hailekidan et al. 2013).

6. *Allium sativum* L. Lilliaceae, garlic.

   Allium sativum is a perennial herb with short bulbs; it is a spice cultivated in India and many other countries. *In vitro* cultivation of two garlic cultivars was reported. MS media supplemented with 8% sucrose gave higher values in most of the studied characters than the B5

medium. Regarding growth regulators, IBA was found to be better than BA and gibberellic acid in root formation, while gibberellic acid was better than BA and IBA in leaf formation. The garlic plantlets were successfully acclimatized and the survival rate of these plantlets was above 70% on transfer to the open field (El-Badry et al. 1998).

In another study, meristems isolated from shoot tips of field-grown mature garlic bulbs of five cultivars were cultured in liquid MS medium with 2-ip and NAA for shoot proliferation. *In vitro* bulblets were produced from meristem-derived shoot clumps in MS with high levels of sucrose. Rooted plantlets with bulblets were gradually acclimatized and successfully established in the field. All plants were normal and free from diseases. Substantial yield increase was observed from meristem-derived plants over their source plants. Shoot tip, leaf base, leaf primordia, and bulbil from field-grown mature garlic bulbs of five cultivars were cultured in MS medium with 2,4-D for callus induction. The calli were transferred to MS medium without any growth regulators for somatic embryogenesis. Plantlet regeneration from somatic embryos was obtained in kinetin-supplemented MS media. After proper acclimatization, rooted callus derived plantlets with bulblets were transplanted in the field, and somaclonal variation were found in plant height, number of leaves/plant, bulb diameter/plant, and bulb weight/plant (Roksana et al. 2013).

7. *Aloe vera* (L.) Burm. f., Synonym: *Aloe barbadensis* Miller, Aloaceae, aloe.

   Aloe vera is a dwarf and perennial herb with fleshy leaves; this plant is a native of Africa and is commercially cultivated in many countries. Natural propagation of *A. vera* is primarily by means of axillary shoots and it is rather a slow way of multiplication to meet the growing demand. In terms of barbaloin content, *A. vera* has many cultivars. A successful micropropagation protocol has been developed using shoot apical meristem as explants in a high barbaloin content cultivar of *A. vera*. The protocol involved induction, multiplication, and *in vitro* rooting of the regenerated shoots and their acclimation under *ex vitro* conditions. All the plantlets survived in the field conditions (Das et al. 2010).

   A method for mass propagation of *A. vera* using different explants and different media containing different PGRs has been reported. Two types of explants (with and without sheath Type A and B, respectively) were cultured on MS, B5, and Schenk and Hildebrandt (SH) media supplemented with different combination of NAA with BA and kinetin for shoot induction. The highest rate of shoot induction was observed in MS medium supplemented with 0.2 mg/L NAA and 4 mg/L BA in type A explants. Also, the highest shoot proliferation response was obtained successfully using MS medium containing 4 mg/L BA. The optimal rooting response was observed on B5 medium supplemented with 2 mg/L NAA, on which 100% of the regenerated shoots developed roots with an average of 7.8 roots per shoot within 3 weeks. The plantlets were acclimatized and transferred to greenhouse with 95% success. This *in vitro* propagation protocol should be useful for conservation as well as mass propagation of this medicinal plant (Abdi et al. 2013). In another study, high-frequency microcloning of *A. vera* and their true-to-type conformity by molecular cytogenetic assessments of 2-year-old field growing regenerated plants was shown (Haque and Shosh 2013). A recent study reported *in vitro* propagation of *A. vera* for commercial production using different concentrations and combination of PGRs. Regenerated plants showed 85% survival rate in the field. In this study, NAA was found to be the best auxin for root induction (Gupta et al. 2014).

8. *Alstonia scholaris* L., Apcynaceae, devil tree.

   Alstonia scholaris is an important anti-DM and anticancer tree. Bulk collection of this plant parts from nature is not recommended in view of sustainable utilization. The induction and proliferation of callus from leaf explants of *A. scholaris* was standardized along with *in vitro* biosynthesis of echitamine, an indole alkaloid. MS medium was optimized with various combinations and concentrations of different auxins and cytokinins for callus induction and proliferation. Best induction and proliferation of callus was noted in 2,4-D and 6-furfurylaminopurine (FAP) combination with their specific concentration at 0.5:0.5 mg/L. Furthermore, the data indicated that both auxin/cytokinin ratio as well as their independent concentration was important for the same. Echitamine biosynthesis was observed in 0.5:0.5 and 0.5:0.3 mg/L of 2,4-D

and FAP under 16:8 h light–dark cycle. However, production of echitamine was increased more than twofold in 0.5:0.3 mg/L of 2,4-D and FAP containing medium upon application of yeast extract at 150 mg/L with 5 days of incubation period. Thus, *in vitro* biosynthesis may offer an alternative source of echitamine without harming the natural plant population (Singh et al. 2015). In this important anti-DM plant, the anti-DM compounds remain to be identified.

9. *Anacardium occidentale* L.

   Anacardium occidentale is an erect spreading tree cultivated for its commercially valuable edible nuts. Regeneration of cashew through embryogenesis from cotyledon, immature embryos, and nucleus has been reported (Sadhana and Shirly 2002). Multiple buds have been induced from cotyledonary nodes of *A. occidentale* on MS medium supplemented with 117 mM sucrose, 14.6 mM maltose, and 22.2 μM BA. The buds were harvested at each subculture after elongation on MS medium supplemented with 100 mL/L coconut water, 14.6 mM maltose, 146 mM sucrose, and 4.4 μM BA. Excised microshoots were rooted *in vitro* on MS medium in the presence of 117 mM sucrose, 2.9 μM IAA, and 4.9 μM IBA. Plantlets have been successfully transferred to soil and have been established in the field (D'Silva and D'Souza 1992). Shoot tips excised from glasshouse-raised seedlings and field-grown plants of cashew were micrografted by a modified side-grafting procedure using *in vitro* raised seedling rootstocks (Mneney and Mantell 2001). Micrografting as a technique to rejuvenate cashew and overcome rooting has also been described (Thimmappaiah et al. 2002).

10. *Anemarrhena asphodeloides* Bunge, Lilliaceae, Zhi Mu (Chinese common name).

    Anemarrhena asphodeloides is a glabrous perennial herb distributed from Mongolia to Korea. An *in vitro* regeneration system of *A. asphodeloides* was established from tiller bud, which provides a technological basis for large-scale production of *A. asphodeloides* plantlets. The tissue culture conditions are as follows: disinfection with 75% ethanol for 30 s and then with 0.1% $HgCl_2$ for 15 min; best medium for bud proliferation was MS + kinetin 1 mg/L + NAA 0.5 mg/L; the best medium for callus induction was MS + kinetin 2 mg/L + NAA 0.5 mg/L; the best callus redifferentiation medium was MS + kinetin 2 mg/L + NAA 0.1 mg/L; the best rooting medium for buds regenerated from callus was 1/2 MS + NAA 0.5 mg/L; the best transplanting substrate of *A. asphodeloides* plantlets was humus soil (Hong et al. 2010). In another study, asexual micropropagation system of *A. asphodeloides* was successfully established. The transplanted tube seedlings had good growth vigor and were in the same growth speed (Ting et al. 2012). A method for high-efficiency encapsulation-vitrification protocols for cryopreservation of embryogenic calli of *A. asphodeloides* has been reported. This encapsulation-vitrification method appears promising for the cryopreservation of *A. asphodeloides* germplasm (Hong and Yin 2012).

11. *Annona muricata* L. Annonaceae, Synonym: *Annona muricata* Vell., Common names: Soursop, Paw-Paw.

    Annona muricata is a small tree and is cultivated in tropical areas of the world for its edible fruit. The explant types on callus and shoot of *A. muricata* in various culture media and growth hormones for increasing the secondary metabolite productions were studied. Shoot regeneration was showed at 60% in the formula including MS medium + 0.5 mg/L BAP + 0.05 mg/L NAA + 0.8% agar + 2% sucrose. The most formation of compact callus (light green color) was showed at 86% in the medium of MS + 0.2 mg/L BAP + 0.2 mg/L NAA + 0.8% agar + 2% sucrose (Inwanna et al. 2014). Biotechnological intervention in *Annona* spp. has been reviewed recently (Encina et al. 2014). To obtain homogeneous and productive orchards, it is necessary to avoid the propagation by seeds of this species. Additionally, the traditional methods of vegetative propagation were inefficient and inadequate, due to the low morphogenetic potential of this species, and the low rooting rate. The *in vitro* tissue culture methods of micropropagation can be applied successfully to *Annona* spp. to overcome these problems (Encina et al. 2014).

12. *Areca catechu* L. Arecaceae, betel nut palm, areca nut.

    Betel nut palm is an important multipurpose single-trunked monocious palm tree. Although it is cultivated, the seeds of this plant are short-lived and the progeny from seeds are not uniform. There is a need to develop efficient propagation methods.

Plantlet formation through shoot formation from callus of *A. catechu* was described. Greenish soft callus was formed from shoot tip explants within 4 weeks, when cultured on Gelrite-gelled MS BM supplemented with BA (0.2 mg /L) plus thidiazuron (0, 0.02 and 0.2 mg/L). The highest percentage of callus formation (100%) was found on the medium supplemented with 0.2 mg/L BA and 0.2 mg/L thidiazuron. During subculture on the same medium for callus induction, most of calluses proliferated and 50–60% formed shoots. About 90% of shoots formed roots on the BM containing 0.1 mg/L NAA after 4 weeks in culture. Regeneration of plantlets from shoot tips via primary callus production and a two-step process of organogenesis, required about 20 weeks (Wang et al. 2003). In another study, a protocol for areca nut tissue culture was standardized with leaf explants excised from 1-year-old seedlings and later modified for immature inflorescence sampled from adult palms. The BM used was MS. Picloram was found to be the most suitable callogenic agent for both types of explants as well as for the varieties tried. Serial transfer of explants from high-to-low auxin concentration was essential for sustained growth of callus and somatic embryo induction. Somatic embryogenesis was achieved in hormone-free MS medium. Somatic embryos were germinated in MS medium supplemented with cytokinin; 20 mM BA was found to be the best. Plantlets with 2–4 leaves and good root system were transferred to sand:soil (5:1) potting mixture (Karan et al. 2004).

13. *Artemisia dracunculus* L. Asteraceae /Compositae, tarragon or dragon herb.

    Artemisia dracunculus is a perennial herb used in culinary traditions and in traditional medicine. Traditional propagation with cuttings has a high percentage of loss and there is incidence of Colombian tarragon crop rust. Micropropagation could be used to induce juvenile characteristics and to increase percentages of rooting and clean plant propagation materials. For establishment of an efficient micropropagation protocol, the effect of both type and concentration of gelling agents and liquid mediums was assessed. For multiplication and rooting, the effect of indole acetic acid (IAA), N-6-furfuril amine purine, planting orientation, and pinching were assessed. Although French tarragon showed susceptibility to hyperhydricity, it was possible to determine protocols from 1 mm meristematic tips established in the liquid MS medium with *in vitro* multiplication/rooted in a solid MS medium supplemented with IAA 0.1 mg/L. Additionally, an alternative multiplication protocol was assessed from propagules horizontally sown in a solid medium (MS) supplemented with kinetin (0.5 mg/L) and IAA (5 mg/L) (Fernandez-Lizarazo and Mosquera-Vasquez 2012).

14. *Artemisia herba-alba* Asso, synonym: *Artemesia sieberi* Bess., Asteraceae.

    Artemisia herba-alba is a perennial anti-DM herbal plant found in the wilds in arid areas of the world including the Mediterranean basin, the Iberian Peninsula, and Spain. The biodiversity of this plant is heavily subjected to loss because of heavy grazing, land cultivation, and collection by people for using it in folk medicine. In a study, two cryopreservation-dependent techniques to conserve the shoot tips of *in vitro* grown plant were evaluated: encapsulation-dehydration and encapsulation-vitrification. The shoot tips were encapsulated into sodium alginate beads. In encapsulation-dehydration, the effect of sucrose concentration (0.5, 0.75 or 1.0 M) and dehydration period (0, 2, 4 or 6 h) under sterile airflow on survival and regrowth of encapsulated shoot tips were studied. Maximum survival (100%) and regrowth (27%) rates were obtained when encapsulated unfrozen *A. herba-alba* shoot tips were pretreated with 0.5 M sucrose for 3 days without further air dehydration. After cryopreservation, the highest survival (40%) and regrowth (6%) rates were achieved when the shoot tips were pretreated with 1.0 M sucrose for 3 days without further air dehydration. Viability of the shoot tips decreased with increased dehydration period. In encapsulation-vitrification, the effect of dehydration of encapsulated shoot tips with 100% PVS2 for various dehydration durations prior to freezing was studied. After cryopreservation, the dehydration of encapsulated and vitrified shoot tips with 100% PVS2 for 30 min resulted in 68% survival and 12% regrowth rates. Further conservation techniques must be evaluated to increase both survival and regrowth percentages (Sharaf et al. 2012).

15. *Asparagus racemosus* Willd., Liliaceae.

    Asparaguous racemosus is a woody climbing medicinal herb found in tropical and subtropical forests of India and elsewhere. *In vitro* shoot proliferation was obtained by culturing single-node segments in MS medium supplemented with 3.69 μM 2-isopentyladenine (2-iP) and 3% sucrose with a multiplication rate of 3.5. For proper root formation, the *in vitro* formed shoot clusters were cultured on half-strength (major salts reduced to half) MS medium with 1.61 μM α-naphthalene acetic acid, 0.46 μM kinetin, 98.91 μM adenine sulfate, 500 mg/L malt extract, 198.25 μM phloroglucinol, and 3% sucrose. On this medium, 85% rooting was observed within 20 days. Following a simple hardening procedure involving sequential transfer of plants to a greenhouse, polyhouse, and shade net, the tissue-cultured plants were transferred to the field, where the survival rate was 100% (Bopana and Saxena 2008).

    Standardization of protocol for induction of callus and regeneration of plantlets was established through *in vitro* culture using nodal explants of *A. racemosus*. The callus induction, multiple shoot regeneration, and root induction was observed using different concentration and combination of growth regulators. The highest percentage of callus induction was observed in MS medium supplemented with 0.1 mg/L NAA. The best response in terms of multiple shoot induction was observed on MS medium with IBA 1.0 mg/L + BAP 1.0 mg/L. When *in vitro* shootlets were inoculated to the half-strength MS basal media, rooting was observed with IBA 1.5 mg/L in nodal explants. Rooted shoots were transplanted in the greenhouse for hardening and their survival rate was 75% in the field condition (Patel and Patel 2015).

16. *Azadirachta indica* A. Juss., Meliaceae, synonym: *Melia azadirachta* L., neem tree.

    Azadirachta indica is an evergreen tree found in most of the tropical and subtropical countries. Plant regeneration via somatic embryogenesis was achieved in embryogenic callus cultures derived from immature zygotic embryos of *A. indica* on semisolid basal MS salts and vitamins supplemented with 1.11 μM 6-benzylaminopurine (BA) and 4.52–6.78 μM 2,4-D. The globular-stage embryos were induced when the callus was transferred to medium with 1.11 μM BA and 0.45 μM 2,4-D. The highest average number of somatic embryos per 200 mg of callus was 153 after 8 weeks of culture on the medium. Maturation and germination of the somatic embryos were achieved on half-strength MS salts and vitamins were supplemented with 0.38–0.94 μM abscisic acid and 2% (w/v) sucrose. The maximum percentage (64%) of germination was obtained with 0.94 μM abscisic acid within 2 weeks of culture. Somatic embryo derived plantlets were acclimatized in a greenhouse and subsequently showed a normal growth (Rout 2005).

    An efficient protocol for micropropagation of *A. indica* has been standardized in another study. Cotyledonary nodes excised from 15- to 20-day-old *in vitro* germinated seedlings were used as explants. The seeds were germinated on half-strength MS medium without phytohormones. Cotyledonary nodes were cultured on MS medium supplemented with different concentrations of cytokinins and auxins. Maximum shoot proliferation from single explant was obtained on MS medium incorporated with thidiazuron (1.5 μM), 2,4-D (0.5 μM), adenine sulfate (40 mg/L), glutamine (100 mg/L), and thiamine (10 mg/L). *In vitro* produced shoots were induced root on half-strength MS medium supplemented with a range of IBA concentrations (0.5–5 μM). The highest frequency of root proliferation was observed on half-strength MS medium supplemented with 2.0 μM IBA. The regenerants were transferred to field conditions after acclimatization with a success rate of 80% (Reddy et al. 2006).

17. *Bauhinia forficata* Link, Fabaceae, Pata de vaca, casco de vaca.

    Bauhinia forficata is a perennial shrub that can be propagated through the conventional sexual and vegetative means. However, the process is time consuming and has limitations including a long time gap between pod formation and maturation and inhibition of germination imposed by the testa. *In vitro* propagation of *B. forficata* has been reviewed (Teixeira da Silva 2013). In *B. forficata*, shoots have been shown to originate from cotyledonary node epidermal and

subepidermal tissue through a process of indirect organogenesis and amitosis (nuclear fragmentation). In another study, adventitious buds of *B. forficata* were obtained from callus grown on hypocotyl segments. Cell suspension cultures could be induced from 5 g of callus placed in 100 mL of liquid callus-inducing medium at 60 rpm in 250 cm^3 Erlenmeyer flasks, when subcultured every 3 weeks. Galactose, sorbitol, and glycerol could not support cell suspension cultures; only sucrose supported the culture (Teixeira da Silva 2013).

18. *Bauhinia variegata* L. Leguminosae, Synonym: *Bauhinia alba* Wall., mountain ebony.

    Bauhinia variegata is a deciduous moderate-sized tree found in India, Burma, Sri Lanka, and so on. Several studies have reported *in vitro* propagation of *B. variegata* and these reports have been reviewed (Teixeira da Silva 2013). Different explants such as nodal explants of mature trees, auxiliary meristems, and *ex vitro* derived shoot tips from young plants were successfully used for *in vitro* propagation of *B. variegata*. In this plant, both picloram and 2,4-D successfully induced somatic embryos either through a direct route or via callus from the subepidermis of cotyledons or hypocotyls (Banerjee et al. 2012). Shoots that formed *in vitro* and that have rooted well could be planted in a mixture of 1:1 sand and soil with fungicides added. For rooting, the plantlets were kept at high humidity for 2 weeks. Watering with 1/10-strength MS medium was sufficient for the survival of *B. variegata* plantlets in soil (Singh et al. 2012; Teixeira da Silva 2013).

19. *Berberis aristata* DC., Berberidaceae (see Section 6.5.1).

20. *Bidens pilosa* L. Syn: *Bidens leucantha* (L.) Willd., Asteraceae.

    Bidens pilosa is a tropical erect perennial medicinal herb; it is an easy-to-grow plant distributed all over the world. Axillary buds developed on shoot tips and single node cuttings after 10 days of culture. Their number increased with the concentration of BP in the medium. Calli were obtained by adding kinetin and 2,4-D. Addition of NAA allowed the development of 10 buds per callus originating from leaves and over 100 buds per stem-derived callus. Plantlets achieved their growth in the basic medium supplemented with 1 mg/L IAA. Hardening of *in vitro* raised plantlets was done on earth/vermiculite substrate (Fotso et al. 2002).

21. *Bixa orellana* L. , Bixaceae, annatto.

    Bixa orellana is a shrub or a small tree growing in the tropics of North and South America. Several studies have been carried out on the *in vitro* regeneration of this plant. Roots of *B. orellana* showed differential response to different PGRs and basal (MS and B5) medium. B5 medium supplemented with 4.9 μM 2-iso pentenyl adenine (2-iP) induced direct somatic embryogenesis in root segments. Though these embryos proliferated and germinated on the same medium, healthy growth of roots occurred when 0.57 μM IAA was added to the B5 medium. There was 80% survival rate of regenerated plants during acclimatization. When MS medium was supplemented with 2-iP, all the three tested concentrations (4.9, 9.8, and 14.7 μM) caused callusing in root explants. Augmentation of MS medium with 2, 4-D resulted in indirect somatic embryogenesis. Plants regenerated via both direct and indirect somatic embryos showed 80% survival rate on cocopeat during hardening. Complete survival of hardened plants in field was observed when these were transplanted during monsoon (Sharan et al. 2012). The organogenic potential of root explants derived from cultured seedlings of *B. orellana* was investigated in response to different incubation conditions and either 4.44 μM 6-benzyladenine (BA), 4.54 μM thidiazuron, or 4.56 μM zeatin. Explants cultured in liquid media with agitation generally showed better development of adventitious buds versus explants cultured on semisolid media. The most adventitious buds developed from explants cultured in liquid media under a 16-h photoperiod. Use of zeatin and thidiazuron promoted the development of more adventitious buds than BA, but morphological abnormalities among regenerating shoots and plants were observed. Fewer adventitious buds developed from explants cultured in liquid media supplemented with BA, but the buds gave rise to the highest percentage of morphologically normal regenerated plants. Seedling root tissue is useful for *in vitro* propagation of *B. orellana* (Ferreira da Cruz et al. 2014).

Efficient methods were developed for both *in vitro* seed germination and micropropagation of *B. orellana*. Mature seeds were inoculated onto MS medium supplemented with different concentrations of gibberellic acid. The highest frequency of germination (93%) was recorded on medium supplemented with 3 μM gibberellic acid against 13% in control. Nodal explants cultured on MS medium fortified with 5 μM 2-iP produced maximum explants response (93%) and highest number of shoots (35.71). Addition of relatively higher concentration (15 μM) of BA resulted in the production of significantly reduced number of shoots. Sucrose at 87.6 mM was found to be the best carbohydrate source for multiple shoot induction compared to glucose and fructose. Regenerated shoots were rooted (96%) on agar-gelled MS medium supplemented with 10 μM IBA. *In vitro* developed plantlets with well-developed roots were potted and acclimatized initially in the growth chamber and then moved to a greenhouse with 83% survival rate. This protocol avoids the use of auxins in shoot multiplication medium, which will lower the cost, avoid callus formation, and thus reduce the possibility of somaclonal variation in the regenerated plants (Joseph et al. 2011). In another study, an *in vitro* propagation technique based on axillary bud proliferation was developed. Nodal segments cultured on MS medium supplemented with 1.0 μM BA and tender coconut water (10%) showed significantly high explant response (67.0%), development of elongated shoots (3.36), shoot buds (8.9), and shoot elongation (3.53 cm). Cytokinins such as zeatin, 2-iP, kinetin, or thidiazuron were inferior to BA to induce multiple shoots. Seasonal variations significantly affected the *in vitro* response of nodal explants. *In vitro* rooting experiments have showed 56% rooting on MS medium containing 15 μM IBA. Alternatively, *in vitro* raised shoots were rooted (61%) *ex vitro*, by 10 mM IBA for 30 s. The results of the RAPD marker system revealed the genetic stability among the micropropagated plants. This protocol can be used for the clonal propagation of the superior genotype and preservation of germplasm (Siril and Joseph 2013).

22. *Boerhaavia diffusa* L., Nyctaginaceae.

    Boerhaavia diffusa is a medicinal herb distributed throughout the world as a weed. A rapid and efficient protocol for the large-scale propagation of the potential medicinal plant *B. diffusa* through *in vitro* culture of nodal segment explants obtained from aseptic seedlings was developed. *In vitro* multiple shoot induction was observed from axillary bud explants cultured on MS medium fortified with BAP (2.0 mg/L) and kinetin (3.5 mg/L). The multiple shoots were separated and subcultured for their elongation on the same medium supplemented with gibberelic acid (0.5 mg/L). Rooting on *in vitro* produced elongated shoots was achieved on half-strength MS medium having IBA (0.5 mg/L). Rooted plantlets were hardened in plastic pots containing sterilized soil and vermiculite (3:1). Well-established plantlets were acclimatized to the field with 70% survival rate (Saini et al. 2010). In another study, protocol for *in vitro* callus induction and regeneration in *B. diffusa* has been developed. Young apical leaves, nodal region, and roots were used as explants for callus induction on MS medium containing 2, 4-D and kinetin. Callus initiation was first recorded in the lamina of leaf and nodal region. After callosogenesis, the regeneration of shoot took place (Kanfade et al. 2011).

    Recently, an efficient protocol for *in vitro* propagation of *B. diffusa* has been standardized using nodal and leaf explants. The complete success in callus induction with an average of 3 shoots was observed on MS BM supplemented with 2,4-D (9.03 μM). Multiple shoot proliferation was achieved on MS BM supplemented with kinetin (4.64 μM). Well-rooted plantlets were hardened and acclimatized in the field and achieved a 65% survival rate (Ragi and Sahaya Shibu 2014). In a study, hairy root cultures of *B. diffusa* were induced and established using *A. rhizogenes* (Khatodia and Biswas 2014).

23. *Bougainvillea spectabilis* Willd., Nyctaginaceae, bougainvillea. Bouganvila.

    Bougainvillea spectabilis is a woody, evergreen, ornamental vine and is commonly propagated by cuttings but this method is tedious and time-consuming with very little success. In certain climatic conditions, it does not produce seeds while success percentage from cuttings is very low.

Shoot development was observed from shoot apices of *B. spectabilis* cultured on MS modified medium containing BAP 0.25 + NAA 0.25 mg/L. Medium containing BAP 0.20 + NAA 0.1 + glutamine 250 mg/L induced maximum number of multiple shoots with 70% of rooting where IBA 5.0 + NAA 5.0 mg/L was added to the medium (Javed et al. 1996). A simple and efficient *in vitro* regeneration protocol for *B. spectabilis* was developed from shoot tips of 5-year-old plants. Shoot tips were cultured on MS medium supplemented with different concentrations of BAP (0.25–2.0 mg/L) or kinetin (0.25–2.0 mg/L) and NAA (0.1–0.5 mg/L) in combination with BAP (0.25–5.0 mg/L). It was observed that BAP (0.25 mg/L) combined with 0.1 mg/L NAA gave the best results, where 90% shoots were developed into plantlets. The best multiple shoot formation was recorded on MS medium supplemented with 1.0 mg/L BAP and 250 mg/L glutamine. The regenerated shoots were successfully rooted on half-strength MS medium with different concentrations and combinations of auxin. It was observed that 2.5 mg/L NAA combined with 2.5 mg/L IBA gave 100% root induction. The plantlets after weaning and acclimatization were transferred to pots and then to soil for establishment (Shah et al. 2006).

A study was carried out to investigate optimum levels of BAP, glutamine, IAA, and IBA to be supplemented to MS medium for micropropagation of *B. spectabilis*. Shoot apices were excised, sterilized, and then cultured on MS medium supplemented with plant regulators for callus induction and plant regeneration. Maximum number of plantlets (81%) with conspicuous callus formation was observed with BAP 1.0 mg/L + glutamine 500 mg/L followed by BAP 1.0 mg/L+ 250 mg/L glutamine, where 65% plantlets have been developed. The minimum number of plantlets developed on control MS basic medium was 12.5%. Plantlets produced were then recultured in full- and half-strength MS medium supplemented with different concentrations and combinations of IAA and IBA. It was found that half-strength MS medium supplemented with IAA 0.5 mg/L and IBA 0.5 mg/L proved the best medium, where 79% of plantlet rooted. Higher average number of roots per plant (30.0) was obtained on IBA 5 mg/L. The lowest number of plantlets (25.0%) rooted when IAA 5.0 mg/L was only used. The lowest average number (2.7) of roots per plant was obtained on MS medium with IAA 2.5 mg/L. The maximum number of plantlets (58%) rooted when full-strength MS medium was supplemented with higher concentrations (5.0 mg/L) each of IAA and IBA. The maximum number of average roots per plant (15.4) was obtained when full-strength MS medium was supplemented with IAA 2.5 mg/L. Full-strength MS medium with IAA and IBA (5.0 mg/L each) proved best for root initiation (Ahmed et al. 2007).

24. *Brassica juncea* Czern. & Coss., Brassicaceae, Indian mustard.

    Brassica juncea is an economically important tall and erect annual herb. It is cultivated mainly for its edible oil in many Asian countries, Europe, and so on. An efficient protocol was developed to transfer snowdrop lectin gene to *B. juncea* through *Agrobacterium tumefaciens* mediated transformation. High-frequency regeneration of transformed plantlets has been achieved using stem segments as explants. Analysis of the putative transformants showed the successful integration of the transgene in the nuclear genome (Sharma et al. 2004). Regarding *in vitro* propagation, the effect of cytokinins on shoot regeneration from cotyledon and leaf segment of *B. juncea* was studied. In most cases, cotyledon gave higher regeneration frequency than leaf segment. Thidiazuron proved to be the best cytokinin to induce shoot from both cotyledon and leaf segments compared to BA, kinetin and N-(2-chloro-4-pyridyl)-n-phenylurea. The shoot regeneration was greatly increased when NAA was added together with cytokinins (Guo et al. 2005).

25. *Caesalpinia bonduc* (L.) Roxb., Synonym: *Caesalpinia bonducella* (L.) Flem., Caesalpiniaceae, Nata Karanja, a prickly shrub.

    Caesalpinia bonduc is a thorny evergreen vine-like shrub distributed all over the world; it is cultivated as an ornamental plant. But it is a threatened species in certain regions of the world; it is very sparsely distributed in the deciduous forests of the Western Ghats of India. It is reported to be critically endangered in Malaysia (Kumar et al. 2012). An efficient plant regeneration method was established for *C. bonduc* by culturing immature epicotyl explants.

Morphogenic calli were initiated from 96% of epicotyl explants on MS medium supplemented with BA 4.0 mg/L and NAA 1.0 mg/L. The calli formed were excised and subcultured on MS medium fortified with 1 mg/L 2,4-D for further proliferation. Maximum percent organogenesis (84%) and average shoots per culture (5.6) were observed on MS medium fortified with 3.0 mg/L BA and 1.0 mg/L IAA. Addition of IBA in half-strength MS medium favored rooting of recovered shoots. Of 30 rooted shoots transferred to soil, 27 survived after acclimatization (Cheruvathur et al. 2010).

An *in vitro* regeneration protocol has been standardized via direct and indirect methods from root explants of *C. bonduc*. MS medium supplemented with 17. 75 µmol/L BAP and 2. 46 µmol/L IBA induced a mean of 3.40 shoots directly from the surface of excised root explants. Subsequently, the shoots rooted readily on half-strength MS medium without growth regulators. In indirect organogenesis, callogenic frequency was optimized at the concentration of 9. 04 µmol/L 2.4-D and 0.88 µmol/L BAP. On average, 15.3 shoots were differentiated from the root callus at 17.57 µmol/L BAP and 2.85 µmol/L IAA. Shoots generated through callus were rooted well on half-strength MS medium with 2.95 µmol/L IBA. Rooted plantlets were transferred to the pots containing sterilized soil and were successfully hardened at greenhouse condition for 3 weeks. Survival rate was more (95%) in plantlets derived through direct organogenesis than (60%) the plantlets regenerated through root calli (Kumar et al. 2012c).

26. *Cannabis sativa* L. [Related species: *Cannabis indica* Lam.; *Cannabis ruderalis* Janisch], Cannabaceae, marijuana..

Cannabis sativa is an annual herb; it is a native to Central Asia and has a worldwide distribution. Its cultivation and use is banned due to the psychoactive effects of certain compounds present in the flowering tops of this plant. In spite of this ban, there are a few research reports about the tissue culture of *C. sativa*. Most of these studies were aimed at developing a cell culture system to obtain secondary metabolites, particularly the THC class of cannabinoids that are distinctive to the genus of *Cannabis*. A study describes the standardization of an efficient *in vitro* propagation and hardening procedure for obtaining plantlets from shoot tips of this plant. *Cannabis sativa* seedlings were germinated on half-strength MS medium supplemented with 10 g/L sucrose, 5.5 g/L agar at a pH of 6.8 under light for 16 h/day. MS medium containing 0.2 mg/L thidiazuron, 0.1 mg/L NAA supported the maximal auxiliary bud multiplication rate of 3.2 per shoot tip. The proliferated buds were successfully rooted on MS medium supplemented with 0.1 mg/L IBA and 0.05 mg/L NAA resulting in 85% of the plantlets rooting. The procedure requires a 54-day cycle for the *in vitro* clonal propagation (14 days for shoot multiplication and 40 days for root induction), which includes 35–42 days for acclimatized plantlet production (Wang et al. 2009b).

In another study, shoot cultures were proliferated *in vitro* using explants obtained from high tetrahydrocannabinal yielding variety of *C. sativa*. Explants of nodal segments containing single axillary bud were excised from *in vitro* proliferated shoot cultures and encapsulated in high-density sodium alginate hardened by 50 mM $CaCl_2$. The encapsulated nodal segments were stored at 5, 15, and 25°C for 8, 16, and 24 weeks on MS medium supplemented with thidiazuron. Encapsulated nodal segments could be stored at 15°C up to 24 weeks with maximum regrowth ability and survival frequency of 60%. Well-developed plantlets regenerated from encapsulated nodal segments were successfully acclimatized in the growing room with 90% survival frequency. Plants grown from encapsulated nodal segments showed cannabinoids content similar to the donor plant. Thus, the encapsulation techniques would allow the prolonged storage of high-yielding *C. sativa* germplasm (Lata et al. 2012).

27. *Cassia auriculata* L., Cesalpinaceae/Leguminaceae, tanner's cassia.

Cassia auriculata is a tall shrub with smooth bark and is found in Asian countries. Micropropagation and histological studies of *in vitro* developed organs were made in

C. auriculata. Explants containing cotyledonary node along with cotyledonary leaves and portion of hypocotyl were cultured on MS media supplemented with different growth regulators in varying concentrations. Maximum multiple shoots were observed in MS medium supplemented with BA (3.0 mg/L) along with IAA (1.0 mg/L). Rooting was seen from the cut end of the hypocotyls in MS medium supplemented with IBA (1.0 mg/L) or NAA (1.0 mg/L). Moderate green to brown, hard, and nodulated callus was observed originating from cotyledonary leaf margins in MS medium supplemented with BA (3.0 mg/L) + 2,4-D (1.0 mg/L). Histological studies showed that the initiation of shoot buds occurred from the peripheral cortical region of the cotyledonary node. The superficial cells in this region become organized into a tunica–corpus arrangement. Roots were seen originating endogenously from the cortical regions and showed only open type of organization similar to the mature primary roots germinated *in vivo* from the seeds. Transverse sections of the regenerated roots showed diarch and triarch conditions, which were significantly different from the tetrach condition observed in the primary roots of seed-grown plants (Negi et al. 2011).

28. *Cassia fistula* L., Cesalpinaceae.

    Cassia fistula is a deciduous tree cultivated as an ornamental tree in India and elsewhere. It is an important anti-DM plant. Indirect organogenesis was induced from embryo, petiole, and stem explants of *C. fistula* treated with B5 + BA (1 mg/L) + IAA (0.5 mg/L) (Parveen and Shahzad 2012).

29. *Cassia occidentalis* L. or *Senna occidentalis* (L.) Link., Leguminosae, coffee senna, fetid cassia.

    Cassia occidentalis is a common herbaceous weed that occurs in many parts of the world. An efficient and reproducible protocol for plant regeneration using nodal explants excised from a field-grown mature plant of *C. occidentalis* has been achieved. The highest shoot regeneration frequency after 8 weeks of culture was observed on MS medium amended with 5.0 μM BA, 100 μM citric acid, and 1.0 μM NAA. A half-strength MS medium supplemented with 1.5 μM IBA proved best for the induction of maximum roots. Plantlets with well-developed shoots and roots were successfully acclimatized in plastic pots containing sterile soilrite (Naz et al. 2015).

30. *Catharanthus roseus* (L.) G. Don f., synonym: *Vinca rosea*, Apocynaceae, Madagascar rosy periwinkle.

    Catharanthus roseus is an annual medicinal herb. It is an important anticancer and anti-DM medicinal plant occurring in many tropical and subtropical regions of the world. An efficient *in vitro* micropropagation protocol was standardized using axillary bud and shoot tip explants of this plant. The highest number of shoots was observed after 45 days of culture in MS medium supplemented with NAA (4 mg/L) and BA (4 mg/L). Shoots were proliferated and elongated in the same medium. High frequency of rooting was obtained in half-strength MS + IBA from axillary bud derived shoots. The rooted plantlets were established in soil (Bakkudeen et al. 2011).

    The effect of PGRs on callus induction using different explants to regenerate shoot/root from different explants as well as from calli in cultures of *C. roseus* was studied (Singh et al. 2011). Earliest and maximum (99%) callus induction response was observed on 10 day of inoculation from hypocotyl explants under dark conditions on MS medium supplemented with BAP (1.0 mg/L) + NAA (1.0 mg/L). For shoot proliferation, MS BM supplemented with BAP (1.5 mg/L) + NAA (1.0 mg /L) was the best, while half-strength MS medium supplemented with IBA (2.5 mg/L) + NAA (0.5 mg/L) gave the best rooting response. Besides maximum shoot regeneration, response was observed from hypocotyl calli both under light and dark conditions on media supplemented with BAP (1.5 mg/L) + NAA (1.0 mg/L).

    In another study where the different media were compared for *in vitro* shoot multiplication, MS medium supplemented with 1 mg/L of BA and 0.2 mg/L α-naphthaleneacetic acid showed better response in terms of the emergence of shoots from axillary buds as well as proliferation and multiplication of shoots. The shoots when placed on half-strength of MS medium with

1 mg/L IBA and 0.25% charcoal showed complete root induction. There were no somaclonal variations among these plants (Kumar et al. 2013).

31. *Cinnamomum cassia* Nees ex Blume, synonym: *Cinnamomum aromaticum* Nees, Lauraceae, Chinese cinnamon, Cassia cinnamon.

    Cinnamomum cassia is an evergreen tree originated in southern China. It is usually grown from seeds, but can be grown from cuttings also. *In vitro* propagation of *C. cassia* has also been reported (Inomoto and Kitani 1989). Callus and suspension cultures of *C. cassia* were found to produce a large amount of condensed tannin. (−)-epicatechin and procyanidins B2, B4, and C1 that are precursors of condensed tannin were isolated from callus cultures. Tannin production in callus cultures was stimulated by coconut milk or malt extract supplemented in the medium. In suspension cultures, cell growth in Linsmaier–Skoog's medium containing coconut milk was better than in the absence of coconut milk. The time course of cell growth and tannin content showed that the production of procyanidin dimer increased in the long lag phase of callus cultures (Yazaki and Okuda 1990). Epicatchin has anti-DM property (Chapter 2).

32. *Cinnamomum verum* J.S. Presl., synonym: *Cinnamomum zylanicum* Blume, Lauraceae, cylon cinnamom.

    Cinnamomum verum is a small evergreen tree indigenous to Sri Lanka and South India. The conventional vegetative propagation methods such as root cutting are not sufficient for the production of large-scale clonal progenies. Micropropagation of *C. verum* is needed for clonal multiplication of selected elite lines. Protocols were standardized for micropropagation of *C. verum* from mature explants and plant regeneration from immature explants and immature seeds by somatic embryogenesis. Multiple shoots were induced from the shoot tips and nodal segments of mature trees on WPM fortified with 3 mg/L BA and 1 mg/L kinetin. Rooting was achieved in WPM supplemented with activated charcoal 2 g/mL (alone or with 0.5 mg/L IBA and 0.5 mg/L NAA). Rooted plantlets were established in a mixture of garden soil, soilrite, and sand in equal proportion with 80% success after maintaining them in a humid chamber for 30–40 days (Mathai et al. 1997). In another study, shoot tip and leaf explants of *C. verum* obtained from field-grown trees were cultured on MS medium supplemented with various levels of BAP and thidiazuron. *Cinnamomum verum* explants reacted to the treatments by sprouting. All shoots (100%) produced roots 2 weeks after transfer on the basic MS medium and the plantlets were successfully transplanted to pots containing topsoil plus compost (2:1) after acclimatization (Soulange et al. 2007).

33. *Citrullus colocynthis* (L.) Schrad., Cucurbitaceae (see Section 6.5.1).

34. *Citrullus lanatus* (Thunb.) Matsumara & Makai, Synonym: *Citrullus vulgaris* Eckl., Cucurbitaceae, watermelon.

    Citrullus lanatus (watermelon) is a prostrate or climbing annual plant and is cultivated in many countries. Watermelon is one of the common summer fruit crops. The farmers generally produce seeds from the crops of previous years, which results in a decrease in size, weight, and food value of watermelon (Khatum et al. 2010). A standard protocol was established for rapid *in vitro* propagation of watermelon from nodal explants of field-grown plant. Multiple shoot proliferation was achieved from nodal explants on MS medium supplemented with 1.0 mg/L BAP + 0.2 mg/L NAA. The elongation of shoots was obtained on the same medium. Highest percentage of root induction was achieved on MS medium supplement with 1.0 mg/L IBA within 25 days of culture. Well-rooted plantlets were transferred to small pots and after acclimatization the plantlets were transplanted in the field condition, where 80% plantlets survived and grew successfully (Khatum et al. 2010). In another study on a subspecies of this plant [*C. lanatus* (Thunb.) Matsumara & Makai, ssp. *mucosospermus*], the medium containing 3/2 strength of MS minerals, 35 g/L sucrose, and 1 mg/L BAP solidified with 6 g/L agar allowed the production of numerous shoots without a callus phase from cotyledon proximal part explants. The induced shoots were directly rooted and the rooted plantlets were acclimatized and transferred to field, where these plants grow well (Gnamien et al. 2013).

35. *Coccinia indica* Wight & Arn., synonyms: *Coccinia cordifolia* (L.) Cogn.; *Cephalandro indica* Naud.; *Bryonia grandis* L. ; *Coccinia grandis* L. Voigt, Cucurbitaceae, Ivy guard, scarlet vine.

    Coccinia indica is a climbing branched perennial tropical vine with promising anti-DM property. It is native to East Africa and occurs in the wild; it is cultivated also and its fruits are used as a vegetable. There are a few reports on *in vitro* propagation of *C. indica*. These include direct shoot regeneration from hypocotyls explants, shoot tip and nodal segments, and direct and indirect regeneration from node and leaf explants. However, these studies reported low regeneration frequency. An efficient protocol for indirect shoot organogenesis and plantlets regeneration of *C. grandis* (*C. indica*) from nodal explants has been reported. The maximum frequency of organogenic callus induction was observed in MS medium supplemented with 0.1 mg/L NAA and 1.0 mg/L BA. Multiple shoot induction was achieved from the surface of callus on regeneration medium. The highest shoot multiplication (90%) with the increased numbers of shoots was achieved on MS medium with 0.1 mg/L NAA, 1.0 mg/L BA, and 0.5 mg/L kinetin. The regenerated shoots were rooted *in vitro* on MS medium containing 0.1 mg/L IBA. Plantlets were successfully acclimatized (83.5%) and exhibited normal morphology and growth characteristics (Thiripurasundari and Rao 2012).

36. *Coffea arabica* L., Syn: *Coffea vulgaris* Moench., *Coffea laurifolis* Salisb., *Coffea moka* Hort. ex Heynh., Rubiaceae, coffee, arbica coffee.

    Coffea arabica is one of the most economically important plants with anti-DM activity. Major milestones in coffee biotech research are successful *in vitro* manipulation and multiplication of coffee, development of gene transfer protocols, and generation of transgenic coffee plants with specific traits. The isolation of genes involved in caffeine biosynthetic pathway has opened up new avenues for generating caffeine-free transgenic coffee. With the initiation of international coffee genomics initiatives, the genomic research in coffee is expected to reach new dimensions (Kumar et al. 2006). Regarding *in vitro* propagation, apical and axillary buds and leaf explants were cultured in modified MS medium. The apical bud incubated in the medium supplemented with coconut water and L-cysteine HCl (10 mg/L) gave the best results. Coconut water promotes growth, while L-cysteine HCl inhibits oxidation of phenolic compounds (Ismail et al. 2003). In another study, seeds were inoculated, supplemented with different salt strengths, and germinated under dark. Proliferation of the coffee cultivars explants was achieved at 8.0 mg/L kinetin and 6 mg/L thidiazuron. Rooting was experienced on half-strength MS media supplemented with different levels of IBA, IAA, or NAA. Highest root number and length was achieved at 3.0 mg/L IAA or IBA. Rooted plantlets were transferred to 1 peat:1 perlite mixture and *ex vitro* acclimatization gave 100% survival rate (Ebrahim et al. 2007).

37. *Coriandrum sativum* L., Apiaceae, coriander.

    Coriandrum sativum is an annual herb with anti-DM property; it a valuable spice crop grown all over the world. Clones of *C. sativum* shoots were obtained from seedlings and micropropagated alternately on modified MS media containing kinetin only and kinetin + IAA. During the first 9 months of culture, the shoots possessed the juvenile phenotype after which a sharp transition to mature phenotype occurred. In 15–17 months, this was followed by shoot necrosis and a decrease in number of shoots in the clones, leading to death of the clones. Mature phase of the shoots was stable in that no reversion to the juvenile phase was observed. Partial rejuvenation of mature shoots took place owing to formation of adventitious shoots in the callus formed at the shoot base. Reduction of the morphogenic potential of the mature shoots after 15–17 months of subculturing, an increase in number of abnormal shoots and shoot necrosis indicated physiological ageing of the clones (Kataeva and Popowich 1993). Subsequently, a highly embryonic callus was obtained from hypocotyls segments of *C. sativum* when cultured in the medium consisting of MS + H vitamins. Induction of somatic embryos required 2,4-D or NAA. Germination of fully developed embryos was accomplished by subculture on half-strength medium containing BP (0.5 mg/L). Plantlets were successfully grown in the field (Stephan and Jayabalan 2001). In another study, seeds of *C. sativum* were germinated *in vitro* and shoots were excised from the seedlings and inoculated in a modified MS medium

containing IBA and BAP. After 6 months in culture, two stable clones differentiated by their pigmentation, clone A presenting a high purple coloration and clone B with the normal green coloration. Clone A plants revealed a higher growth rate despite the production of anthocyanins (Dias et al. 2011).

38. *Costus pictus* D. Don, (*Costus igneus* N. E. Br.), Zingiberaceae, cana agria or cana de jabali in Mexico.

    Costus pictus is a slow growing, perennial herb of tropical and subtropical regions. It is one of the medicinally important plants cultivated in garden as an ornamental plant. *In vitro* propagation studies were carried out on this plant species. The nature of the explant, medium type, PGRs, complex extracts (caseinhydrolysate, coconut milk, malt extract and yeast extract), and antioxidants (activated charcoal, ascorbic acid, citric acid and polyvinylpyrrolidone) markedly influenced *in vitro* propagation of *C. pictus*. A maximum number of shoots percentage (50.8) from rhizome explants and multiple shoots were observed from MS medium containing 6-benzyladenine (2.5 mg/L) and kinetin (1.0 mg/L). High frequency of rooting was obtained in rhizome explant derived shoots (50%) on half-strength MS medium supplemented with IAA (1.5 mg/L). *In vitro* propagated plantlets were successfully acclimatized in the greenhouse (Bakrudeen et al. 2009).

    In another study, the dormancy of axillary buds (the axillary buds are dormant) was broken when cultured in MS medium supplemented with specific concentrations of 6-benzylaminopurine (BAP or BA) in combination with NAA. The sprouted axillary buds were transferred onto medium supplemented with NAA and BAP for shoot multiplication. The shoots were successfully rooted when transferred onto media supplemented with NAA or IAA and BAP. Rhizomes were induced when 4-month-old plantlets were cultured on half-strength MS medium supplemented with NAA, BAP, and 5–13% sucrose (Punyarani and Sharma 2012). In another study, protocol for callus culture was standardized using various concentrations of hormones (2, 4-D, kinetin, IAA, BAP), MS medium (full-strength, half-strength, one-fourth strength), pH (4.5–7), and carbon sources (sucrose, fructose, glucose, galactose, sorbitol, mannitol at 3% and 6% concentration). The highest callus growth was observed on half-strength MS medium supplemented with 2,4-D/ kinetin (1/0.5 mg/L) and IAA/BAP (1 mg/L) with glucose (3% and 6%) and at pH 5.5 (Wani et al. 2014). Recently, a micropropagation study in *C. pictus* has been carried out using various growth regulators (BAP, kinetin, and IAA) and various explants (shoot tip, leaf, nodal segment, and eye of rhizome). Nodal part of stem was proven suitable for micropropagation, and rate of micropropagation was higher with 3.0 mg/L BAP and 0.5 mg/L IAA (Jadhav and Waghmare 2015).

39. *Costus speciosus* (Koenig) Sm., synonym: *Cheilocostus speciosus* (J. Koenig) C. Specht, Zingiberaceae/ Costaceae, spiral flag.

    Costus speciosus is an ornamental rhizomatous perennial herb with anti-DM properties. It is found along roadsides, streams, and wastelands in India. A protocol has been reported for micropropagation of *C. speciosus* using segments of pseudostem as explants. The highest shoot proliferation was obtained on MS medium supplemented with 0.05 mg/L BA. Shoot length gradually decreased by addition of increasing concentrations of BA. Maximum number of roots was obtained in MS medium supplemented with 0.1 mg/L IBA. High survival percentage, over 75%, was obtained when the plantlets were transferred to greenhouse conditions (Robinson et al. 2009).

    In another report, nodal segments of *C. speciosus* containing single axillary buds were cultured on MS medium supplemented with PGRs for inducing plantlets. For breaking of axillary bud dormancy, nodal segments were cultured on 40–70 g/L sucrose or 1–13 μM adenine sulfate supplemented MS BM containing 5 μM BAP and 1 μM NAA. The nodal segments cultured on 1–13 μM adenine sulfate, 5 μM BAP, 1 μM NAA, and 50 g/L sucrose showed simultaneous production of shoots and roots, whereas those cultured on 5 μM BAP, 1 μM NAA, and 40–70 g/L sucrose produced shoots only. The best response for shoot multiplication was on 10 μM adenine sulfate, 7 μM BAP, 1 μM NAA, and 50 g/L sucrose. The well-rooted shoots were

hardened and transferred to the soil, where they showed 95% survival rate (Punyarani and Sharma 2010).

40. *Cucumis sativus* L., Cucurbitaceae, cucumber.

    Cucumis sativus is an annual hairy prostrate or climber. It is cultivated for its fruit (vegetable) in tropical and subtropical regions of the world. An efficient protocol for the *in vitro* multiplication of *C. sativus* was developed from nodal explants. Addition of casein hydrolysate to the shoot induction medium (MS + BA) significantly enhanced the number of shoots and growth of the regenerants. Optimum shoot regeneration was observed on MS medium containing 1 μM BA and 200 mg/L casein hydrolysate. Rooting of the microshoots was achieved with 1 μM NAA in half-strength MS medium. The plantlets thus obtained were successfully established in greenhouse (Ahmad and Anis 2005). In another study, a short-term protocol for plantlet proliferation using nodal segments was developed for *C. sativus* as a tolerant cultivar to the root-knot nematode. Nodal explants were cultured on MS medium containing various concentrations of kinetin in combination with IBA. The best response for proliferation rate, mean number of nodes per plantlet, and percentage of rooted *in vitro* propagated shoots was observed on medium supplemented with kinetin (1.5 mg/L) after about 3–4 weeks (Mahmoud and Arash 2014).

41. *Cuminum cyminum* L., Apiaceae, Cuminum, cumin.

    Cuminum cyminum is a small slender annual herb. It is an important seed spice and is cultivated in many countries; it is grown from the seeds. *In vitro* embryogenesis of cumin hypocotyls segments have been reported in 1998. Following this, indirect somatic embryogenesis and indirect shoot organogenesis in callus culture derived from seedling explants such as hypocotyls and intermodal stem segments have been reported. Besides, a rapid and efficient method of regeneration of plantlets from embryo explants was developed. Further, direct regeneration protocols in tissue culture of different cumin genotypes based on preexisting meristems have been reported (Chittora and Tiwari 2013). In another study, a large number of shoots were produced within 30–40 days without any subculturing. Simultaneous callus and shoot regeneration were also obtained. The best response for shoot regeneration was observed on B5 medium containing 0.1 mg/L NAA and 4 mg/L kinetin. The B5 medium containing 2 mg/L NAA and 2 mg/L kinetin was the best treatment for callus and root induction and regeneration simultaneously (Valizadeh et al. 2007). Another study reported adventitious shoot proliferation from aseptically germinated seedlings of *C. cyminum* (Mann et al. 2008). Thus, the above studies show the feasibility in germplasm conservation and genetic improvement of cumin by *in vitro* cloning and genetic studies.

42. *Curcuma longa* L., Zingeberaceae, turmeric.

    Curcuma longa is a perennial rhizomatous traditional medicinal herb. It is cultivated in the warmer parts of the world for its rhizomes that are used as spice and condiment. Multiple shoots of *C. longa* were induced by culture of bud explants for 1 week in MS liquid medium supplemented with 72.64 μM thidiazuron prior to culture on MS gelled medium without growth regulator for 8 weeks. The regeneration rate was up to 11 shoots per explant. Rooting was spontaneous and the regenerated plants were successfully transferred to soil. This protocol can be useful for the rapid production of *C. longa* raw material for phytomedicine preparation (Prathanturarug et al. 2005).

    In another study, a micropropagation method of *C. longa* has been developed using rhizome bud explants. WPM supplemented with different concentrations of BAP alone or in combination with different concentrations of NAA produced varying degree of multiple shoots. A supplementation of 4 mg/L BAP and 1 mg/L NAA gave the best result. In this case, 95% of the explants induced multiple shoots within 8–10 days and the average number of shoots per explants was 6.7. Rooting was spontaneous and most of the regenerated plantlets were successfully transferred to soil under field conditions (Nasirujjaman et al. 2005). Effect of NAA, BA, and sucrose on shoot induction and rapid propagation by trimming shoot of *C. longa* was also

studied. MS medium supplemented with 2 mg/L BA produced the highest average number of shoot and leaves per shoot (Jala 2012).

In a recent study, plant density was varied with P, Ca, Mg, and KNO_3 in a multifactor experiment to improve *C. longa* micropropagation, biomass, and microrhizome development in fed-batch liquid culture. Increasing P from 1.25 to 6.25 mM increased both multiplication and biomass. The multiplication ratio was greatest in the nutrient sucrose fed-batch technique with the highest level of P and the lowest level of Ca and KNO_3. The highest plant density produced the highest fresh biomass at the highest concentrations of KNO_3 and P with nutrient sucrose-fed batch, and moderate Ca and Mg concentrations. However, maximal rhizome dry biomass required highest P, sucrose-fed batch, and a moderate plant density. Different media formulations and fed-batch techniques were identified to maximize the propagation and storage organ responses. A single experimental design was used to optimize these dual purposes (El-Hawaz et al. 2015).

43. *Cyamopsis tetragonoloba* (L.) Taub., Fabaceae, gowar plant, cluster bean, guar bean.

Cyamopsis tetragonoloba is an erect annual herb. It is a drought-tolerant and multipurpose legume cash crop grown primarily under rain-fed conditions in several countries. Its pods are used as a vegetable.

The effect of various growth regulators and their combinations on a variety of explants has been studied, and an efficient system for callus induction and regeneration from callus has been developed. It was established that MS medium containing 10.0 μM 2,4-D in combination with 5.0 μM BA with embryo or cotyledon explants was most suitable for induction of green morphogenic callus. Efficient *de novo* shoot regeneration was achieved by culturing the callus obtained on this medium or MS medium containing 13.0 μM NAA in combination with BA (5.0 μM) with a range of 82.1–88.4% of callus clumps producing 20–25 shoots. *In vitro* rooting of cultured shoots was obtained on half-salt concentration of the medium supplied with 5.0 μM IBA on which 82–90% of cultured shoots produced healthy roots. The *in vitro* regenerated plants were grown to pod setting and subsequent maturity under greenhouse conditions (Prem et al. 2005).

In another study, an efficient *in vitro* mass protocol for *C. tetragonoloba* has been developed. Four weeks exposure to thidiazuron containing medium prior to transfer to BA supplemented medium was sufficient to induce maximum number of shoots in cotyledon node explants. Optimum multiple shoot induction occurred in MS medium containing 5.0 μM thidiazuron or 10.0 μM BA in cotyledon node explants after 8 weeks of incubation. Elongated shoots were rooted on half-strength MS medium containing 5.0 μM IBA. The plants thus obtained were transferred to pots and the survival rate was more than 80% (Ahmed et al. 2013). Another study reported that a novel combination of PGRs comprising IBA, 6-benzylaminopurine (BA), and gibberellic acid in MS BM has been formulated for *in vitro* induction of both shoot and root in one culture using cotyledonary node explants of *C. tetragonoloba*. Highest percentages of shoot (92%) and root (80%) induction were obtained in the medium containing 2 mg/L IBA, 3 mg/L BA, and 1 mg/L gibberellic acid. Shoot regeneration from the cotyledonary node explants was observed after 10–15 days. Regeneration of roots from these shoots occurred after 20–25 days. The regenerated plantlets showed successful acclimatization on transfer to soil (Verma et al. 2013).

44. *Dioscorea bulbifera* L., Dioscoreaceae, air yam or bitter yam.

Dioscorea bulbifera is a perennial vine. The bulbils of the vines sprout and become new vines. If the plant is cut to the ground, the tubers can survive for extended periods and produce shoots subsequently. Many *in vitro* propagation studies were carried out on *Dioscorea* species. The protocols are designed to provide the optimal levels of mineral nutrients, environmental factors, vitamins, and carbohydrates to achieve highest regeneration rate of different *Dioscorea* species (Das et al. 2013). Nodal stem segments of *D. bulbifera* were induced to form plantlets *in vitro*. Rooted plantlets were obtained on MS revised medium supplemented initially with 5 mg/L kinetin and subsequently with 5 mg/L IBA. By increasing the kinetin concentration

from 5 mg/L to 10 mg/L, the number of shoots formed per node increased from five to eight. When kinetin was substituted with BA at only 1 mg/L, nine shoots formed on each node. Each shoot could be excised from the node and induced to form a new crop of multiple shoots. Rooted plantlets could be successfully transferred to *in vivo* conditions (Forsyth and Staden 1981).

45. *Elephantopus scaber* L., Compositae, Prickly leaved elephant foot, dila-dila.

Elephantopus scaber is an erect, small perennial herb that grows wildly in many Asian countries. It is an important multipurpose medicinal herb. The seeds of *E. scaber* were cultured on half-strength MS medium without any PGR. The germinated seed explants were transferred to callus induction medium fortified with different concentrations of 2, 4-D or 6-benzylaminopurine (BAP or BA) alone and in combination with kinetin. The maximum callus induction (92%) was observed with 1.5 mg/ L 2,4-D + 1.5 mg/ L kinetin. Following callus culture, the proliferated calli were transferred for shoot regeneration. Combination of 2.0 mg/ L BAP + 1.0 mg/L NAA was the most effective for shoot regeneration from callus. The elongated shoots rooted in half-strength MS medium supplemented with different concentrations of auxins (NAA, IAA and IBA). NAA was more suitable for root induction when compared to IAA and IBA (3.5 and 3.7, respectively). The *in vitro* regenerated plantlets were successfully transferred to the greenhouse for acclimatization. The survival of the plantlets under *ex vitro* condition was 77% (Rout and Sahoo 2013).

Recently, an efficient protocol for the rapid micropropagation of *E. scaber* has been standardized using cotyledonary node explants. Direct multiple shoot induction was observed when the cotyledonary node explants at various age groups were cultured on MS medium supplemented with various PGRs. The highest shoot induction was obtained when the cotyledonary node explants from 20-day-old seedlings were cultured on MS medium supplemented with 1.5 mg/L thidiazuron and 0.5 mg/L NAA. On this medium, 98% of the cultures responded, with an average number of 33.7 shoots per explant. The highest frequency of rooting (100%) and mean number of roots (3.3 per shoot) were observed when the shoots were transferred to MS medium supplemented with 1.0 mg/L IBA. The plantlets raised *in vitro* were acclimatized and transferred to soil with a 92% success rate (Abraham and Thomas 2015).

46. *Enicostema hyssopifolium* (Willd.) Verd., Synonym: *Enicostema littorale* Blume, Gentianacea, nahi, vellarugu.

Enicostemma hyssopifolium is an erect perennial glabrous herb. *Enicostema hyssopifolium* was established in cultures from leaf and single-node stem segments. Multiple shoots were elicited from leaf explants on MS medium supplemented with BAP (0.5 mg/L) and IAA (0.5 mg/L), while from nodal explants on BAP (1.0 mg/L) and IAA (0.5 mg/L). Maximum shoot proliferation and elongation was established in shoots derived from leaf explants on MS medium supplemented with kinetin (1.0 mg/L) and BAP (1.0 mg/L), while in shoots derived from nodal explants it was on MS medium supplemented with kinetin (1.0 mg/L) and BAP (0. 5 mg/L). Plantlets were rooted on half-strength MS medium supplemented with IAA (1.0 mg/L). The *in vitro* raised plantlets were successfully transplanted to the nursery (Seetharam et al. 2002).

Another study showed *in vitro* epiphyllous buds (buds upon a leaf or leaf homologue) development on tender excised leaves of *E. hyssopifolium* cultured on MS medium supplemented with cytokinins (BA and kinetin). This phenomenon was shown to be due to cytokinins and occurred only when abaxial surface was in contact with the media. A 2-day exposure to BA (2.0 mg/L) was sufficient for epiphyllous buds induction, although an exposure for more than 4 days yielded maximal shoot development from these buds. Culture of excised leaves on media supplemented with BA (2.0 mg/L) and subsequent subculture on hormone-free medium was insufficient to induce epiphyllous buds formation indicating cytokinin dependence. Buds become microscopically visible after 14 days. These epiphyllous buds originate from subepidermal cells on the adaxial side and consisted of functional meristems producing shoots formed by multicellular processes (Barad et al. 2014).

47. *Eriobotrya japonica* Lindl., Rosaceae, loquat, logat, nokkotta.

    Eriobotrya japonica is an erect perennial glabrous medicinal herb with several pharmacological properties (Subramoniam 2016). *Eriobotrya japonica* is also an important evergreen fruit crop of subtropical regions. It is a native to China and Japan. Using the method of micropropagation, conditions of mass production of somatic clones in *in vitro* culture have been established for loquat. Cytokinin (BA) at low concentration stimulated apical morphogenesis, which was less expressed when adding higher concentrations to the cultivation medium. It has been shown that introduction of auxin together with cytokinin into the cultivation medium caused an intensive callogenesis in the basal part of the main shoot. IBA proved to be the most effective of all growth regulators used in the rooting of regenerated shoots (Lomtatidze et al. 2009). *In vitro* cultures of loquat cultivar Mardan were established using shoot apices after surface sterilization with NaOCl and $HgCl_2$. Caulogenic response was assessed on MS medium fortified with assorted combinations of the cytokinins, BA, kinetin, and 2-iP. Treatment of BA 1.5 mg/L combined with 2-iP 9.0 mg/L and kinetin 1.5 mg/L was found to be optimum for shoot morphogenesis, while the highest shoot length was yielded by the combination of BA 0.5 mg/L, kinetin 0.5 mg/L, and 2-iP 3 mg/L. Higher levels of cytokinins induced callogenesis, and stunted growth to some extent. The best rooting expression was observed with NAA (1 mg/L) combined with IBA (2 mg/L) and paclobutrazol (1 mg/L) (Abbasi et al. 2013).

48. *Ficus benghalensis* L., Moraceae, Banyan tree.

    Ficus benghalensis is a very large tree with branches bearing aerial roots forming accessory roots. It occurs in the wild in forests and planted in the plains of India. Nodal segments containing axillary buds of *F. benghalensis* were induced to produce a large number of multiple shoots by culturing on MS medium supplemented with 1.0 mg/L BA+ 0.1 mg/L NAA, and 20% (v/v) coconut milk. Excised shoots from this culture were rooted best on half-strength MS medium fortified with 0.5 mg/L IBA. The complete plantlets thus obtained were successfully transferred to soil (Munshi et al. 2004). In another study, nodal segments of an about 100-year-old banyan tree was found to be the best for multiple axillary shoot production on modified MS1 medium supplemented with 0.5 mg/L BA. Subculturing of the nodal segments from regenerated shoots in the same medium profoundly stimulated shoot proliferation and elongation. These shoots were devoid of any root and induced to develop roots by culturing the isolated individual shoots on modified MS 2 medium containing 0.1 mg/L IBA. The success of rooting was 100%, while only 65% of the plantlets thus obtained were finally established in soil (Rahman et al. 2004). The flavonal quercetin has been produced from callus cultures of *F. benghalensis* (Bandekar and Lele 2014). Quercetin has anti-DM activity (see Chapter 2).

49. *Ficus carica* L., (*Ficus sycomorous*), Moraceae.

    Ficus carica is a deciduous tree. This has been cultivated for its edible fruits (since very ancient times) in many parts of the world. Since seeds are nonviable, *F. carica* trees are propagated via cutting of mature wood or grafts. However, the multiplication rates are relatively low because those materials can be obtained only from upright branches, which results in poor rooting. Various researchers reported regeneration of multiple shoots from cultures of apical meristems and axillary buds. Callus induction techniques and biochemical assessment of active compounds from calli have also been achieved. Further, shoots were also successfully regenerated from the axillary bud of mature trees and from the calli of stem segments.

    In a study, an *in vitro* protocol for *F. carica* was optimized. Nodal explants containing two buds from field-grown mature plants were transferred to different proliferation media consisting of combinations of distinct concentrations of activated charcoal with BA, kinetin, gibberellic acid, and WPM. The regular strength of WPM in combination with 0.5 mg/L kinetin was the best condition for shoot proliferation of these plants. The addition of activated charcoal, in the medium, completely inhibited proliferation of shoots. The inclusion of BA in the medium induced excessive callus formation as well as small and vitrified shoots, while gibberellic acid induced excessive elongation associated with vitrification, chlorosis, and tip-burned shoots (Fraguas et al. 2004). In another study, the most suitable conditions and media for propagating

three selected *F. carica* clones through tissue culture were determined. One of the clones displayed a higher performance than the other two clones. MS medium containing specific amounts of IBA, gibberellic acid, and 6-benzyladenine was the best multiplication medium, whereas MS medium complemented with 1.2 and 2.5 μM IBA or NAA was better with respect to rooting. Peat followed by volcanic tuff gave the best performance for acclimatization to outdoor conditions (Hepaksoy and Aksoy 2006). In another study, shoot tips of two *F. carica* cultivars proliferated *in vitro* were cultured on MS medium supplemented with 0.5 mg/L BAP. Full and double MS medium strengths enhanced both shoot number and shoot length significantly. Fructose as a carbon source was better than sucrose for multiplication. In rooting stage, MS medium with half strength markedly increased rooting. Rooting of *F. carica* shoots was better on MS medium containing 1 M fructose as a carbon source compared to medium containing sucrose (Taha et al. 2013).

Rapid clonal propagation of this plant from the shoot apices from actively growing adult plants was also achieved using MS medium supplemented with various combinations of growth regulators to induce shoot proliferation and subsequent rooting. The acclimatized plantlets were successfully transferred to the out-air conditions with 95% survival rate (Danial et al. 2014).

50. *Ficus racemosa* L., Moraceae, synonym. *Ficus glomerata* Roxb., *Ficus lucescens* Blume.

Ficus racemosa is an evergreen tree found in India, Myanmar, Sri Lanka, and so on. It is propagated by cuttings of stem and root suckers. Seeds can also be used for propagation. Micropropagation studies on this plant are limited and there is a report on the micropropagation of *F. racemosa* using shoot tip and nodal explants. Shoot tips and nodal explants from *in vitro* growing seedlings of this plant showed best shoot induction on MS medium supplemented with 0.5 mg/L BAP. *In vitro* raised shoots rooted well on half-strength MS medium with 2.0 mg/L IBA + 0.1 mg/L NAA. The survival rate of regenerated plant was 82% (Hassan and Khatun 2010).

51. *Fraxinus excelsior* L., Oleaceae.

Seeds of *F. excelsior* are as food and condiment and the plant is widely distributed in Europe. Embryos extracted from dried seeds of *F. excelsior* were germinated on growth regulator free culture medium. Cotyledonary nodes from these seedlings were placed onto MS medium, WPM, or Driver and Kuniyuki medium with 22.2 or 44.4 μM benzyladenine, on which these nodes developed into shoot cultures following the outgrowth of axillary buds. With MS medium, cultures often died. With WPM, survival of the cultures was considerably improved, but large amounts of callus were produced at the cut ends of the explants, and new axillary shoots had long internodes and small leaves. With Driver and Kuniyuki medium, both survival and callus formation were much improved, and the shoots produced were of high quality. Proliferation of axillary shoots was obtained from both shoot tip and nodal explants placed onto Driver and Kuniyuki medium with 22.2 μM benzyladenine. Adventitious root formation was best with shoots inserted into half-strength WPM containing 2.45, 4.9, or 9.8 μM IBA. All of the rooted plantlets tested were successfully established in soil (Hammatt et al. 1992).

In another study, embryogenic tissues were obtained from immature zygotic embryos and cultured on a modified MS medium containing 8.8 μM 2,4-D and 4.4 μM BA. Embryogenic tissue was subcultured and multiplied on medium supplemented with reduced concentrations of plant growth hormones. Somatic embryos developed and matured by transfer to hormone-free medium and subsequent culture on medium containing a low amount of BA. Somatic embryo germination and conversion were enhanced by cold storage at 4°C and successive transfer onto WPM. Fully developed plantlets were then transferred to pots and acclimatized in greenhouse (Capuana 2013).

52. *Ginkgo biloba* L., Ginkgoaceae, Ginkgo, maidenhair tree, kew tree.

Ginkgo biloba is the oldest living tree species. It occurs in many parts of the world and is grown mainly as an ornamental tree. In a study, apical and nodal meristems removed from plantlets or apical buds from *G. biloba* tree produced an extensive callus and single or

rare multiple shoots on MS medium with different growth regulators and endosperm extract obtained from mature seeds of the same species. For successful root production, it was necessary to transfer the shoots to a rooting medium with endosperm extract (Tommasi and Scaramuzzi 2004).

Multiple shoot formation *in vitro* from nodal segments of adult *G. biloba* has been reported. Woody nodal segments did not produce axillary shoots and presented bacterial and fungal contamination in culture. However, nodal segments from herbaceous shoots were successfully disinfected and displayed high *in vitro* morphogenic capacity. Hydrolyzed casein was essential for the axillary shoots induction and further multiplication, stimulating shoot formation in 85% of the cultured nodal segments and multiple shoots induction in 35% of them at establishment stage. During the multiplication stage, 66.6% of propagules formed new shoots and 33.3% of them formed multiple shoots when cultured with hydrolyzed casein. Kinetin and activated charcoal inhibited the organogenic process. Two distinct patterns of sprouts development were observed *in vitro*, similar to what occurs *in vivo*: (1) short shoots with crowded internodes and expansion of only a few leaves and slow growth; (2) long shoots with separated nodes and marked apical growth (Mantovani et al. 2013).

53. *Glycyrrhiza uralensis* Fisch, Fabaceae, Chinese licorice.

Glycyrrhiza uralensis is a perennial oriental herb that has been widely used in traditional medicine including Chinese medicine. Because of plant depletion and the loss of its natural habitat, there is a need to apply *in vitro* culture methods for micropropagation, conservation, and to provide for the increasing demand of *G. uralensis*. Propagation by the conventional methods takes a long time for germination, fruit setting, and these depend on climate and other conditions as well. Use of *in vitro* cultures of *G. uralensis* and a related species *G. glabra* have been reported by a number of authors. In a report, sterilized explants (root and cotyledon from seedlings) of *G. uralensis* with one node were used for micropropagation. Callus and multiple shoots were induced in half-strength MS medium and Gamborg's B5 medium with different supplements (Oyunbileg et al. 2005).

54. *Gymnema sylvestre* R. Br., Asclepiadaceae, periploca of the wood.

Gymnema sylvestre is a slow-growing, woody, perennial climber. This well-known anti-DM plant is a vulnerable species. The natural habitats of the species are tremendously under pressure due to unsustainable wild harvest and the poor natural regeneration. It is cultivated as a medicinal plant in many parts of the world. This species is thoroughly dependent upon the seed germination for survival. No alternative mode of multiplication is found under natural conditions. However, vegetative propagation through stem cuttings and micropropagation has been proved as viable sources of planting materials. Production of planting materials at an affordable cost would have positive impacts on the *ex situ* conservation of the species (Arunakumara et al. 2013).

Different aspects of *in vitro* propagation of *G. sylvestre* have been investigated by several authors, and the *in vitro* propagation methods have been reviewed recently (Gupta and Solanki 2015). In one study, MS medium supplemented with BA (5.0 mg/L) and NAA (0.2 mg/L) could induce shoots. The best root induction resulted in half-strength MS medium without growth regulators. The best sterilization procedure was found to be l0 min exposure to 0.5% $HgCl_2$; the best results for shoot proliferation were achieved with BA (1.0 mg/L). According to another study, a maximum number of shoots could be induced from 30-day-old seedling axillary node explants. High frequency of rooting (50%) was observed on half-strength MS medium supplemented with IBA (3 mg/L). These rooted plantlets were hardened and successfully established in natural soil (Arunakumara et al. 2013). Apical bud was used as the explant in another study to achieve successful micropropagation of the species (Sharma and Bansal 2010). Stem and nodal segments as well as basal, middle, and terminal cuttings have been successfully employed with MS medium supplemented with different concentrations of various growth regulators (Arunakumara et al. 2013). In another study with nodal explants, a maximum number of roots could be obtained

on MS medium supplemented with NAA (1.0 mg/L) (Manonmani and Francisca 2012). Using young stem cuttings as explants, in a hydroponic experiment conducted with plastic tubes, MS medium containing 1/10 strength of MS salts supplemented with IBA (0.5 mg/L) resulted in the highest rooting (66%) and survival (96%) (Karthic and Seshadri 2009).

Another study reported that MS medium supplemented with IBA (3 mg/L) is the best medium for root induction; the best shoot proliferation was recorded on MS medium containing BA (1 mg/L), IAA (0.5 mg/L), riboflavin (100 mg/L), and citric acid (100 mg/L) (Subatra and Srinivasan 2008). Besides, another study reported that MS medium containing kinetin (0.5 mg/L), and IAA (0.5 mg/L) was the best medium for shoot and root induction. All the plantlets were found survived after transplanting to the pots containing sterile soil and sand (3:1) (Jaybhaye and Deokule 2010). Another study concluded that in order to get the maximum germination, immature seeds should be cultured on half-strength MS medium under dark condition (Gupta et al. 2012).

A system for the somatic embryogenesis was optimized via embryogenic suspension cultures of *G. sylvestre* (Ahmed et al. 2009). In this study, callus cultures was induced on MS medium with growth regulators 2, 4 -D (0.5 mg/L) or NAA (1.0 mg/L) and 10% coconut water. The callus cultures were then transferred into MS liquid medium containing NAA (1.0 mg/L), BA (1.0 mg/L), 3.0% sucrose (w/v), 10% coconut water, citric acid (1 mg/L), and glutamine (10 mg/L) for somatic embryogenesis from callus. Five to seven percent of embryos formed plantlets on semisolid medium containing basal MS medium with B5 vitamin, 3.0% sucrose, and 0.8% agar (w/v). All plantlets established in the field exhibited morphological characters similar to those of the mother plants. However, the nature of the explant, seedling age, medium type, PGRs, complex extracts (casein hydrolysate, coconut milk, malt extract and yeast extract), and antioxidants (activated charcoal, ascorbic acid, citric acid and polyvinylpyrrolidone) could markedly influence *in vitro* propagation of *G. sylvestre*.

Callus Culture and Gymnemic Acids Production: Callus cultures were initiated from nodal segments and leaf explants of *G. sylvestre* on MS medium containing basic salts and 30 g/L sucrose supplemented with different concentrations of 2,4-D, NAA, IAA, IBA, kinetin, and BA. Callus induction was observed in 0.5 mg/L of 2,4-D supplemented medium for both explants. At the initial stage, some parts of explants enlarged and produced pale yellowish calli after 2–3 weeks of incubation. The harvested cell biomass was subjected to extraction of active principles. In this study, cell biomass extracts were compared with extracts from leaves of naturally growing gymnema plants. HPLC analysis of these extracts showed that the main components of the active principles (gymnemic acids and gymnemagenin) were present in sufficiently large amounts in the cultured undifferentiated cells (Gopi and Vatsala 2006).

In vitro callus with the active compounds, gymnemic acid, and gymnemagenin presenting in sufficiently large amount has been reported (Kanetkar et al. 2006). External phytohormone, shaking speeds, and pH of the medium played important roles in growth and gymnemic acid production in suspension culture (Devi et al. 2006). According to this study, the production of gymnemic acid is significantly higher in callus treated with 2,4-D and kinetin. Furthermore, the blue light increases gymnemic acid accumulation up to 4.4-fold as compared with fluorescent light treatment. Gymnemic acid content in callus cultures varied from 2.5 to 5 mg/g dry weight. However, the maximum gymnemic acid content (53.94 mg/g dry weight) could be obtained after 45 days of culture under blue light exposure (Arunakumara et al. 2013; Bakrudeen et al. 2012).

Maximum gymnemic acid and biomass production was observed in the suspension cultures on day 12 and 16, respectively. $CdCl_2$ at 2 mM concentration displayed the maximum response (59.97 mg/g dry callus) within a time period of 24 h, while, $AgNO_3$ at 1 mM concentration gave the least response (18.35 mg/g dry callus), in terms of gymnemic acid accumulation. Based on the above findings, it is apparent that the demand for the anti-DM gymnemic acids could substantially be met with *in vitro* extraction which, in turn, reduces the pressure on wild stock of the species (Ch et al. 2012).

Hairy Root Culture and Gymnemic Acids Production: Hairy root cultures are established to maximize production of gymnemic acids by genetic transformation of plant cells with *A. rhizogenes*. In the hairy

root cultures, production of biomass showed 9.4 times increase with 4.7-fold increase in the gymnemic acid amount as compared to nontransformed cultures. When hairy root cultures were given elicitation with linolenic acid (5 μM), an increase of 7.78-fold in gymnemic acid yield was obtained as compared to the nonelicited cultures (Gupta and Solanki 2015; Praveen et al. 2014).

55. *Helicteres isora* Linn., Sterculiacease, Indian screw tree.

    Helicteres isora is a shrub or small tree. The plant is easily propagated through rhizome pieces. It is normally collected from the wild for medicinal purposes and the plant population is declining due to overexploitation. Natural fruit production is very low in this plant due to inadequate pollinators. Further, seed dormancy is a major constraint in its natural regeneration. In this context, an efficient method for plant regeneration via shoot organogenesis from callus cultures has been developed using nodal explants of this plant. MS medium containing 2,4-D, IAA, IBA, BA, and kinetin either singly or in specific combinations produced granular callus except BA + kinetin that resulted in compact, hard greenish-white callus. Optimum shoot organogenesis was achieved in compact, hard greenish-white callus with lower levels of BA and kinetin and produced shoots within 35 days of culture. Microshoots were rooted successfully on half-strength MS medium containing 4.9 μM IBA (Shriram et al. 2008).

    In a recent study, rapid regeneration of this plant was achieved via shoot tip explants with highest response of shoot induction (100%) on MS BM supplemented with 12 μM BAP (BA) and 16 μM kinetin alone. This combination of phytohormones was found suitable for complete plant regeneration through meristem culture. The developed method can be successfully employed for large-scale regeneration and conservation of this medicinal plant (Deshpande and Bhalsing 2015).

56. *Hemidesmus indicus* (L.) R. Br., Asclepiadaceae, Indian sarsaparilla.

    Hemidesmus indicus is found throughout India growing under mesophytic to semidry conditions in the plains and up to an altitude of 600 m. It is quite common in open scrub jungles, hedges, uncultivated soil, and so on. It is found in India, Sri Lanka, Pakistan, Iran, Bangladesh, and Moluccas (Satheesh George et al. 2008). It is a diffusely twining, sometimes prostrate, under herb having numerous slender laticiferous branches. The overexploitation of *H. indicus* leads to endangered status of this plant in certain areas (Purohit et al. 2014), which requires developing *in vitro* culture for conservation and maintaining the sustainable demand of the plant.

    Tissue culture studies were carried out on this traditional medicinal plant. Organogenesis and somatic embryogenesis were induced from callus initiated from leaf and/or stem explants of *H. indicus* cultured on MS and B5 medium supplemented with 2,4-D, NAA, BA and kinetin. Somatic embryogenesis was dependent on the type of explant, hormone, and age of the callus. Callus induced in MS medium containing 1 mg/L each of 2,4-D and kinetin developed somatic embryos upon transfer to half-strength MS BM. Organogenesis was induced from the callus developed in MS medium containing NAA (2 mg/L) and kinetin (0.5 mg/L), and subculturing to the medium supplemented with 1.5–2 mg/L kinetin and 10% v/v coconut milk. The isolated shoots were rooted in half-strength MS BM. The plantlets, derived through both somatic embryogenesis and organogenesis, were successfully established initially in vermiculite and subsequently on soil (Sarasan et al. 1994). Following this study, a few more *in vitro* propagation studies were carried out. Micropropagation through axillary bud culture was also reported (Austin 2008). Another study reported *in vitro* propagation of *H. indicus* from nodal explants. Half-strength semisolid MS medium with 1.5 mg/L IBA showed the best *in vitro* rooting. One hundred percent of the rooted shoots survived during the acclimatization (Nagahatenna and Peiris 2007).

    In another study as well, *in vitro* regeneration of this plant was achieved. Cotyledons from *in vitro* germinated seeds were used as initial explants, inoculated in MS medium supplemented with various cytokinins, BAP (0.5–2.0 mg/L) and kinetin (0.5–1.0 mg/L), in combination with

auxin, NAA (0.5–1.0 mg/L) and IAA (0.1–0.5 mg/L). The optimal response of shoot initiation (80%) with average number of shoots, 6.8, was observed in the medium containing 2.0 mg/L BAP and 0.5 mg/L NAA within 4 weeks. The maximum shoot multiplication (84%) was observed on MS medium containing BAP (1.0 mg/L) in combination with kinetin (0.5 mg/L). Regenerated shoots were excised aseptically and implanted on half- and full-strength MS medium fortified with various concentrations of IBA, IAA, and NAA for root formation. Full-strength MS medium having 0.5 mg/L IAA was found to be better, with 60% root formation after 16–18 days. The rooted plantlets were successfully acclimatized in pots containing sterilized soil and sand mixture (3:1) with 95% survival rate in the field conditions (Purohit et al. 2014). An image of tissue-cultured plantlets of *H. indicus* is shown in Figure 6.3.

57. *Ipomoea batatas* L., Malvaceae, sweet potato.

    Ipomoea batatas is a tuberous rooted creeping vine. Sweet potato is cultivated for food in more than 100 countries including Asia, America, and Africa. Studies have established that it is an important anti-DM nutraceutical (Subramoniam 2016). *In vitro* regeneration protocols for *I. batatas* have been developed for producing disease- and pest-free planting materials. *Ipomoea batatas* plantations are normally established using cuttings obtained from the shoots grown from tubers buried in warm, humid soil or from plants growing in greenhouses. However, this method is inefficient with respect to larger plantations. Larger numbers of uniform, well-rooted disease- and pest-free sweet potato plants can be produced by means of *in vitro* culturing (Chee et al. 1992; Doliński and Olek 2013; Feyissa and Dugassa 2011; Mvuria and Ombori 2014). Production of plantlets from the node explants by *in vitro* propagation methods has been reported. The properties of the plantlets depended on the cultivar, weight of the explants, and composition of the medium. The sweet potato microplants displayed an ability to acclimatize quickly (Doliński and Olek 2013). Viral disease is one of the major factors causing significant yield loss in sweet potato. *In vitro* production of virus-free sweet potato by

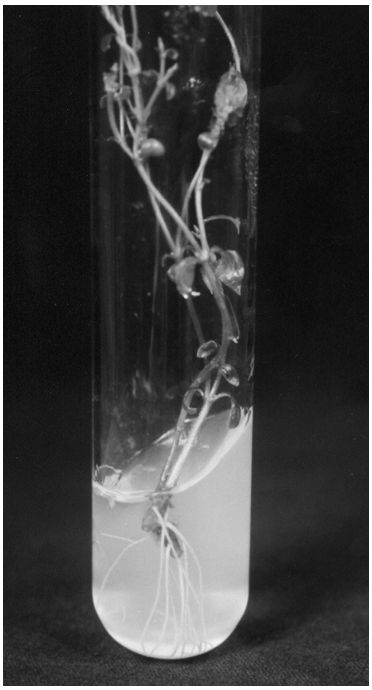

FIGURE 6.3 Tissue-cultured plantlets of *Hemidesmus indicus.* (Photo courtesy of Dr. Madhura Shrotri and Prof. Usha Mukundan.)

meristem culture and thermotherapy has been reported. There was sweet potato virus elimination from two varieties of sweet potato by meristem culture and thermotherapy as observed by using enzyme-linked immunosorbent assay on nitrocellulose membranes (NCM-ELISA) technique. This work indicates the practical applicability of plant tissue culture using meristem culture and thermotherapy to produce virus-free planting materials of sweet potato (Feyissa and Dugassa 2011). Generally, micropropagation costs are high. In one study, three micronutrients (ammonium nitrate, potassium nitrate, and magnesium sulfate) were substituted with low-cost ammonium fertilizer, potassium fertilizer, and epsom salt. In this study, nodal cuttings were used as explants (Mvuria and Ombori 2014).

58. *Lagerstroemia speciosa* (L.) Pers, Lathraceae, Banaba, queen's flower.

Lagerstroemia speciosa is a tropical tree found in many parts of Asia. Micropropagation of *L. speciosa* an important anti-DM and ornamental tree was achieved. Shoot tips were found to be inferior to nodal segments when cultured on MS medium supplemented with kinetin + IAA. Kinetin (0.5–10 mg/L) had no effect on explant growth, while IAA (0.5–2 mg/L) produced the best callus and shoot growth. Excised shoots achieved 100% rooting on MS agar + 6 mg IBA/L, while at best only 50% rooted in sand + 10 mg IBA/L. Once rooted the plantlets were potted in cocopeat : sand or sand : cocopeat : soil and covered for 2 weeks with plastic sheeting. Ninety percent of agar-rooted plantlets survived, but only 50% of sand-rooted plantlets survived (Lim-Ho and Lee 1985). In another study, shoot multiplication and plantlets regeneration were achieved from single-nodal explants of mature trees of *L. speciosa*. Nodal explants directly produced multiple shoots when cultured on MS medium with BAP (1.5 mg/L) and IAA (0.1 mg/L). The differentiated shoots were rooted on half-strength MS medium with 0.5 mg/L IBA (Zobayed 2000).

In a recent study, a rapid *in vitro* propagation protocol for large-scale cultivation of *L. speciosa* was established using nodal explants in SH medium optimized with various concentration and combinations of auxins and cytokinins. The study revealed, for the first time, accumulation of corosolic acid, an anti-diabetic and antiobese pentacyclic triterpene in the *in vitro* plantlets. Multiple shoot induction was maximum in SH medium supplemented with 4.44 μM benzyl amino purine (BAP or BA) and shoot initials, when transferred to SH medium supplemented with 2.22 μM BAP, resulted in shoot multiplication and elongation. Rooted plantlets, after 2 weeks of hardening in mist-house and 3 months of rearing under shade net, transferred to forest segments showed successful establishment (100%). In a short duration of 24 weeks, ~2,450 hardened plantlets were obtained from a single-nodal explant. The inter-simple sequence repeat (ISSR) banding profiles of the regenerants and the mother plant were highly monomorphic and similarity matrix confirmed genetic fidelity of the clones. Chemical analysis using HPLC showed that corosolic acid content is more in mature than young leaves of the *in vitro* derived plantlets. The study signifies the role of *in vitro* methodology for true-to-type regeneration and its possible utility for biosynthesis of corosolic acid, throughout the year (Vijayan et al. 2015).

59. *Lepidium sativum* L., Brassicaceae or Cruciferae, cress.

Lepidium sativum, a cool season annual herb, is cultivated mainly for its edible leaves in India and elsewhere. It is commonly known as garden cress and possesses several bioactive compounds.

Various juvenile (cotyledonary leaves, hypocotyl, radicle) as well as mature explants (leaf, shoot apex, nodal segments) callused on MS supplemented with NAA + BA + casein hydrolyzate. Regeneration from hypocotyl callus and nodal segments occurred after NAA/BA was replaced with IAA/kinetin. Marker compound, lepidine, was monitored at regular intervals. Significant amounts of lepidine were detected in *in vitro* regenerated plants obtained from juvenile and mature explants. The yield, however, was variable, depending upon the source and type of explant used. High levels of lepidine was detected in 8-week-old hypocotyl callus. Among the regenerants, maximum lepidine was obtained from the plantlets at the vegetative

stage (Pande et al. 2002). In another study, three explants (seeds, shoot, and root) of *L. sativum* were used for the standardization of previously reported protocol of callus initiation from seed and shoot explants under *in vitro* conditions. The various combinations of different concentrations of NAA, kinetin, and 2, 4-D were used in MS medium to analyze the effect on explants for callus initiation. PGRs, 2, 4-D (4.0 and 6.0 mg/L) and kinetin (2.0 mg/L) were found to be the most efficient combinations for calli formation. Globular and pale yellow callus was formed in the MS medium containing 2, 4-D (4.00–6.00 mg/ L). Similar trends were also obtained for callus formation from shoot explants using MS medium containing 2,4-D (4.00–6.00 mg/L) and kinetin (2.0 mg/L). However, higher concentrations of kinetin (more than 2.0 mg/ L) did not show any improvement on callusing and also reduced the callus induction frequency from both explants. The highest amount and number of callus formation (50% callus initiation) were observed in culturing of seed in MS medium than the culturing of shoot and root explants (Sharma et al. 2014).

60. *Lupinus mutabilis* Sweet, synonym: *Lupinus albus*, Fabaceae.

    Lupinus mutabilis is a traditional annual legume cultivated in Mediterranean region and in many other regions. This food plant has promising anti-DM properties.

    Somatic embryos were obtained from immature cotyledons of *L. mutabilis*. Different types of basal media and PGRs in primary and secondary cultures were tested. The best induction media were based on B5 and were supplemented with 5 mg/L 2,4-D alone or with 0.25 mg/L kinetin. Somatic embryos were obtained on media containing abscisic acid (0.1–0.5 mg/L) and high NH_4/NO_3 ratio. Embryo germination and plantlet development occurred on MS media supplemented with glutamine or gibberellic acid (Nadolska-Orczyk 1992). The complete protocols for long-term micropropagation of some cultivars of *L. mutabilis* were studied. The shoots were regenerated *in vitro* via induction of axillary buds development. Plantlets were multiplicated on low-salts MS-derived media containing BAP in diverse and generally low concentrations. Regenerated shoots were rooted *in vitro* on low-salts MS-derived media with B5 vitamins. Media were supplemented with different auxins that affected roots formation. Rooting ability of regenerated shoots decreased rapidly through *in vitro* culture. For that reason, grafting was applied as an alternative method of transfer of shoots to *in vivo* conditions. This method turned out to be successful. Completely rooted or grafted plantlets were cultivated in pots with perlite in greenhouse (Pniewski et al. 2002).

61. *Mangifera indica* L., Anacardiacea, mango.

    Mango (*M. indica*) is a large fruit tree cultivated in many tropical and subtropical regions of Peninsular India and elsewhere. The leaves and fruit peels are rich in anti-DM phytochemicals. It is a highly heterozygous crop and seed propagation may not ensure true-to-type progeny. Vegetative propagation methods used include grafting, budding, and enarching. In this context, establishment of micropropagation techniques in mango will facilitate the production of large-scale elite planting materials to the mango growers. Micropropagation studies on mango are described in detail elsewhere (Chandra et al. 2011). Tissue culture has been pursued in mango for the last two decades to develop regeneration protocols for clonal multiplication and genetic transformation studies. Of the various *in vitro* approaches tried for cloning mango tree, success has been achieved only with nucleus explants, but not with vegetative explants. Various investigators have demonstrated *in vitro* regeneration of mango through nuclear embryogenesis. The *ex vitro* survival of *in vitro* raised plantlets of *M. indica* is the major problem with *in vitro* cloning of mango. The field establishment of micropropagated mango plantlets has not been successful. Thus, mango seems to be a difficult plant species with respect to tissue culture response. The main problem in tissue culture of mango is the development of axenic cultures, phenol leaching, browning of tissue explants, poor conversion rate of somatic embryoids, and poor shoot and root development (Chandra et al. 2011). Further research is needed in this important area.

62. *Melothria maderaspatana* (Linn.) Cogn., synonyms: *Mukia maderaspatana, Cucumis maderaspatana* or *Mukia scabella,* Cucurbitaceae, madras pea pumpkin.

Melathria mederaspatana is distributed throughout the tropics and subtropics of the Old World. It is an indigenous medicinal food plant that is currently tending to transform as an endangered taxon (Petrus 2013).

Effective protocols have been developed for the *in vitro* regeneration of *M. mederaspatana* in liquid and solid culture systems. Organogenesis has been achieved from liquid culture calluses derived from leaf and petiole explants of mature plants. Organogenic calluses were induced from both leaf and petiole explants on MS liquid medium containing 6 μM 2,4-D and 0.5 μM thidiazuron, and 6 μM 2,4-D and 1 μM BA combinations, respectively. Adventitious shoot regeneration was achieved on MS medium supplemented with BA, thidiazuron, coconut water, and glutamine from leaf-derived calluses. Petiole-derived calluses have produced adventitious shoots on MS medium fortified with BA, thidiazuron, coconut water, and glutamine. Elongation of shoots has been reported to occur in MS medium with gibberellic acid. Regenerated shoots rooted and hardened, when these have been transferred to half-strength MS medium supplemented with IBA followed by garden soil, vermiculate, and sand mixture. The plants were successfully established in the field with varying survival rates, depending on the seasonal variations (Baskaran et al. 2008a).

In another micropropagation system, prolific shoot regeneration have been achieved on an enriched MS medium containing watermelon juice, sucrose, and agar, supplemented with BA, coconut water, and casein hydrolysate. A higher number of shoots have been observed on an enriched MS medium supplemented with BA, coconut water, and casein hydrolysate. The regenerated shoots, after dipping in IBA for 15 min, have been transplanted into plastic pots containing a mixture of vermiculite and sand to induce rooting. As a result, a mean of 10.4 roots per shoot with a length of 60–75 mm has been realized. The *in vitro* raised plantlets with well-developed shoots and roots have subsequently been established successfully in a greenhouse with 85% survival rate. The protocol has been recommended by its developers for mass propagation and germplasm conservation of *M. mederaspatana* (Baskaran et al. 2008b).

In yet another protocol, cotyledon explants isolated from *in vitro* germinated seedlings (5–6 days old) have been cultured on MS medium containing different concentrations of BA alone or in combination with IAA. Cotyledon explants cultured on medium containing BA and IAA had induced a significantly higher number of multiple shoots (9.0) with increased mean shoot length (2.70) within 5 weeks of culture. Leaf segments from *in vitro* grown plants (20 days) have been cultured on MS medium with different concentrations of BA alone or together with IAA. Maximum number of shoots (10) with increased mean shoot length (2.9) have been obtained directly from leaf explants (without intervening callus phase) using a combination of BA and IAA within 5 weeks of culture. Inclusion of IAA to MS medium with BA has been reported to have triggered a high frequency of regeneration from leaf and cotyledon explants. Elongation of regenerated shoots had occurred when cotyledon cultures (3 weeks) have been transferred to MS BM. Leaf cultures with emerging shoots have then been subcultured onto the same treatment medium for further elongation. The elongated shoots (2–3 cm) have subsequently been excised and rooted on MS medium, supplemented with IBA. Rooted plants have then been acclimatized in the greenhouse with a 70% survival rate. In another study, the leaf explant produced callus effectively in the MS medium supplemented with BAP and NAA, while the nodal explant has yielded a higher amount of direct shoots (89%) in the MS medium containing BAP and NAA. The leaf-derived calluses (calli) have been claimed to have yielded shoots effectively (88%) when subcultured onto the MS medium with BAP. Similarly, the percentage of node for shooting has been higher (85%) in the MS medium fortified with BAP and gibberellic acid. The response of leaf-callus-derived shoots for rooting has been greater when subcultured onto the MS medium supplemented with IBA alone, while the node-derived shoots rooted well when subcultured on MS medium fortified with IBA and IAA (Petrus 2013).

63. *Momordica charantia* L., Cucarbitaceae, bitter melon, bitter gourd, Karela.

    Momordica charantia is an economically important common vegetable with established anti-DM properties. *Momordica charantia* is a climbing monoecious tropical vine, used in the treatment of diabetes and many other ailments. Many varieties of this plant have been reported. Biotechnological intervention could facilitate improvement of this crop including its anti-DM properties. In this context, *in vitro* propagation of bitter gourd was achieved by many investigators. Tissue culture of *M. charantia* has been reviewed recently (Agarwal 2015). *In vitro* regeneration system of this plant has been established from seedlings, cotyledon nodes, and so on. *In vitro* plant production through apical meristem culture has been demonstrated. Further, *in vitro* plant regeneration from both direct and indirect organogenesis has been shown. The best callogenic response of *M. charantia* was observed from leaf, stem, and cotyledon on MS medium supplemented with 1.0 and 1.5 mg/L BAP with 1.5 mg/L NAA and 1.0 mg/L 2,4-D, respectively. In one study, nodal segments produced the highest percentage (93) of callus in MS medium supplemented with 1 mg/L 2,4-D and 1 mg/L BAP, whereas root segments produced the highest (85%) callus in 0.6 mg/L NAA and 2.5 mg/L BAP combination (Al-Munsur et al. 2009). In MS medium containing 1.0 mg/L 2,4-D, about 90% leaf explants gave rise to well-organized friable calli. At different concentrations of BAP and kinetin green, compact and hard calluses (calli) were produced. High-frequency shoot regeneration from leaf explants through organogenesis as well as *in vitro* induction of multiple buds from cotyledonary nodes has also been described. Studies have also established hairy root cultures for the production of biologically active phenolic compounds (Agarwal 2015).

64. *Morus alba* L., Moraceae, white mulberry.

    Morus alba is a shrub or a small tree cultivated throughout the world wherever silkworms are raised. It is also an important anti-DM plant. *In vitro* propagation will facilitate large-scale cultivation of this plant.

    Callus cultures were raised from intermodal segments of mature *M. alba* on MS medium supplemented with 1 mg/L 2,4-D and 0.5 mg/L BAP. Shoots were regenerated when the induced calli were transferred to medium containing 0.5–3.0 mg/L BAP. Callus-derived shoots produced roots and developed into plantlets when transferred to the medium supplemented with 0.5 mg/L NAA (Narayan et al. 1989). Later on, micropropagation of *M. alba* through *in vitro* culture of shoot tip and nodal explants was also reported (Anis et al. 2003). Recently a protocol for rapid multiplication of *M. alba* (cv. al-taify) through *in vitro* culture was reported. Using axillary bud explants from mature plants, shoot initiation was induced on MS medium supplemented with different concentrations of BA. A higher percentage of shoot initiation (90) was observed on MS medium supplemented with 2 mg/L BA. Initiated shoots gave a higher number of shoots when it was subcultured on MS medium containing 2 mg/L BA and 1 mg/L kinetin. A maximum percentage of root formation was observed when shoots were subcultured on MS medium containing 2 mg/L IBA. Rooted plantlets were acclimatized and transferred in greenhouse with 80% survival rate (Attia et al. 2014).

    A related species with anti-DM activity is *M. indica.* A high frequency of regeneration (80%) and shoot differentiation was observed in the primary cultures of nodal explants of *M. indica* on MS medium supplemented with 2,4-D (0.3 mg/L). *In vitro* proliferated shoots were multiplied rapidly by culture of shoot tips in MS medium with BAP (0.5 and 1.0 mg/L), which produced the greatest multiple shoot formation. Gibberellic acid (0.05 mg/L) facilitated the elongation of shoots followed by sprouting of axillary buds of *in vitro* grown shoots. A high frequency of rooting (87%) with development of healthy roots was observed from shoots cultured on medium with 2,4-D (1.0 mg/L) (Vijaya Chitra and Padmaja 1999). Colonal propagation of *M. indica* cultivar-M5 was achieved through *in vitro* culture of nodal explants (Balakrishnan et al. 2009).

65. *Murraya koenigii* (Linn.) Spreng, Rutaceae, curry leaf.

    Murraya koenigii is a small tree or shrub cultivated throughout India and elsewhere for its leaves (spice). There are only a few reports on tissue culture of *M. koenigii* that are limited

to *in vitro* shoot multiplication from intact seeding and nodal cuttings. Internodal segments of mature *M. koenigii* plants produced adventitious shoots on MS medium supplemented with different concentrations of BAP or kinetin. The best response was obtained with 1 mg BAP/L, with 40 buds/explant after 2 weeks and over 24 microshoots after 4 weeks. Of the various auxin treatments used for *in vitro* rooting of the shoots, 0.1 mg IBA/L proved to be the best. *Ex vitro* rooting of microshoots was achieved only with a combination of 1 mg IBA and 1 mg phloroglucinol/L (Rajendra and D'Souza 1998). In another study, shoot tips from mature *M. koenigii* cultured in MS medium supplemented with 2.5 mg/L IBA and 1.5 mg/L BAP produced eight to nine multiple shoots per explants after 4 weeks of inoculation (Kumar et al. 2013). In a recent study, an effective and reproducible *in vitro* regeneration protocol in *M. koenigii* has been standardized. Shoot tip explants from mature plants were found highly effective for the large-scale *in vitro* shootlets production; and an efficient root regeneration protocol has been standardized in the shootlets using *in vitro* liquid culture technique. Developed shootlets were successfully acclimatized by utilizing 70 days acclimatization period. The protocol could contribute to the *in vitro* production and conservation of *M. koenigii* (Perveen et al. 2015).

66. *Nelumbo nucifera* Gaertn., Nymphaeaceae, sacred lotus.

    Lotus (*N. nucifera*) is a large aquatic herb with creeping branches. It is found throughout the warmer parts of India. This plant exhibits promising anti-DM activity and is used to treat various ailments in the traditional medicine. *In vitro* lotus shoot formation was greatly influenced by growth regulators, explants size, and season of explants collection. The maximum number of shoots was induced from bud explants on MS medium containing 4.44 μM BA + 0.54 μM NAA. Explants collected in spring gave encouraging results of shoot production. Higher temperature favored shoot induction and subsequent growth was much better at 25°C compared to that at 20°C and 30°C (Shou et al. 2008). In another study, *in vitro* direct regeneration of *N. nucifera* was achieved from immature explants (yellow plumule) cultured on solid MS media supplemented with combinations of 0.5 mg/L BAP and 1.5 mg/L NAA. In the study involving light distance, the tallest shoot (16.67 ± 0.23 mm) obtained from the immature explants was at a light distance of 200 mm from the source of inflorescent light. The plantlets were successfully acclimatized in clay loam soil after being maintained for 8 months under *in vitro* conditions (Mahmad et al. 2014). In a recent study using shoot apical meristems from the buds and 1-week-old embryo as explants, a regeneration system for lotus was established. Multiple shoot clumps were induced on MS BM supplemented with various concentrations of BA and NAA. The maximum response was obtained with 2.22 μM BA. After subcultures, the shoot clumps were transferred to MS medium supplemented with various combinations of IBA, NAA, and sucrose for root induction. After 4 weeks, plantlets with roots were achieved on MS BM supplemented with 0.54 μM NAA and 30 g/L sucrose with 100% rooting rate. The acclimated plantlets were successfully transferred to greenhouse with 97% survival rate (Xia et al. 2015).

67. *Ocimum sanctum* Linn., Lamiacea, Holy basil, tulasi.

    Ocimum sanctum is one of the common, largely scented, berbacious, medicinal plants found in India and elsewhere. *In vitro* micropropagation of *O. sanctum* has been accomplished on MS medium utilizing young inflorescence explants. MS supplemented with 2,4-D or thidiazuron produced only nonmorphogenetic callus. Direct multiple shoots differentiated within 2–3 weeks when explants were cultured on MS medium containing BAP. Incorporation of IAA (0.05 mg/L) along with BAP (1.0 mg/L) in the culture medium showed a marked increase in the number of shoots. About 92% of the *in vitro* regenerated shoots rooted on MS hormone-free medium within 2–3 weeks of culture and 85% of the micropropagated plantlets could be successfully established in soil (Singh and Sehgal 1999). In another report, eugenol production was noted in *in vitro* propagated calli (calluses) obtained from leaves from seedlings. Callus developed from leaves of seed-germinated plantlets on MS BM supplemented with 0.5 mg/L 2,4-D (Bodhipadma et al. 2005).

In another study, shoot tip and leaf explants of *O. sanctum* were cultured on different concentrations and combinations of growth regulators (BAP, kinetin, 2,4-D, IAA, and IBA) in MS medium to observe shoot multiplication, callus induction, callus regeneration, and root induction. Among the different concentrations and combinations of growth regulators, the highest percentage of shoot formation and highest average number of shoots were obtained in 0.2 mg/L BAP from shoot tip explants. Callus induction was obtained within 12–15 days of culture from leaf explants. The highest frequency (90%) of organic callus induction was observed in MS medium containing 1.0 mg/L NAA. Shoot regeneration occurred when the calli were subcultured in MS medium supplemented in BAP. The highest percentage of shoot regeneration was obtained in 0.2 mg/L BAP. *In vitro* grown shoots rooted best on MS medium containing 0.1 mg/L NAA. *In vitro* grown plantlets were transferred to pots containing sand and soil mixture, acclimatized in a culture room, and transferred to soil (Banu and Bari 2007).

In a recent report, a protocol for rapid propagation of *O. sanctum* was developed using leaf explants culture. Callus induction was found within 7–10 days; callus formation was found to be the highest when MS medium was supplemented with 3 mg/L picloram. The best response for shoot induction was obtained using 1 mg/L BA in combination with 0.5 mg/L IAA. *In vitro* shoots were rooted on 1.5 mg/L IBA supplemented medium. The rooted plantlets were acclimatized and established under natural conditions with 90% survival rate (Mishra 2015).

68. *Olea europaea* L., olive, Oleaceae.

Olea europaea is a native of Southern Europe and this evergreen tree exhibits promising anti-DM activities and is cultivated as an ornamental plant; it is also cultivated commercially for the production of olive oil. The traditional propagation methods *O. europaea* include rooting of cuttings and grafting stem segments onto rootstocks. Rooting of cuttings is achieved only when the cuttings are collected in spring or beginning of autumn; success of grafting depends on skilled grafting. *Olea europaea* propagation is a laborious practice. The regeneration of whole plants from ovules is used only occasionally. Micropropagation of olive has hindrances such as explants oxidation and problems with explants disinfection. However, a micropropagation protocol based on the segmentation of nodal segments from elongated shoots was achieved (Lambardi et al. 2013). In another study, the Oueslati cultivar of *O. europaea* displayed a high capacity to proliferate during the multiplication phase in a modified Rugini medium with zeatin (1 and 2 mg/L). Almost 91% of the proliferated shoots rooted in 40 days when their basal parts were dipped in an IBA solution and transferred to an agar medium enriched with the same growth regulator. The acclimatization of the *in vitro* derived plantlets was carried out under greenhouse conditions that yielded a success rate of about 88% (Chaari Rkhis et al. 2011).

In a recent study, a protocol for plantlet regeneration from nodal segments of olive cv. Frontio has been developed. Media and explants browning due to exudation of phenolics from the explants were controlled by fortification of the medium with 100 mg/L ascorbic acid. Best establishment of olive explants was observed on half-strength MS salts fortified with 2.0 mg/L 6-benzylaminopurine (BAP), which resulted in 56% of bud break and 94% survival rate, whereas a combination of full-strength MS medium with 1. 0 mg/L each of IBA and kinetin was found to be the best for shoot multiplication. The *in vitro* shoots were rooted on half-strength MS medium fortified with 0.2 mg/L IBA and 0.2 mg/L NAA with 1.5 g/L activated charcoal, which supported optimum rooting (Mangal et al. 2014).

69. *Opuntia streptacantha* Lemaire, synonym: *Opuntia cardona* F.A.C., Cactaceae, nopal, prickly pear cactus.

Opuntia streptacantha is a xerophytic plant with flattened stems (cladodes) that are used as food and medicine. Prickly pear cactus (*Opuntia* spp.) is adapted to grow and produce under low-water regimes and poor soils. The cactus is mainly propagated through the rooting of cladodes. However, seeds, tissue culture, and grafting could also be used for propagation. Grafting in commercial propagation has been restricted because of poor success. A potential alternative to avoid some of these problems in grafting is micrografting of plantlets that are performed under aseptic and high relative humidity conditions. *In vitro* microcrafting may provide several

advantages such as elimination of viruses, rejuvenation of mature tissues, and so on. A study has shown that *in vitro* horizontal graft was successful, easy, and reliable method to graft micropropagated *Opuntia* species particularly since no contamination or tissue dehydration occurred and no special structures or adhesive were needed for successful graft union formation (Estrada-Luna et al. 2002).

70. *Panax ginseng* C.A. Meyer, Araliaceae, Asian ginseng.

Panax ginseng is a perennial medicinal herb cultivated extensively in China, Korea, Japan, Russia, and so on. This plant requires a period of more than 3 years to produce seeds. At time of seed harvest, zygotic embryos of ginseng are still in an immature globular stage, thus the seeds require stratification and cold treatment for several months. Therefore, tissue culture procedures could contribute to clonal propagation and breeding in ginseng. In many reports on tissue cultures, the regenerated plantlets from somatic embryos developed into multiple shoots without or inadequate roots, indicating low plant conversion. However, efficient *in vitro* protocols have been established for somatic embryogenesis and plantlet conversion of *P. ginseng.*

A recent report showed that wild-type and mutant adventitious roots derived from the ginseng produced calluses on MS medium supplemented with 0.5 mg/L 2,4-D and 0.3 mg/L kinetin. Embryogenic callus proliferation and somatic embryo induction occurred on MS medium containing 0.5 mg/L 2,4-D. The induced somatic embryos further developed to maturity on MS medium with 5 mg/L gibberellic acid. The germinated embryos were developed to shoots and elongated on MS medium with 5 mg/L gibberellic acid. The shoots developed into plants with well-developed tap roots on one-third strength SH BM supplemented with 0.25 mg/L NAA. When the plants were transferred to soil, about 30% of the regenerated plants developed into normal plants (Zhang et al. 2014). A procedure was also described for the initiation, subculture, and continued proliferation of adventitious roots of *P. ginseng* and *P. quinquefolium* that resemble hairy roots (Kevers et al. 1999).

In another study, *P. ginseng* embryogenic tissues were cultured in three types of reactors and the ginsenoside productivities in these tissues were compared. The saponin (gingenoside) productivity was the best when an airlift reactor was used, and more than twice of that when a paddle or internal turbine reactor was used. The tissues grew ninefold during 42 days, and the ginsenoside pattern resembled that of ginseng leaves (Asaka et al. 1993).

A lot of ginseng embryoids were produced by culturing on high concentrations of sugar media from the embryogenic tissues obtained by moderately high temperature treatment. At 100 g/L sucrose, the number of embryoids (calli) produced was about 10 times more than that produced at 30 g/L of sucrose. Glucose showed an effect similar to sucrose on the basis of weight percentage. However, mannitol did not show this effect. The embryoids obtained by these processes redifferentiated to normal plantlets on culturing on the medium containing 30 g/L of sucrose. The saponin components of the tissue containing embryoids showed a similar pattern to those of natural ginseng (Asaka et al. 1994). *In vitro* propagation may pave the way for the production specific ginsenosides with anti-DM activities as per requirement.

71. *Panax quinquefolius* L., synonym: *Panax quinquefolium* (L.) Alph., Araliaceae, American ginseng.

Panax quinquefolius is a medicinal herb with fusiform roots. It is a native to North America and is cultivated; it is also found in wild. *Panax quinquefolius* has a long production cycle as seeds are usually produced after a 3-year cultivation and must stratify for additional 12–18 months before germination. A clonal propagation method based on *in vitro* procedures would contribute to its genetic improvement by reducing the generation cycle time. Further, it would allow for the reduction in confounding genotype effects in field evaluations through the use of clonal material and would be useful for germplasm preservation. Because of declining wild population and the long time required in field cultivation to produce the root, *in vitro* propagation has been sought as a potential alternative to supply bioactive components (specific ginsenosides) of ginseng.

The tissue culture of *P. ginseng* is well studied with reports on callus cultures, protoplast culture, shoot organogenesis, and somatic embryogenesis as mentioned above. To a large extent, these techniques have not been used successfully with *P. quinquefolius*. There are only a few reports on the *in vitro* cultivation of *P. quinquefolius*. These reports are on the formation of somatic embryos on callus culture of embryonic, seedling, root, or leaf explants. *Panax quinquefolius* is still considered to be recalcitrant *in vitro* because of the difficulty in obtaining plants with a well-developed root system. However, an efficient protocol for micropropagation of this ginseng has been reported (Zhou and Brown 2007). *In vitro* propagation using a bioreactor system was evaluated as an effective approach to accelerate plant production. An efficient method was developed to multiply nodal explants of *P. quinquefolius* using liquid-culture medium and a simple temporary immersion culture vessel. The effects of PGRs, phenolics, and chemical additives (activated charcoal, melatonin, polyvinylpolypyrrolidone, and ascorbic acid) were evaluated on *in vitro* grown plants. The highest number (12) of shoots per single node was induced in half-strength SH BM containing 2.5 mg/L kinetin. In a culture medium with 0.5 mg/L NAA, roots were induced in 78% of the explants compared to 50% with a medium containing IAA. All of the resulting plants appeared phenotypically normal, and 93% of the rooted plants were established in the greenhouse. Phenolic production increased significantly over a 4-week culture period with a negative impact on growth and proliferation. Activated charcoal (50 mg/L) significantly reduced total phenolic content and was the most effective treatment for increasing shoot proliferation. Shoot production increased as the phenolic content of the cultures decreased. The most effective treatment for *P. quinquefolius* development from cultured nodal explants in the bioreactor was 2.5 mg/L kinetin, 0.5 mg/L NAA, and 50 mg/L activated charcoal in liquid culture medium. This protocol may be useful in providing *P. quinquefolius* tissues or plants for a range of ginseng-based natural health products (Uchendu et al. 2011).

Panax quinquefolius root grows into different morphotypes notably bulb or round, man-like, and straight or stick, and these roots are assumed to have different medicinal qualities. In an interesting study, explants from the three different types of roots exhibited varied callus induction response, growth, and production of ginsenosides. Explants from man-like line induced callus faster, were prolific in growth, and accumulated more biomass compared with explants from the other two lines. Man-like lines (both stock roots and calli) had significantly higher total content of ginsenosides than the other two lines. There were positive and highly significant correlations between total content of ginsenosides of rootstocks and callus tissues. Man-like lines exclusively exhibited low Rg1 and high Re ginsenoside profiles, whereas (bulb or round) and (straight or stick) lines exhibited mixed Rg1 and Re profiles. Thus, these results showed that ginsenoside profile of stalk roots directly influenced callus induction response and gingenoside profile. This information would be useful in advancing breeding efforts toward selecting superior cultivars (Obae et al. 2011).

72. *Peganum harmala* L., Zygophyllaceae.

Peganum harmala is an erect bushy, perennial medicinal herb that grows in wild and is propagated by seeds. The very short span of seed viability limits its natural propagation. Further, owing to increasing exploitation of the natural population, it is facing the depletion of plant population in the wild (Saini and Jaiwal 2000). However, this plant can be propagated *in vitro*. In one study, cotyledonary node explants exhibited shoot regeneration from axillary region on MS medium supplemented with 5 μM BAP. BAP (5 μM) in combination with NAA (0.1 μM) was found to be the optimal for inducing shoots. Regenerated shoots were rooted on MS medium containing IBA (8 μM) with 80% efficacy. The plantlets were successfully established in soil (Saini and Jaiwal 2000). In another study, the plant was propagated from shoot apices and first axillary buds on agar solidified MS medium supplemented with BAP in combination with NAA. MS medium containing 1.11 μM BAP and 0.11 μM NAA was optimal for shoot regeneration. Rooting was achieved on MS medium containing 4.9 μM IBA. Rooted plants were successfully acclimatized (Khawar et al. 2005). The frequency of multiple shoot regeneration of shoot apex and cotyledonary node of *P. harmala* was affected by the concentration

of BAP in the regeneration medium as well as significantly influenced by the preconditioning of seeds with 0.5–11.1 μM BAP prior to excision of explants. Regenerated shoots were rooted on MS medium containing half-strength salts, 3% sucrose, and 5 μM IBA with 80% efficiency. The plantlets were successfully established in soil where 90% of them survived into normal plants (Goel et al. 2009).

73. *Phyllanthus amarus* Schum & Thonn, Phyllanthaceae (formerly Euphorbiaceae), Gale-o-wind, hurricane weed.

Phyllanthus amarus is an annual glabrous herb distributed in tropical and subtropical regions of the world. Indiscriminate harvesting has threatened the status of *P. amarus* in the wild.

Shoot tips of *P. amarus* were cultured in MS medium supplemented with kinetin/BAP singly or in combination with IAA. Growth regulators at lower range (0.1–1.0 mg/L) stimulated direct regeneration of shoots. Kinetin was superior to BAP and kinetin-IAA combination was more suitable than kinetin alone. The cluster of proliferated shoots was elongated and rooted simultaneously under the same treatment following another subculture. Shoot tips of regenerated shoots were continuously used to regenerate new shoots with periodic transfer to fresh medium resulting in a steady supply of normal, healthy plants without any deviation in the production rate during a continuous 1-year culture. Micropropagated plants were successfully established in soil with high survival (Bhattacharyya and Bhattacharya 2001). In another study, high-frequency shoot generation from *P. amaurus* was shown. High-frequency shoot production was recorded on MS medium supplemented with BAP (0.5 mg/L). Maximum number of roots was induced in medium containing 0.5 mg/L IBA. Rooted plantlets were successfully hardened and transferred to greenhouse (Ghanti et al. 2004). In another report, an efficient *in vitro* plant regeneration protocol was developed for *P. amarus* using nodal segment as explant. Maximum multiplication of shoots was achieved on MS medium supplemented with BAP (0.5 mg/L) after 3–4 weeks of inoculation. The shoots were separated from cluster and subcultured for their elongation on the same medium. *In vitro* flowering was also observed on the elongated shoots after 3–4 weeks of subculturing on the shoot elongation medium. *In vitro* rooting was obtained on half-strength MS medium supplemented with IBA (0.5 mg/L). Regenerated plants were successfully hardened and acclimatized; 80% of plantlets survived well under natural conditions after transplantation (Sen et al. 2009). A procedure for indirect organogenesis of *P. amarus* using leaf bits and internodes has also been reported. Profuse callusing of the explants was obtained on MS medium supplemented with NAA and 2,4-D. When the callus was subcultured on MS medium supplemented with BAP (1.0 mg/L) and glycine (50 mg/L), high frequency of callus proliferation was obtained. Complete plantlets were obtained when the callus was subcultured on MS medium supplemented with BAP (2 mg/L) and giberllic acid (0.5 mg/L). Rooting of the shoots were achieved on half-strength MS medium supplemented with IBA and IAA (Chitra et al. 2009).

In another study, micropropagation protocol for *P. amarus* was standardized with shoot tip and single-node explants. Shoot tips and single-node explants gave a maximum number of shoots per explant with BAP (1.0 mg/L). Upon subculturing, a shoot length of around 7 cm with an average of eight internodes per shoot was observed after 20 days in the elongation medium supplemented with BAP (0.2 mg/) and IAA (2.0 mg/L). Seven to ten adventitious roots developed when the elongated microshoots were cultured in half-strength MS medium, IBA (2.0 mg/L) and NAA (1.0 mg/L) in 15–20 days after transfer. The rooted shoots acclimatized successfully to field conditions. A method for successful micropropagation of the valuable medicinal plant was established, which will provide a better source for continuous supply of plants for manufacturing drugs (Xavier et al. 2012). An image of tissue-cultured plantlets of *P. amarus* is shown in Figure 6.4.

74. *Phyllanthus emblica* L., synonym: *Emblica officinalis* Gaertn, Euphorbiaceae, Indian gooseberry.

Phyllanthus emblica is a medium-sized deciduous tree with pubescent slender branches. The seeds of *P. emblica* are semiorthodox and exhibit a long dormancy period hindering the

FIGURE 6.4 Tissue-cultured plantlets of *Phyllanthus amarus.* (Photo courtesy of Dr. Anuja Deo and Prof. Usha Mukundan.)

natural sexual propagation. In a recent study, seed dormancy was overturned with a germination percentage of 43% by the seed pretreatment with 1% gibberellins (Mawalagedera et al. 2014). In an *in vitro* study, tissue culture of *P. emblica* was made using shoot, cotyledon, hypocotyl, and root explants of 20–30 days old seedlings and cultured on MS medium with 2 mg/L BA (6-benzylaminopurine). Hypocotyle explants produced the greatest number of shoots at 60 days. Then shoots were cultured on medium with BA and kinetin, and it was found that BA promoted shoot proliferation and the 4 mg/L BA treatment produced the highest number of shoot. Root were induced in MS medium with IBA or NAA or reduction of both ammonium nitrate and potassium nitrate or increase of sucrose (3–12 percent) on MS medium. The maximum percentage of rooting and number of root were found in MS without ammonium nitrate and potassium nitrate treatment (Chuthamat et al. 1999).

In another *in vitro* propagation study, aseptic cultures were established using various sterilizing agents and *in vitro* shoots of *P. embilica* were developed using nodal explants on different media (Goyal and Bhadauria 2008). In another study, shoots were regenerated adventitiously on epicotyl segments from *in vitro* seedlings of *E. officinalis* var. Kanchan. Epicotyls derived from 2-week-old aseptic seedlings were most responsive and produced a maximum number of 303 shoots per explant in MS medium augmented with 8.8 μM BA + 1.425 μM IAA. Shoots readily elongated in MS lacking growth regulators and rooted in half-strength-salt MS supplemented with IBA or NAA. The highest rooting response was recorded in half strength-salt MS medium containing 14.7 μM IBA. Plantlets were acclimatized inside the greenhouse and 80% of the plantlets survived on transfer to garden soil (Nayak et al. 2010a). In another study, a simple protocol was developed for induction of somatic embryogenesis from *in vitro* derived juvenile leaf tissue. Highest percentage of callus was obtained on MS media containing 0.45 μM 2,4-D in combination with 22 μM BAP. Maintenance of proliferating callus on the media led to high frequency of somatic embryogenesis. Somatic embryos were matured within 2 weeks when treated with 3.78 μM BAP. Matured embryos were transferred to MS media fortified with 0.46 μM kinetin for germinating healthy plants (Thilaga et al. 2013).

75. *Pongamia pinnata* (L.) Pierre, synonym: *Pongamia glabra* Vent. Derris, Leguminosae, Indian beech.

Pongamia pinnata is a fast-growing evergreen, deciduous tree. It is an important anti-DM plant as well as an important source of biofuel. The present production of seeds of this plant is inadequate and planting of such important plant species on a massive scale is useful. Germination and plant vigor decreases following storage of seeds for 3 months or more. Plants propagated through stem cutting are not deep-rooted (Satapathy et al. 2014).

A protocol is presented for the micropropagation of *P. pinnata* using cotyledonary nodes derived from axenic seedlings. Multiple shoots were induced *in vitro* from nodal segments through forced axillary branching. MS medium supplemented with 7.5 μM BAP induced up to 6.8 shoots per node with an average shoot length of 0.67 cm in 12 days. Incorporation of 2.5 μM gibberellic acid in the medium during the first subculture after establishment and initiation of shoot buds significantly improved the shoot elongation. Single use of gibberellic acid during the first subculture eliminated the need for prolonged culturing on BAP medium. Further use of gibberellic acid in the medium was not useful. Shoot culture was established for at least two subcultures without loss of vigor. From a single cotyledonary node, about 16–18 shoots were obtained in 60 days. Shoots formed *in vitro* were rooted on full-strength MS medium supplemented with 1.0 μM IBA. Plantlets were successfully acclimated, established in soil, and transferred to a nursery (Sugla et al. 2007).

MS BM with BAP, kinetin, zeatin, and thidiazuron were tested for induction of multiple shoots from mature tree derived axillary meristems of *P. pinnata*. Sprouting of buds was 64% on medium devoid of PGRs. Incorporation of BA, kinetin, or zeatin was ineffective in enhancing sprouting frequency or induction of multiple shoots. Sprouting was completely suppressed in the presence of thidiazuron. Caulogenic buds appeared in nodal meristems of these explants after withdrawal of thidiazuron. The number of shoot buds was more on explants precultured in higher concentrations. At higher concentrations of this PGRs, a swelling developed at the axil. Multiple shoot primordia appeared and differentiated from this swelling after culturing these explants on MS medium for six passages of 2 weeks each. Shoots were harvested and cultured on 0.45 μM thidiazuron for further proliferation. Primary explants after harvesting of shoots were identified as "stump." Reculturing of stumps on 0.45 μM thidiazuron produced more shoots. Shoots maintained on 0.45 μM thidiazuron elongated and rooted (70%) on growth regulator free medium. Rooted shoots (65%) survived transfer to a sand/soil mixture. Recycling of mature stock to produce a stream of useable shoots for subculturing and eventual stabilization is of great value and can possibly be generalized as an isolation protocol especially for woody species. Repeated proliferation of caulogenic buds from the same origin may also find application in rescue of endangered germplasm (Sujatha and Hazra 2007). Recently an efficient and reproducible mass propagation protocol was developed for raising clonal garden of *P. pinnata* through *in vitro* cotyledonary node culture (Satapathy et al. 2014).

76. *Prunella vulgaris* L., Labiatae.

Prunella vulgaris is a perennial herb distributed in warmer regions of the world. It was regenerated from seedling shoot tips cultured on medium containing selected concentrations and combinations of various PGRs. The highest frequency of multiple shoot regeneration was obtained with 3.0 mg/L BA with 0.1 mg/L IAA. Regenerated shoots obtained from shoot tips readily rooted on media containing IAA, IBA, NAA, or 2,4-D, with medium containing 3.0 mg/L IAA or 3 mg/L IBA being the most effective. Rooted explants transferred to vermiculate and acclimated for 2 weeks could be planted into potting soil and maintained in an environmentally controlled plant growth room (Turker et al. 2009). In another study, half-strength MS medium with 1.5 μM BAP yielded highest number of shoots from shoot tip explants and was superior to full-strength MS medium with same level of BAP. Medium with combination of NAA and BAP favored multiple axillary shoot regeneration accompanied by rooting. Plantlets transferred to field conditions showed 70% survival rate (Rasool et al. 2009).

77. *Prunus amygdalus* Batsch, synonyms *Prunus communis* Fritsch.; *Prunus dulcis* (Muller) D.A. Webb., Rosaceae, almonds.

    Prunus amygdalus (almond) is a small deciduous tree cultivated in the cooler parts of India and elsewhere. An *in vitro* culture scheme has been developed that allows rapid clonal multiplication of shoots starting with excised shoot apexes from flushing buds of almond cultivar, Ferragnes. Up to 55% of these shoots could then be rooted *in vitro* for establishment in the soil. After initial three to four subcultures on media allowing slow growth, shoots were placed on MS medium with 0.9% agar, 0.7 mg/L BAP, and 0.01 mg/L NAA. Shoot multiplication rates of six could be obtained with 20-day periods of subculture continued for at least 24 months. At any points, these shoots could be elongated by placing them on identical medium, lowering the BAP (0.2 mg/L) and omitting NAA. Rooting was induced quickly in the dark in about 55% of the microcuttings using the medium of Bourgin and Nitsch with only the macronutrients reduced to half, but containing 0.9% agar and 1 mg/L NAA or 1 mg/L IBA. Further proliferation of roots was successfully achieved in the liquid medium in the absence of any added auxin; sterile vermiculite served as the support (Rugini and Verma 1983). In another study, the effect of zygotic embryo isolated from mature seeds was investigated. MS medium containing 30 g/L sucrose, 1.0 mg/L, and 7 g/L agar resulted in multiple shoot initiation. The best results for new shoot production were obtained from MS medium supplemented with 1 mg/L BA. The rooting was achieved in half-strength MS medium supplemented with 8 mg/L IAA. The *in vitro* raised plants were acclimatized and successfully transplanted to the field (Isikalan et al. 2008).

78. *Psidium guajava* Linn., Myrtaceae, guava.

    Psidium guajava is an arborescent shrub or small tree. It is indigenous to Mexico and is cultivated in most of the tropical countries for its edible fruits. This plant is difficult to propagate using the conventional asexual techniques, with most growers using seedling planting stock. However, these seedlings are highly variable. In a report, various concentrations of BAP and thidiazuron were used to regenerate and micropropagate the plants. Explants from greenhouse-grown plants with BAP (2 mg/L) gave 3.7 shoots per single node cutting with an average length of 0.7 cm. Explants from *in vitro* harvested axillary buds exhibited the largest number of shoots (3.9 per explant) with BAP (0.25 mg/L). Generally, lower concentrations of BAP gave fewer but longer shoots. The highest number of roots per shoot was obtained with 1 mg/L IBA. A protocol for producing clonal plants over 8 weeks was described (Ali et al. 2003).

    The introduction of new cultivars of *P. guajava* deserves its mass propagation, which can only be satisfied by micropropagation. However, the conventional micropropagation was stopped as it was economically not efficient due to the use of gelling agents and the high number of manual operations. Efforts were made to reduce production costs by exclusion of gelling in culture media, assessing temporary immersion systems in the *in vitro* multiplication of guava. The study concluded that specific immersion culture favored the multiplication in growth and proliferation of shoots of guava (Vilchez and Albany 2014).

79. *Pterocarpus marsupium* Roxb., Fabaceae, Indian kino tree (see Section 6.5.1).

80. *Punica granatum* L., Punicaceae, pomegranate.

    Punica granatum (pomegranate) is a shrub or small tree. It is cultivated for its fruit in many countries such as Iran, Afghanistan, and India. The conventional method of propagation of pomegranate is time-consuming and tiresome, and it does not ensure disease-free and healthy plants. A protocol to get healthy and well-formed plants from nodal explants of pomegranate (cv. Bhagava) has been reported (Patil et al. 2011b). In another study, an efficient *in vitro* propagation using shoot tips and nodal explants was described. WPM proved to be more efficient medium compared to MS. The best concentration of kinetin was 9.2 μM, resulting in the highest number of nodes, shoot length, and leaf number. Half-strength WPM medium supplemented with 5.4 μM NAA was most effective for rooting of shoots. Rooted plantlets were successfully acclimatized and transferred to the soil (Kaji et al. 2013). Callus induction and

plant regeneration in *P. granatum* from leaf explants has also been reported (Bonyanpour and Khosh-Khui 2013).

81. *Salacia oblonga* Wall. ex Wight. & Arn., Celastraceae (see Section 6.5.1).
82. *Salvia officinalis* L., Lamiaceae.

    Salvia officinalis is an evergreen perennial culinary shrub commonly seen all over the Mediterranean and southeastern Europe (Balkan) regions. The cultivated forms of this plant species include purple sage and red sage. In a recent study, nodal segments from *in vitro* seedlings were used to establish a micropropagation system. The maximum shoot proliferation was obtained when explants were cultured on MS medium supplemented with 0.5 mg/L BAP and 0.1 mg/L IAA. Then the shoots were rooted and successfully adapted in *ex vitro* conditions (Petrova et al. 2015). In another study, the content of carnosic acid and carnosol (anti-DM and antioxidant compounds) in *in vitro* cultures of *S. officinalis* was determined. Production of these compounds was found to be closely related to shoot differentiation; the highest yield was achieved in shoots of 10-week-old micropropagated plants (Grzegorczyk et al. 2005). The effect of triacontanol on micropropagation and production of diterpenoids (carnosol and carnosic acid) in liquid shoot cultures of *S. officinals* was reported in another study. Shoot proliferation and diterpenoid content increased when triacontanol (5, 10 or 20 µg/L) was added to the liquid medium (Grzegorczyk and Wysokinska 2008). An image of tissue-cultured plantlets of *S. officinalis* is shown in Figure 6.5.
83. *Scoparia dulcis* L., Scrophuilariaceae, sweet broom weed.

    Scoparia dulcis is an erect or ascendingly leafy perennial herb. It is widely distributed in many tropical countries. It is conventionally propagated by vegetative cuttings. However, due to nonjudicial collection of this plant species from natural resources, this plant population is decreasing. An efficient method for micropropagation of this important medicinal herb was

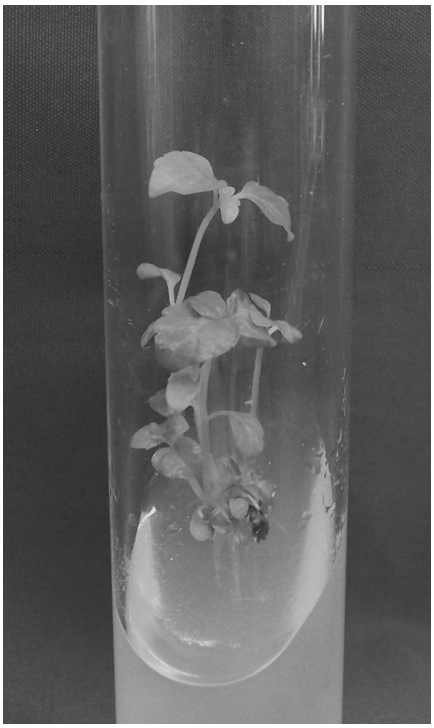

FIGURE 6.5 Tissue-cultured plantlets of *Salvia officinalis*. (Photo courtesy of Dr. Sadhana Yadav and Prof. Usha Mukundan.)

established from shoot tips and nodal segments. Shoot tips and nodal segments were cultured in MS medium supplemented with different concentrations of cytokinins for multiple shoot induction. The highest number of shoots per explant was recorded on the MS medium supplemented with 1 mg/L BAP from nodal segments after 8 weeks of culture. The highest number of roots per shoot was observed in the MS medium containing 0.5 mg/L NAA. The well-rooted plantlets were acclimatized and successfully transferred to natural field condition where about 80% of plants survived (Rashid et al. 2009). In another study also, large-scale micropropagation was achieved from leaf and node explants on MS medium supplemented with 2.4-D and BAP. The maximum numbers of shoots were produced in the combination of BAP and IAA (1.5 mg/L each). Transfer of roots into MS solid and liquid medium favored rooting in 4 weeks and rooted plants were hardened and established with 70–85% success (Sakthi and Mohan 2012).

84. *Semecarpus anacardium* L.F., Anacardiaceae, Ballatak or Bhilwa.

Semecarpus anacardium is a tree with grey bark. Poor seed viability of *S. anacardium* limits the conventional propagation practice. Proliferation of shoots from axillary meristem was achieved in semisolid WPM supplemented with BAP 4.44 μM and kinetin 4.64 μM. Factors including culture vessels, gelling agents, and antioxidants were identified and optimized for proliferation and growth of shoots *in vitro.* Cotton-plugged culture vessels were more favorable. Phytagel 0.2% as a gelling agent and activated charcoal (0.2%) as an antioxidant were superior to other agents and antioxidants tested. All the shoots rooted in half-strength WPM (liquid medium) with IBA 2.46 μM. Rooted shoots survived (91%) in the soil:sand 1:1 mixture. *Ex vitro* rooting of shoots and hardening of plants were achieved in 80% of the explants in the soil (Panda and Hazra 2010).

In another report, three different morphogenic responses (caulogenesis, direct somatic embryogenesis, and callusing) were noted in cotyledon explants of *S. anacardium* cultured in WPM containing thidiazuron. Thidiazuron induced organogenic as well as embryogenic responses. The organogenic buds differentiated to shoots and the embryogenic mass gave rise to globular embryos that differentiated up to cotyledon-stage embryos on repeated culture in growth regulator free WPM containing 0.2% activated charcoal after the removal of thidiazuron. Elongated shoots rooted in half-strength liquid WPM with 2.46 μM IBA. Plants were successfully acclimatized and transferred to soil. The embryogenic mass produced somatic embryos on repeated culture in charcoal incorporated growth regulator free medium. Morphogenic callus formation from the cotyledon explants was also noted. This callus on repeated culture in WPM with charcoal differentiated into somatic embryos. Repetitive somatic embryogenesis was evident from direct and indirectly formed primary embryos (Panda and Hazra 2012).

In another study, shoot culture derived nodal explants were cultured in WPM supplemented with thidiazuron. Meristems swelled to form meristematic mass in higher concentrations of thidiazuron. Swelling of meristem was attributed to the proliferation of meristematic cells. Development of shoots from meristematic mass on withdrawal of thidiazuron in culture medium indicated the inhibitory influence of thidiazuron on differentiation of buds to form shoots. All shoots rooted in the medium with IBA (2.46 μM). Plantlets survived on transfer to sand : soil (1:1) mixture and acclimatized. This is the first report on micropropagation of *S. anacardium* from seedling derived nodal buds using thidiazuron (Panda and Hazra 2012a).

85. *Silybium marianum* (L.) Gaertn, Asteraceae, Milk thistle.

Silybum marianum is an erect, shining annual or biennial. It is a wild medicinal plant with therapeutically promising hepatoprotective and anti-DM properties. *In vitro* propagation of this medicinal crop was achieved using explants from seedlings produced *in vitro* from seeds. Sterile seeds were inoculated on the surface of hormone-free MS medium until full germination occurred. MS medium supplemented with 0.5 mg/L kinetin and 0.1 mg/L NAA was used for multiplication of mother stock obtained from developed seedlings. Proliferation was experimented with different levels of kinetin, BA, or 2-ip. The highest proliferation of *S. marianum* was obtained when BA and 2-ip were used at 2.0 and 0.4 mg/L, respectively. Kinetin gave the highest proliferation at 1.6 mg/L. Rooting was experimented at different levels of IBA, IAA,

and NAA. The highest root number (4.0) and length (6.14 cm) was achieved at 1.0 mg/L NAA, and no roots were shown on MS media supplemented with IAA or IBA. Rooted transplants were acclimatized *ex vitro* successfully with a 70% survival rate (Al-Hawamdeh et al. 2014).

In a recent study, a protocol for initiation of callus and shoot cultures from leaves and shoot tips explants of different silybium genotypes collected from different locations in Egypt was established. Callus cultures were initiated from leaves explants and exposed to different concentrations of the precursor (coniferyl alcohol). Shoot cultures were initiated from shoot tips explants. The optimum medium for growth and maintenance of friable callus was MS medium supplemented with 0.25 mg/L 2,4-D + 0.25 mg/L kinetin. The best medium for proliferation of a high number of shoots was MS medium with 0.25 mg/L each of BA and NAA. Coniferyl alcohol (30 μM) caused an increase in accumulation of silymarin contents in most callus cultures. SDS–PAGE of different *Silybium* shoots revealed that the protein profiles of *in vitro* produced plantlets were similar to their control (Rady et al. 2014).

In another study, *in vitro* production of silymarin was experimented at different concentrations of growth regulators kinetin, BA, or 2-ip and carbon sources (glucose, fructose, and sucrose). *In vitro* grown *S. marianum* on MS medium supplemented with 1.6 mg/L kinetin and 0.1 mg/L NAA gave the highest silymarin content of 0.84% silybin and 0.49% silydanin as compared with cultures grown on hormone-free MS medium that contained 0.36% silybin and 0.30% silydanin. The *in vivo* (wild) grown shoots of *S. marianum* gave 1.07% for silybin and 0.46% for sildyanin. Among carbon sources, glucose at 45 g/L gave 1.6% of silymarin content. Results indicated a significant use of *in vitro* grown cultures for silymarin production (Al-Hawamdeh et al. 2013).

Hairy root cultures of *S. marianum* were established using cotyledons as explants. Hairy roots were induced by inoculation of explants with *A. rhizogenes* strain A4. Hairy roots were formed in high frequency on wounded regions of the young (3 weeks old) leaves (Bekheet et al. 2013).

86. *Smallanthus sonchifolius* (Poepp. & Endl.) Robinson, synonym: *Polymnia sonchifolia* Asteraceae, yacon.

Smallanthus sonchifolius is a perennial herb with a root system composed of 4–20 edible tubers. A report showed that for medium-term conservation of *S. sonchifolius* under *in vitro* slow-growth conditions, half-strength MS medium and media supplemented with 10 or 20 g/L mannitol or sorbitol can be satisfactorily used (Skalova et al. 2012). In a recent study, axillary and apical buds (explants) were cultured in basal MS medium supplemented with BAP, agar, and so on. Cultures were transferred with a growth chamber and after 2 weeks small buds were observed. For rooting, the small plantlets were cultured in the BM with IAA. The rooted plantlets were transferred to the greenhouse (Buitrago-Hurtado et al. 2014).

87. *Stevia rebaudiana* (Bert.) Bertoni, Asteraceae, Stevia, sweet leaf of Paraguay.

Stevia rebaudiana is a perennial semishrub native to Paraguay. Now, it is commercially cultivated in many countries. *Stevia rebaudiana* produces sweet steviol glycosides. It has been used to sweeten tea for centuries dating back to the Guarani Indians of South America. Stevia (*S. rebaudiana*) is native to the valley of the Rio Monday in highlands of North-eastern Paraguay. It has been introduced as a crop in a number of countries. *Stevia rebaudiana* is a semihumid subtropical plant that can be grown easily like any other vegetable crop (Madan et al. 2010).

Several *in vitro* propagation studies and production of steviosides (anti-DM compounds) were carried out on this plant (Madan et al. 2010). Somatic embryos from leaf explants were induced on a medium supplemented with the cytokinin N-(4-Pyridyl)-N'-phenylurea (4-PU). Several cell lines were obtained from a predominantly diploid cell suspension culture of *S. rebaudiana*. Somatic embryogenesis occurred from floret explants cultured on MS medium supplemented with 2,4-D (9.05 and 18.19 μ M) and kinetin (0–9.2 μ M). A multiple shoot culture was induced from nodal segments on MS medium containing half concentration of macroelements, 1% sucrose, and NAA (0.01 mg/L).

The composition and content of steviosides (anti-DM compounds) in *in vitro* cultures were investigated. A comparative analysis of production of these compounds in intact plants, and

in vitro produced plant tissues and cells was conducted. Qualitative composition of steviosides in *in vitro* plants was found to be identical to that of intact plants, but their content in the *in vitro* propagated plant materials appeared to be about five or six times lower. Nondifferentiated cell cultures, such as callus and cell suspension, were shown to synthesize only minor amounts of steviosides, and their content varied greatly during the growth cycle of the culture. No correlation between the steviosides content in organs of the donor plants and that in the cell cultures obtained was found. Factors determining plant cultivation conditions and influencing the accumulation of both fresh and dry cell biomass were not able to completely induce steviosides synthesis in nondifferentiated cell cultures. This process was restored only after the appearance of morphogenic structures and shoot formation. Its shoots were cultivated in the roller bioreactor to study the production of steviosides. It was found that, owing to the highly favorable conditions of shoot cultivation created in such an apparatus, the intensity of shoot growth and steviosides production appeared to be 1.5–2.0 times higher than those of the shoots grown in tubes. The data obtained suggest that the enhanced steviosides production is due to the differentiation of chlorenchyma cells and formation of specific subcellular structures for steviosides to be accumulated (Madan et al. 2010).

Twofold elevation of the concentration of mineral salts considerably stimulated growth of the shoots in the roller bioreactor, whereas the content of the steviosides in their leaves decreased. Addition of 0.1 mg/L 6-benzylaminopurine (BA or BAP) together with NAA resulted in a 1.5-fold increase in the number of shoots. However, the shoots grown on the BA supplied medium displayed a strong inhibition of the development of their root system. When the medium was supplied with gibberellic acid, lengthening of shoots and roots of *S. rebaudiana* was observed. All the PGRs used strongly inhibited production of steviosides. The changes in nutrition medium composition had practically no effect on the ratio of individual glycosides in *S. rebaudiana* leaves (Madan et al. 2010). Thus it appears that intact field-grown plants are better for the production of steviosides than *in vitro* cultured cells; however, tissue culture propagation can produce bulk plantlets for cultivation in the field. Image of tissue-cultured plantlets of *S. rebaudiana* is shown in Figure 6.6.

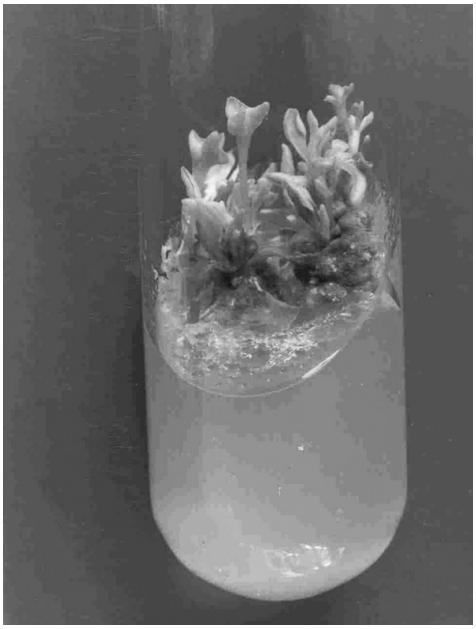

FIGURE 6.6 Tissue-cultured plantlets of *Stevia rebaudiana*. (Photo courtesy of Dr. Latha Sivaram and Prof. Usha Mukundan.)

88. *Syzygium cumini* (L.) Skeels., Synonym: *Eugenia jambolana* (Lam.) DC., Myrtaceae, black berry, black plum.

    Syzygium cumini is a tree with glabrous branches and distributed in South Asia, Malaysia, Australia, and so on. Multiple shoots were obtained from nodal and shoot tip segments of 10- to 15-day-old seedlings of *S. cuminii* on MS revised medium supplemented with BA (0.23–8.90 M) singly or in combination with NAA, IAA, or IBA. Excised shoots were placed for root induction on MS medium containing NAA and/or IBA and then transferred to MS BM to form complete plantlets. The regenerated plantlets have been acclimatized and successfully transferred to the soil (Yadav et al. 1990). In another study, multiple shoots were induced from mature nodal explants cultured on WPM supplemented with combinations of benzyl adenine, kinetin, and NAA. The shoots were rooted in WPM supplemented with IBA. *Ex vitro* rooting was also successful in this species. Plantlets were established with 80% survival rate in the field (Remashree et al. 2007). In a recent study, immature seeds of this plant produced seedlings after a week when cultured on MS medium supplemented with BA and NAA. The seedling explants were induced to form callus on MS medium containing 2,4-D with BA. The calli subsequently produced shoot buds when subcultured on MS medium supplemented with BAP. Up to 85% of cultures showed shoot formation with about 25 shoots/culture from callus cultured on medium containing 1.0 mg/L of BA along with 0.05 mg/L of NAA. Adventitious shoots showed root initiation when subcultured on MS medium containing IBA. About 75% of rooted shoots have successfully been established to soil (Yadav et al. 2014).

89. *Syzygium malaccense* (L) Merr. & Perr, Myrtaceae, wax jambu, malay-apple, rose apple.

    S*zygium malaccense* is a tropical evergreen tree with a cone-shaped crown. It a native of Malaysia and is widely planted through the tropics for its edible fruits or/and as an ornamental plant. Recently vegetative propagation of five cultivars of Malay apple in Ternate Island was standardized. Hardwood cuttings of Malay apple with topsoil + sand and NAA (1,000 ppm) had the best performance in producing shoots and roots for cuttings of this plant in a short period. This observation is useful in the conservation and vegetative propagation of this plant (Ryadin et al. 2014).

90. *Tamarindus indica* L., Fabaceae.

    Tamarindus indica is a multipurpose tropical tree species with medicinal properties, but remains unimproved and neglected. It is found in India, Africa, and so on. Tissue culture has the potential to propagate elite genotypes of trees. Tamarind is economically important for its edible fruits and for sustainable development of wasteland due to its hardy nature and adaptability to various agroclimatic conditions.

    Optimal culture conditions for high-frequency plant regeneration from excised cotyledons of *T. indica* were established. Maximum shoot bud differentiation (100%) occurred when the adaxial surface of the entire cotyledon was in contact with MS medium containing BAP. On MS alone only roots were formed. Shoot or root formation was confined to nodal tissue at the top of the notch present on the adaxial surface at the proximal end of the cotyledon. Shoots were rooted on MS with 5.7 μM IAA. Regenerated plants were established in the soil with 70% success rate (Jaiswal and Gulati 1991). In another study, direct differentiation of shoot buds from hypocotyl segments of 12-day-old seedlings of *T. indica* was obtained on MS medium with or without growth regulators. The highest regeneration (66%) and the maximum number of shoots (3–4) per explant were obtained from the explants on MS medium containing 6-benzylaminopurine (BA or BAP). Maximum roots per shoot were produced on medium containing IBA. The resulting plantlets were hardened and transferred to soil in pots, where 75% of them survived and resumed growth (Jaiswal Sonia et al. 1998).

    In another study, micropropagation of *T. indica* was achieved through adventitious shoots or axillary bud proliferation from nodes of adult trees (10–15 years old) on MS medium with BA and kinetin. Proliferation of shoots continued on the medium with reduced levels of growth regulators and vitamins. Rooting was obtained with IBA. Nodal explants from young shoots

responded better in comparison with the explants from mature shoots in the early stages of establishment of cultures and rooting of shoots (Farooq and Farooq 2003).

In another study, an attempt was made to induce meristematic activity in seedling explants. Seedlings were germinated in medium with or without thidiazuron. This growth regulator restricted the differentiation of the apical meristem to form shoots. It triggered proliferation of the meristematic tissue at the cotyledonary node, and a large number of meristematic buds appeared in a radial pattern around the node. The meristematic activity extended to the junction of the epicotyl and hypocotyl, giving rise to buds in the form of protuberances in all sides of the junction. These buds differentiated to form shoot primordia and subsequently to shoots in medium devoid of growth regulators. Plants developed by micrografting of these shoots on seedling-derived rootstocks survived in soil (Mehta et al. 2004).

91. *Tectona grandis* L., Lamiaceae, teak.

Tectona grandis is a large tree yielding valuable timber. Multiple shoots of high quality were produced *in vitro* from nodal explants of *T. grandis*. Shoots were obtained within 4 weeks of culture on MS medium modified by 50% reduction in NH_4NO_3 concentration, supplemented with BAP (1.5 mg/L), IBA (0.01 mg/L), and gibberellic acid (0.1 mg/L). One hundred percent of shoots rooted on modified MS medium containing IBA (0.5 mg/L) and putrescine (160 mg/L). Putrescine promoted both strong and highly ramified roots and fast-growing shoots during the rooting phase, conditioning the plantlets for a good survival rate and quality. Plantlets were acclimatized and transferred to greenhouse where they survived (Gyes et al. 2007).

In another study, a method for rapid *in vitro* propagation was developed using nodal segments, shoot tips, and cotyledonary nodes from seedlings. MS medium supplemented with thidiazuron (2.5 μM) induced direct shoot formation and growth. The regeneration frequency enhanced in the third subculture passage on the medium supplemented with BA. Successful *in vitro* rooting was induced from cut end of the microshoots when placed on MS with different concentrations of IBA and NAA. The regenerated shoots with developed root system were successfully acclimatized and established under greenhouse conditions (Kozgar and Shahzad 2012). *In vitro* propagation of shoot and callus culture of *T. grandis* from leaf and node explants was also reported. The study concluded that the addition of 3.0 mg/L BAP can be used for the prominent growth of *T. grandis* in tissue culture (Srinivasan et al. 2012). In a recent study, multiple shoot formation was induced from excised terminal buds of 100-year-old elite tree on a defined medium supplemented with BAP and kinetin either singly or in various combinations. One hundred percent of shoot regeneration frequency was obtained from nodal segments on MS medium fortified with 2 mg/L IBA and 1.5 mg/L IAA. Regenerated plantlets with developed shoot and roots were hardened and successfully transferred to soil (Sreedevi and Damodharam 2015).

92. *Tephrosia purpuria* (L.) Pers, Fabaceae.

Tephrosia purpurea is a highly branched perennial herb found in the tropical regions of the world. It is a common wasteland weed with important medicinal properties. In an investigation, *in vitro* callus cultures of root of *T. purpurea* were developed and maintained on MS medium supplemented with 2,4-D (4.52 μM), IAA (28.5 μM), and kinetin (9.29 μM) for 5 months (Mujeeb et al. 2012).

93. *Terminalia chebula* Retz. , Combretaceae, ink-nut tree.

Terminalia chebula is an evergreen flowering tree found in many Asian countries. A protocol for multiple shoot induction from cotyledonary node explants of *T. chebula* has been developed. Germination of embryos was obtained on MS medium supplemented with gibberellic acid. Maximum number of shoots was obtained on half-strength MS + 3 mg/L gibberellic acid + 10 mg/L IBA + 100 mg/L BAP after 4 weeks of culture. When the cotyledonary nodes along with the axillary shoot buds were allowed to grow in the same medium, up to 19.2 shoots were obtained after 8–9 weeks. Best rooting was observed when shoots were excised and transferred to half-strength MS medium containing 10 mg/L IBA + 1% mannitol and 1.5% sucrose.

Survival of rooted plants *in vivo* was low (35–40%) when these plants were directly transferred to soil in glasshouse. However, transfer to soil with MS nutrients and 10 mg/L IBA in culture room for a minimum duration of 2 weeks increased the survival percentage of plants to 100% (Barampuram et al. 2003).

94. *Tinospora cordifolia* (Willd.) Miers. ex Hook. f. & Thoms., Menispermaceae, guduchi.

Tinospora cordifolia is a large deciduous climbing shrub. It is an important medicinal plant that grows as a climber on various trees. The nodal explants of *T. cordifolia* were regenerated *in vitro*. The explants was surface sterilized with 70% ethanol for 1 min and 0.1% mercuric chloride for 5 min and cultured on nutrient medium containing salts of MS medium, vitamins, and various concentrations of combinations of BAP and NAA. The nodal segments exhibited basal callusing after 2 weeks and shoots emerged from the axillary bud after 3 weeks. The emerging shoots were subcultured to a fresh medium with 1 ppm NAA and 2 ppm BAP. After 2 weeks of subculture, shoots emerged from the single shoot along with root. The subculture of the callus on medium containing BAP (2 ppm) and NAA (1 ppm) resulted in only shoot differentiation (Tabassum and Nag 2008).

In callus induction studies from leaf explants, the best results were obtained with 2,4-D alone or in combination with kinetin. The calli thus obtained grew in size with time in culture medium, but failed to differentiate. Shoot induction from nodal explants was best achieved on MS BM with kinetin (8 μM or 12 μM) and BAP (2 μM) in combination. Rhizogenesis on regenerated shoots was induced by transferring them into medium fortified with NAA at 8 μM (Bhalerao et al. 2013). In a recent study, the successful protocol for *in vitro* propagation was achieved using nodal and apical shoot tip segments as explants. *In vitro* plantlets were raised on MS medium containing BAP in combination with IAA. The regeneration protocol provides an important method for micropropagation of this plant (Tupe and Pandhure 2015). In another study, a protocol was established for rapid clonal propagation of this plant through *in vitro* culture using nodal explants. Best shoot induction was observed on MS medium with 4.36 μM kinetin. The elongated shootlets were transferred to half-strength MS medium and 6.43 μM IBA with 3% sucrose for root production. Rooted plantlets were transplanted *ex vitro* (Sivakumar et al. 2014). An image of tissue-cultured plantlets of *T. cordifolia* is shown in Figure 6.7.

95. *Trigonella foenum-graecum* L., Leguminosae, fenugreek.

Trigonella foenum-graecum is an annual aromatic herb and important vegetable, spice, and medicinal legume used as fresh and dried leaves and seeds in many parts of the world. It is widely cultivated.

Many studies using cell suspension and callus culture emphasized increased production of protein and economically important metabolites such as trigonelline, sapogenin, isoflavonoid pterocarpans, diosgenin, gitogenin and tigogenin from callus, leaves, stems and roots explants. Trigonelline and diosgenin are known anti-DM compounds. Plant tissue culture studies have emphasized use of callus, cotyloden, hypocotyls and shoot tip epicotyls, apical meristem, cotyledon node, and cotyledon leaf explants. Most of the researchers experienced difficulty in *in vitro* rooting. Protoplast studies have also been reported using leaf mesophyll and root apices. Leaf mesophyl protoplasts could be converted to leafy shoots, whereas root apices protoplasts gave cell colonies or roots only. Genetic transformation studies using *A. rhizogenes* and *A. tumefaciens* are at initial stages. There is a single report on molecular characterization of fenugreek from India using 10 RAPD and ISSR primers that revealed interspecific polymorphism (Aasim et al. 2014).

A study presents an efficient shoot regeneration protocols from 8- to 10-day old *in vitro* grown cotyledon node explants cultured on MS medium supplemented with PGRs. All culture mediums were solidified with 0.22% gelrite. Maximum shoot regeneration and number of shoots per explant were recorded on MS medium supplemented with thidiazuran with or without IBA. Maximum of about 22 shoots per explant were recorded on MS medium containing 0.4 mg/L thidiazuran. Presence of auxins in the culture medium positively increased the

FIGURE 6.7 Tissue-cultured plantlets of *Tinospora cordifolia*. (Photo courtesy of Dr. Rahul Gavhane and Prof. Usha Mukundan.)

mean shoot length. Regenerated shoots were transferred to rooting media containing 0.1–1.0 mg/L IBA or NAA (Aasim et al. 2010). Another study reported *in vitro* callus induction from 8- to 20-day-old *in vitro* grown cotyledons node explants. The maximum callus formation was observed in the MS medium containing 2.0 mg/L NAA (El-Nour et al. 2013). *In vitro* callus induction from cotyledons and hypocotyls explants supplemented with various plant hormones was also reported (Elaleem et al. 2014).

96. *Vaccinium angustifolium* Ait., synonym: *V. britonnii* Porter ex C. Bicknell., Ericaceae, lowbush blueberry.

    Vaccinium angustifolium (lowbush blueberry) is an erect low-growing shrub that occurs in North America and is extensively harvested from wild as well as cultivated plants. Cultures of three lowbush blueberry clones collected from natural stands in Newfoundland were established *in vitro* on a modified cranberry (*V. macrocarpon*) tissue culture medium containing zeatin (5 μM) or 2-ip (10 μM). Best total shoot proliferation was obtained when basal nodal segments were cultured in the medium supplemented with 2–4 μM zeatin. In another experiment, nodal explants were more productive than shoot tips. Shoots growing for more than 12 weeks on media that contained more than 4 μM zeatin occasionally produced adventitious shoot masses, which appeared to arise from dense calli growing at the base of the shoots in the medium. The lower concentration of sucrose and lower irradiance improved shoot proliferation with respect to vigor compared to the control treatments. In all experiments with subculture, there was an increase in shoot multiplication rate for all clones. A 50- to 100-fold multiplication rate was obtained every 3 months with the clones (Debnath 2004).

    In another study, cultures of cultivar Fundy and two wild clones were established *in vitro* on a gelled modified cranberry BM containing 5 μM zeatin or 10 μM 2-ip. Multiple shoots were obtained within 8 weeks by transferring zeatin-induced shoots from the gelled BM to a

bioreactor containing liquid BM with 1–4 μM zeatin. Genotypes differed significantly with respect to multiplication rate in liquid and gelled BM containing 1 μM zeatin. With subculture, there was an increase of shoot multiplication rate for all genotypes. Bioreactor proliferated and gelled medium proliferated shoots were treated with 39.4 mM IBA powder, rooted in a 2 peat:1 perlite (v/v) medium, plantlets acclimatized, and eventually established in the greenhouse with 64–74% rooting of microshoots and 90–99% survival rate of rooted shoots. Results obtained suggested the possibility of large-scale multiplication of lowbush blueberry shoots in bioreactors (Debnath 2009).

97. *Zingiber officinale* Rosc, Zingiberaceae, ginger.

Zingiber officinale is a rhizomatous biennial herb widely cultivated in tropical Asia. The rhizome is a valued spice and traditional medicine. The rhizomes are the planting materials in the conventional propagation of *Z. officinale*; it has a low multiplication rate. *In vitro* propagation of ginger through direct organogenesis has been reviewed (Thayamini 2013). A protocol for *in vitro* propagation of *Z. officinale* using sprouting buds was developed. Sprouting buds were sterilized and cultured on MS medium supplemented with different growth regulators. Augmentation of MS medium with 4.5 mg/L BAP recorded the highest percentage of shootlets multiplication. Shootlets were highly rooted on half-strength of B_5 medium supplemented with 1.0 mg/L NAA. The maximum percentage of acclimatization, hardening and rhizomes production of *in vitro* derived plants in a greenhouse was 80–100% (Abbas et al. 2011). A study was conducted to select the suitable explants size for initial culture establishment of ginger and their subsequent plant regeneration. Results revealed that explants of 0.5 cm length exhibited a high rate of survival and morphogenic response among the explants sizes tested (Sathyagowri and Seran 2011).

The *in vitro* propagation via direct organogenesis from rhizome buds or shoots tips of ginger has been reviewed recently (Kadambari and Bhawna 2014). In contrast to field gene bank, *in vitro* repositories offer safety from environmental vagaries and diseases.

98. *Ziziphus jujube* Mill., Rhamnaceae, ilanthai pazham.

Ziziphus jujube is a small fruit tree that occurs in tropical Asia, Europe, Australia, and so on. *In vitro*, rapid proliferation and rooting of *Z. jujube* were studied. The number and length of shoots regenerated varied significantly depending on the types and concentrations of PGRs. The highest number of new microshoots per explant (5.75) was obtained on Gambourg's B5 modification medium supplemented with 0.6 mg/L BAP + 0.2 mg/L kinetin. The gibberellic acid in combination with BAP promoted shoot elongation. Half-strength solidified MS media with and without IAA induced root, but a concentration of 0.2 mg/L IAA proved to be the best for rooting. *In vitro* rooted plantlets were successfully acclimatized, with 80% survival rate in plastic pots containing garden soil, sand, and peat moss (1:1:1) (Melyan et al. 2014). In a recent study, the effects of different growth regulator combinations, carbon sources (sucrose, glucose and fructose), and silver nitrate concentrations on *in vitro* propagation of two selected jujube genotypes were investigated. The highest percentage of explants that produced shoots (100 %) and the number of shoots per explant (5.5) were obtained on MS medium supplemented with 0.1 mg/L thidiazuron + 0.5 mg/L BAP + 0.1 mg/L IBA + 0.3 mg/L gibberellic acid. Different amounts of carbon sources and silver nitrate did not increase the percentage of explant that developed into shoots and the number of shoots per explant. The highest rooting percentage (76.7 %) was obtained on MS and half-strength MS media supplemented with 2.0 mg/L IBA (Yildirim et al. 2015).

In another study, *in vitro* clonal propagation methods for three different cultivars of jujube were standardized from nodal segment explants. One of the cultivars slightly differed from the other two in the requirement of growth regulators for optimum *in vitro* growth. The best medium for the *in vitro* establishment of two curtivars (Comethry and Balady) was MS medium containing 0.05 mg/L NAA + 2 mg/L 2-ip. Rooting could be produced from shoots cultured on MS medium containing IBA or IBA + NAA. Rooted plantlets were successfully acclimatized in the greenhouse conditions (Soliman and Hegazi 2013).

99. *Ziziphus spina-christi* (L.) Willd, Rhamnaceae, Christ's thorn jujube.

    Ziziphus spina-christi is a deciduous shrub or small tree occurring in warm temperature and tropical regions of the world. It is cultivated for its edible fruit, honey production, medicinal property, and so on. Since it is a cross-pollinated tree, a wide range of genetic variability exists in nature. Vegetative propagation (macropropagation) and micropropagation studies were carried out on *Z. spina-christi*. A simple and efficient protocol for the colonal micropropagation of this plant has been established using shoot tips and stem nodal segments as explants. The explants were cultured on MS medium with and without growth regulators. The nodal segments and shoot tips isolated from primary cultures were cultured on hormone-free MS medium containing 100 mg/L myo-inositol, 150 mg/L glutamine, and 2–5% sucrose for plant growth and elongation. Explants cultured in higher concentrations of cytokinins and auxin induced callus. Shoots transferred to MS medium containing 10 mg/L IBA were rooted (Sudhersan and Hussain 2003). Studies showed that the best time for explants harvesting was mid summer. In another study, rooting on media containing IBA as well as activated charcoal and disinfection with $Ca(OCl)_2$ at concentrations of 5% for 20 min were found to be the best treatment for tissue culture of nodal segments bearing axillary buds (Assareh and Sardabi 2005). In another report, improved inorganic and organic media constituents for *in vitro* shoot tip multiplication of this plant have been reported (Al-Sulaiman et al. 2010). *In vitro* shoot multiplications were obtained successfully from shoot tips by placing explants into solidified MS medium supplemented with 0.1 mg/L each of NAA, BA, or IAA and kinetin. The shoots rooted best on MS medium supplemented with 1 mg/L IBA. Plantlet survival after transfer to soil was found to be more than 90% (Al-Sulaiman and Barakat 2010). Improving effect of salicylic acid on tissue culture of this plant has been reported. Salicylic acid showed positive effects and good response on callusing, shooting, and rooting of this plant; cultures that received small amounts of salicylic acid were better than those that lack it (Galal 2012).

6.6 Development of Cultivation Conditions/Agrotechniques for Anti-DM Plants

There is a need to develop agrotechnology/cultivation conditions for high-value medicinal plants for providing uniform quality raw materials for the preparation of plant-based drugs. Most of the anti-DM medicinal plants are collected from the wild even today. This could gradually lead to inaccessibility to these medicinal plants, and species extermination due to indiscriminate collection, forest destruction, and so on. In a long run, there is a need to cultivate required medicinal plants under specific growth conditions, to maintain medicinal value and availability of the medicinal plants. Standardization of techniques for cultivation of medicinal plants is very essential. This should include impact of environmental changes on the active ingredients. The cultivation techniques developed for a medicinal plant species in a particular agroclimatic and soil conditions may not be suitable to apply in another agroclimatic zone with different soil conditions. Therefore, agrotechniques have to be developed locally for desired medicinal plants, keeping in view the desired medicinal properties of the candidate medicinal plant.

In cultivation of medicinal plants, insecticides and pesticides should not be used, and the organic cultivation is the recommended method of cultivation. However, fertilizers may be used to some extent, if those do not affect the medicinal value (content of active principles) of the plant. The desired medicinal properties should be determined by phytochemical and pharmacological studies. Since many of the medicinal plants are weed-like plants, these plants can be grown easily in villages without much financial input. Many of the plants produce more medicinally valuable phytochemicals in relatively adverse conditions. These conditions should be established. These plants may not require much fertilizer and watering. However, modern pharmacological and phytochemical yardsticks should be used to determine suitable growth conditions for optimum medicinal value.

6.6.1 Selection of Best Genotypes and Phenotypes

Authentication of botanical identity of herbal drugs including genotypes and chemotypes is also a problem in some cases. Ecotypes and genotypes variations are one of the major hindrances in the development of phytomedicines (refined crude extracts, decoctions, herbal formulations, and so on, with safety and efficacy comparable to the conventional medicine). This can be overcome, to a large extent, by developing agrotechnology (suitable cultivation conditions) for deserving medicinal plants, using the best genotype and phenotype. Appropriate chemotypes and genotypes should be determined with the help of phytochemical and/or pharmacological screening.

Medicinal plants are cultivated in many countries. For example, currently, there are 250 kinds of medicinal plants being cultivated in China, encompassing 33.3 million hectares of farmland (Pan et al. 2013). Agrotechniques have been described in the final report of a project sponsored by Forest Department of Andhra Pradesh, India [This project work was carried out by Foundation for Revitalization of Local Health Traditions, India.], for the cultivation of anti-DM plants such as *A. marmelos* (L.) Correa, *A. indica* A. Juss., *B. diffusa* L., *C. bonduc* (L.) Roxb., *C. fistula* L., *H. isora* Linn., *T. purpuria* (L.) Pers, *T. chebula* Retz, and *T. cordifolia* (Willd.) Miers. ex Hook. f. & Thoms., in selected areas of Andhra Pradesh, India, based on experiments and information collected (Ved et al. 2002). In India, important anti-DM plants with developed agrotechnology include *A. augusta* L. Fabaceae; *A. racemosus* Willd. Liliaceae; *D. bulbifera* L., Dioscoreaceae; *G. sylvestre* R. Br. Asclepiadaceae; *H. indicus* (L.) R. Br., Asclepiadaceae; *P. marsupium* Roxb., Fabaceae; *T. chebula* Retz., Combretaceae; and *T. cordifolia* (Willd.) Miers. ex Hook. f. & Thoms., Menispermaceae (National Medicinal Plant Board 2008). Agrotechnology for plants such as *A. racemosus* Willd., *C. rosus* (L.) G. Don f., *H. indicus* (L.) R. Br., *O. sanctum* Linn., and *P. amarus* Schum & Thonn has been standardized or studied by National Botanic Research Institute (C.S.I.R., Government of India) located in Lucknow, North India. Development of agrotechniques for medicinal plants in different intercropping models with, trees, shrubs, and herbs, adopting the principles of organic farming has been attempted in view of, among other things, limited availability of cultivable land. For, example, a number of experiments has been conducted at National Botanic Research Institute, Lucknow, to study the feasibility of cultivation in different intercropping systems.

However, the above-said development of agrotechniques is not developed keeping in view with anti-DM compounds and/or anti-DM activities. For optimization of medicinal value, the development of agrotechniques should be linked to pharmacological and phytochemical evaluation. Determining suitable cultivation techniques should not be limited to the production of optimum biomass, but it should take care of phytochemical profile and medicinal value. Since in most of the medicinal plants, fuller information on the active principles and toxic compounds, if any, is not available, pharmacological standardization is required in these cases to establish medicinal quality of the plants (Subramoniam, 2003, 2014). Although elucidation of marker compounds has a key role in the standardization of herbal medicine, medicinal value of a plant cannot be established based on marker compounds alone because in many cases the marker compounds are not the major active molecules and the relative amounts of the bioactive compounds may differ due to so many factors. The hindrances in determining the therapeutic value of the anti-DM plants while developing agrotechniques include lack of knowledge on all the active principles and occurrence of more than one important pharmacological property in the same medicinal plant. For the cultivation of plants to be used for anti-DM therapy, anti-DM properties and safety should be given priority.

6.7 Conclusion

Some of the anti-DM plants come under vulnerable or threatened category. These plants are to be conserved and propagated using micropropagation techniques and/or large-scale cultivation for sustainable utilization. In the long run, development of agrotechniques for cultivation using best genotype is required. Although agrotechniques have been developed in some cases, anti-DM compounds and/or anti-DM activity in animal models are not taken into account. There is a need to compare the anti-DM activity of wild plants with those of cultivated plants. This gap remains to be filled. Collection of medicinal plants from the wild is not only not sustainable, but also could vary in efficacy and safety depending

on the place of collection, and so on. It is heartening to note that more than 40 anti-DM plants have anti-DM activity in the edible parts and most of these plants are cultivars. However, it is better to evaluate different chemotypes/genotypes and cultivation techniques to optimize anti-DM activity in these plants. Uniform good quality plant materials are required as per demand for the preparation of crude herbal drug/phytomedicine and polyherbal formulations. Further, for the conventional drug development also, good-quality raw materials are required. This can be achieved by the judicious application of cultivation techniques and biotechnological approaches. Finally, it should be remembered (while developing agro-technology and *in vitro* propagation protocols) that almost all anti-DM plants are endowed with several pharmacological properties including toxic molecules in rare cases.

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References

Aakruti, A. K., Swati, R. D., and Vilasrao, J. K. 2013. Overview of Indian medicinal tree: *Bambusa bambos* (Druce). *Int. Res. J. Pharm*. 4: 52–56.

Aasim, M., Hussain, N., Umer, E. M., Zubair, M., Hussain, S. B., and Saeed, S. 2010. *In vitro* shoot regeneration of fenugreek (*Trigonella foenum-graecum* L.) using different cytokinins. *Afr. J. Biotechnol*. 9: 7174–7179.

Aasim, M., Khawar, K. M., Yalcin, G., and Bakhsh, A. 2014. Current trends in fenugreek biotechnology and approaches towards its improvement. *AJSIH (American Journal of Social Issues and Humanities*), Fenugreek Special Issue, Basu, S. K. and Agoramoorthy, G. (Eds). 128–136.

Abate, N. and Chandalia, M. 2007. Ethnicity type 2 diabetes and migrant Asian Indians. *Indian J. Med. Res*. 125: 251–258.

Abbas, M. S., Taha, H. S., Aly, U. I., El-Shabrawi, H. M., and Gaber, E. I. 2011. *In vitro* propagation of ginger (*Zingiber officinale* Rosco). *J. Genetic Eng. Biotechnol*. 9: 165–172.

Abbasi, N. A., Pervaiz, T., Hafi, I. A., Yaseen, M., and Hussain, A. 2013. Assessing the response of indigenous loquat cultivar Mardan to phytohormones for *in vitro* shoot proliferation and rooting. *J. Zhejiang Univ. Sci. B*. 14: 774–784.

Abdel-Hassan, I. A., Abdel-Barry, J. A., Tariq, M. S. 2000. The hypoglycaemic and antihyperglycaemic effect of *Citrullus colocynthis* fruit aqueous extract in normal and alloxan diabetic rabbits. *J. Ethnopharmocol*. 7: 325–330.

Abdel-Wahab, W. M. 2013. Protective effect of thymoquinone on sodium fluoride-induced hepatotoxicity and oxidative stress in rats. *J. Basic Appl. Zool*. 66: 263–270.

Abdel-Zaher, A. O., Salim, S. Y., Assaf, M. H., and Abdel-Hady, R. H. 2005. Antidiabetic activity and toxicity of *Zizyphus spina-christi* leaves. *J. Ethnopharmacol*. 101: 129–138.

Abdi, G., Hedayat, M., and Modarresi, M. 2013. *In vitro* micropropagation of *Aloe vera*—Impacts on plant growth regulators, media and type of explants. *J. Biol. Environ. Sci*. 7: 19–24.

Abid, S., Lekchiri, A., Mekhfi, H., Ziyyat, A., Legssyer, A., and Aziz, M. 2014. Inhibition of alpha-glucosidase and glucose intestinal absorption by *Thymelaea hirsuta* fractions. *J. Diabetes* 6: 351–354.

Ablat, A., Mohamad, J., Awang, K., Shilpi, J. A., and Arya, A. 2014. Evaluation of antidiabetic and antioxidant properties of *Brucea javanica* seed. *Sci. World J*. 2014(786130): 8.

Abraham, J. and Thomas, T. D. 2015. An efficient shoot regeneration system for medicinally important *Elephantopus scaber* Linn. *Crop Breed. Appl. Biotechnol*. 15: 94–99.

Abudula, R., Jeppesen, P. B., Rolfsen, S. E., Xiao, J., and Hermansen, K. 2004. Rebaudioside A potently stimulates insulin secretion from isolated mouse islets: Studies on the dose-, glucose-, and calcium-dependency. *Metabolism* 53: 1378–1381.

Abudula, R., Matchkov, V. V., Jeppesen, P. B., Nilsson, H., Aalkjaer, C., and Hermansen, K. 2008. Rebaudioside A directly stimulates insulin secretion from pancreatic beta cells: A glucose-dependent action *via* inhibition of ATP-sensitive K-channels. *Diabetes Obes. Metab*. 10: 1074–1085.

AbuKhader, M. M. 2012. Thymoquinone: A promising antidiabetic agent. *Int. J. Diabetes Dev. Ctries*. 32: 65–68.

Adebajo, A. C., Iwalewa, E. O., Obuotor, E. M., Ibikunle, G. F., Omisore, N. O., Adewunmi, C. O., et al. 2008. Pharmacological properties of the extract and some isolated compounds of *Clausena lansium* stem bark: Anti-trichomonal, antidiabetic, anti-inflammatory, hepatoprotective and antioxidant effects. *J. Ethnopharmacol*. 122: 100–109.

Adebajo, A. C., Iwalewa, E. O., Obuotor, E. M., Ibikunle, G. F., Omisore, N. O., Adewunmi, C. O., et al. 2009. Pharmacological properties of the extract and some isolated compounds of *Clausena lansium* stem bark: Anti-trichomonal, antidiabetic, anti-inflammatory, hepatoprotective and antioxidant effects. *J. Ethnopharmacol*. 122: 10–19.

Adejuwon, A. A., Crooks, P. A., Fadhel-Albayati, Z., Miller, A. F., Zito, S. W., and Adeyemi, O. O. 2013. Antihyperglycemic profile of erinidine isolated from *Hunteria umbellata* seed. *Afr. J. Tradit. Complement. Altern. Med*. 10: 189–202.

Adeneye, A. A. and Adeyemi, O. O. 2009. Hypoglycmic effects of the aqueous seed extract of *Hunteria umbellata* in normoglycemic and glucose and nicotine-induced hypoglycemic rats. *Int. J. Appl. Res. Nat. Prod.* 2: 9–18.

Adeneye, A. A., Amole, O. O., and Adeneye, A. K. 2006. The hypoglycemic and hypocholesterolemic activities of the aqueous leaf and seed extracts of *Phyllanthus amarus* in mice. *Fitoterapia* 77: 511–514.

Adewole, S. O. and Caxton-Martins, E. A. 2006. Morphological changes and hypoglycemic effects of *Annona muricata* Linn. (Annonaceae) leaf aqueous extract on pancreatic β-cells of streptozotocin-treated diabetic rats. *Afr. J. Biomed. Res.* 9: 173–180.

Adeyemi, D., Komolafe, O., Adewole, S., Obuotor, E., and Adenowo, T. 2007. Effects of *Annona muricata* (Linn.) on the morphology of pancreatic islet cells of experimentally-induced diabetic Wistar rats. *Int. J. Altern. Med.* 5: 7–16.

Ae-Park, S., Choi, M. S., Cho, S. Y., Seo, J. S., Jung, U. J., Sung, M. K., et al. 2006. Genistein and daidzein modulate hepatic glucose and lipid regulating enzyme activities in C57BL/KsJ-db/db mice. *Life Sci.* 79: 1207–1213.

Affourtit, C. and Brand, M. D. 2006. Stronger control of ATP/ADP by proton leak in pancreatic beta-cells than skeletal muscle mitochondria. *Biochem. J.* 393: 151–159.

Agarwal, M. 2015. Tissue culture of *Momordica charantia* L.: A review. *J. Plant Sci.* 3: 24–32.

Agarwal, V., Sharma, A. K., Upadhyay, A., Singh, G., and Gupta, R. 2012. Hypoglycemic effects of *Citrullus colocynthis* roots. *Acta Pol. Pharm.* 69: 75–79.

Agius, L. 1987. Human liver *in vitro* techniques for metabolic studies. In: *Balliere's Clinical Endocrinology and Metabolism*, Alberti, K., Home, P. and Taylor, R. (Eds). London: Balliere Tindall, 999–1021.

Aguilar-Santamaría, L., Ramírez, G., Nicasio, P., Alegría-Reyes, C., and Herrera-Arellano, A. 2009. Antidiabetic activities of *Tecoma stans* (L.) Juss. ex Kunth. *J. Ethnopharmacol.* 124: 284–288.

Ahad, A., Ganai, A. A., Mujeeb, M., and Siddiqui, W. A. 2014. Ellagic acid, an NF-κB inhibitor, ameliorates renal function in experimental diabetic nephropathy. *Chem. Biol. Interact.* 219: 64–75.

Ahmad, F., Khan, M. M., Rastogi, A. K., Chaubey, M., and Kidwai, J. R. 1991. Effects of epicatechin on cAMP content, insulin release and conversion of proinsulin to insulin in mature and immature rat islets *in vitro*. *Indain J. Exp. Biol.* 29: 516–520.

Ahmad, N. and Anis, M. 2005. *In vitro* mass propagation of *Cucumis sativus* L. from nodal segments. *Turk. J. Bot.* 29: 237–240.

Ahmed, A. B., Rao, A. S., and Rao, M. V. 2009. *In vitro* production of gymnemic acid from *Gymnema sylvestre* (Retz) R. Br. ex Roemer and Schultes through callus culture under abiotic stress conditions. *Methods Mol. Biol.* 547: 93–105.

Ahmed, B., Al-Rehaily, A. J., Al-Howiriny, T. A., El-Sayed, K. A., and Ahmad, M. S. 2003. Scropolioside-D2 and harpagoside-B: Two new iridoid glycosides from *Scrophularia deserti* and their antidiabetic and antiinflammatory activity. *Biol. Pharm. Bull.* 26: 462–467.

Ahmed, I., Adeghate, E., Sharma, A. K., Pallot, D. J., and Singh, J. 1998. Effects of *Momordica charantia* fruit juice on islet morphology in the pancreas of streptozotocin diabetic rats. *Diabetes Res. Clin. Pract.* 40: 145–151.

Ahmed, I., Lutfullah, G., Zamir, R., and Shah, S. T. 2007. In vitro response of various growth regulators on the regeneration of *Bougainvillea spectabilis* Willd. *Suranaree J. Sci. Technol.* 14: 157–162.

Ahmed, N., Faisal, M., and Anis, M. 2013. Role of PGR on *in vitro* shoot propagation in *Cyamopsis tetragonoloba* L. (Taub.): A drought tolerant grain legume. *Rend. Fis. Acc. Lincei* 24: 7–12.

Ahmed, O. M., Moneim, A. A., Yazid, I. A., and Mahmoud, A. M. 2010. Anti-hyperglycemic, anti-hyperlipidemic and antioxidant effects and the probable mechanisms of action of *Ruta graveolens* infusion and reutin in nicotinamide-streptozotocin-induced diabetic rats. *Diabetol. Croat.* 39: 15–35.

Ahmed, S., Lin, H. -C., Nizam, I., Khan, N. A., Lee, S. -H., and Khan, N. U. 2014. A trimeric proanthocyanidin from the bark of *Acacia leucophloea* Willd. *Rec. Nat. Prod.* 8: 294–298.

Ahmed, Z., Chishti, A. M., Johri, R. K., Bhagat, A., Gupta, K. K., and Ram, G. 2009. Antihyperglycemic and antidyslipidemic activity of aqueous extract of *Dioscorea bulbifera* tubers. *Diabetol. Croat.* 38: 63–72.

Ahn, J., Um, M. Y., Lee, H., Jung, C. H., Heo, S. H., and Ha, T. Y. 2013. Eleutheroside E, an active component of *Eleutherococcus senticosus*, ameliorates insulin resistance in type 2 diabetic db/db mice. *Evid. Based Complement. Altern. Med.* 2013: 934183, 9 pages.

Ahrén, B. 2007. DPP-4 inhibitors. *Best Pract. Res. Clin. Endocrinol. Metab.* 21: 517–533.

Ajikumaran, N. S. 2008. Studies on the anti-diabetic properties of a folklore medicinal fern, *Hemionitis arifolia* (Burm.) Moore. PhD Thesis, University of Kerala, India.

Ajikumaran, N. S. and Subramoniam, A. 2005. Indian medicinal plants with anti-diabetes properties. In: *Modern and Alternative Medicine for Diabetes*, Khan, I. A., Khanum, A. and Khan, A. H. (Eds). Hydrabad, India: Ukaaz Publications, 43–193.

Ajikumaran, N. S., Sabulal, B., Radhika, S., Arunkumar, R., and Subramoniam, A. 2014. Promising anti-diabetes mellitus activity of β-amyrin palmitate isolated from *Hemidesmus indicus* roots. *Eur. J. Pharmacol*. 734: 77–82.

Ajila, C. M., Rao, L. J., and Prasada Rao, U. J. S. 2010. Characterization of bioactive compounds from raw and ripe *Mangifera indica* L. fruit peel extracts. *Food Chem. Toxicol*. 48: 3406–3411.

Akanksha, S. A. K. and Maurya, R. 2010. Antihyperglycemic activity of compounds isolated from Indian medicinal plants. *Indian J. Exp. Biol*. 48: 294–298.

Akhtar, M. S., Sajid, S. M., Akhtar, M. S., and Ahmad, M. 2008. Hypoglycemic effect of *Berberis aristata* root, its aqueous and methanolic extracts in normal and alloxan induced diabetic rabbits. *Pharmocologyonline* 2: 845–856.

Akhtar, M. S., Zafar, M., Irfan, H. M., and Bashir, S. 2012. Hypoglycemic effect of a compound herbal formulation (Ziabeen) on blood glucose in normal and alloxan-diabetic rabbits. *Diabetologia Croatica*. 41: 87–94.

Akinmoladun, A. C., Farombi, E. O., and Oguntibeju, O. M. 2014. Antidiabetic botanicals and their potential benefits in the management of diabetes mellitus. In: *Antioxidants-Antidiabetic Agents and Human Health*. Oguntibeju, O. (Ed.). InTech. http://dx.doi.org./10.5772./57339.

Alam, M. R., Rahman, A. B., Moniruzzaman, M., Kadir, M. F., Haque, M. A., Alvi, M. R., et al. 2012. Evaluation of anti-diabetic phytochemicals in *Syzygium cumini* (L.) Skeels (Family: Myrtaceae). *J. Appl. Pharm. Sci*. 2: 94–98.

Alarcon-Aguilar, F. J. and Roman-Ramos, R. 2005. Antidiabetic plants in Mexico and Central America. In: *Traditional Medicines for Modern Times: Antidiabetic Plants,* Amala, S. (Ed.). Boca Raton, FL: CRC Press, Taylor & Francis, 221–224.

Alarcon-Aguilar, F. J., Fortis-Barrera, A., Angeles-Mejia, S., Banderas-Dorantes, T. R., Jasso-Villagomez, E. I., Almanza-Perez, J. C., et al. 2010. Anti-inflammatory and antioxidant effects of a hypoglycemic fructan fraction from *Psacalium peltatum* (H.B.K.) Cass. in streptozotocin-induced diabetes mice. *J. Ethnopharmacol*. 132: 400–407.

Alarcon-Aguilar, F. J., Valdes-Arzata, A., Xolalpa-Molina, S., Banderas-Dorantes, T., Jimenez-Estrada, M., Hernandez-Galicia, E., et al. 2003. Hypoglycemic activity of two polysaccharides isolated from *Opuntia ficus-indica* and *O. streptacantha*. *Proc. West. Pharmacol. Soc*. 46: 139–142.

Al-Azzawi, A. M., Al-Khateeb, E., Al-Sameraei, K., and Al-Jaboori, A. G. 2012. Antibacterial activity and the histopathological study of crude extracts and isolated tecomine from *Tecoma stans* Bignoniaceae in Iraq. *Pharmacog. Res*. 4: 37–43.

Alese, M. O., Adewole, S. T., Ijomone, M. O., Ajayi, S. A., and Omonisi, A. 2013. Histological studies of β-cells of streptozotocin-induced diabetic Wistar rats treated with ethanolic extract of *Sphenocentrum jollyanum*. *J. Pharm. Sci. Innov*. 2: 8–12.

Algandaby, M. M., Alghamdi, H. A., Ashour, Q. M., Abdel-Naim, A. B., Ghareib, S., Abdel-Sattar, E. A., et al. 2010. Mechanisms of the antihyperglycemic activity of *Retama raetam* in streptozotocin-induced diabetic rats. *Food Chem. Toxicol*. 48: 2448–2453.

Al-Ghaithi, F., El-Ridi, M. R., Adeghate, E. E., and Amiri, M. H. 2004. Biochemical effects of *Citrullus colocynthis* in normal and diabetic rats. *Mol. Cell. Biochem*. 261: 143–149.

Al-Habori, M., Raman, A., Lawrence, M. J., and Skett, P. 2001. *In vitro* effect of fenugreek extracts on intestinal sodium-dependent glucose uptake and hepatic glycogen phosphorylase A. *Int. J. Exp. Diabetes Res*. 2: 91–99.

Al-Hawamdeh, F. M., Shibli, R. A., and Al-Qudah, T. S. 2013. *In vitro* production of silymarin from *Silybum marianum* L. *Med. Aromat. Plants* S1: 001. doi:10.4172/2167-0412.S1-001.

Al-Hawamdeh, F. M., Shibli, R. A., and Al-qudah, T. S. 2014. *In vitro* propagation of *Silybum marianum* L. *Jordan J. Agric. Sci*. 10: 120–129.

Ali, M., Malik, A. R., and Sharma, K. R. 2008. Vegetative propagation of *Berberis aristata* DC, an endangered Himalayan shrub. *J. Med. Plants Res*. 2: 374–377.

Ali, N., Mulva, R. M. S., Norton, M. A., and Skirvin, R. M. 2003. Micropropagation of guava (*Psidium guajava* L.). *J. Hortic. Sci. Biotechnol*. 78: 739–741.

Ali, S., Igoli, J., Clements, C., Semaan, D., Alamzeb, M., Rashid, M. U., et al. 2013. Antidiabetic and antimicrobial activities of fractions and compounds isolated from *Berberis brevissima* Jafri and *Berberis parkeriana* Schneid. *Bangladesh J. Pharmacol*. 8: 336–342.

Al-Khateeb, E., Hamadi, S. A., Al-Hakeemi, A. A. N., Abu-Taha, M., and Al-Rawi, N. 2012. Hypoglycemic effect of trigonelline isolated from Iraqi fenugreek seeds in normal and alloxan-diabetic rabbits. *Eur. Sci. J.* 8: 16–24.

Al-Mamum, M. A., Akhter, R., Rahman, A., and Ferdousi, Z. 2015. Efficient *in vitro* propagation of *Andrographis paniculata* and evaluation of anti-diabetic activity from its crude protein extract. *Eur. J. Med. Plants* 6: 231–241.

Almasri, M., Mohammad, M. K., and Tahaa, M. O. 2009. Inhibition of dipeptidyl peptidase IV (DPP IV) is one of the mechanisms explaining the hypoglycemic effect of berberine. *J. Enzyme Inhib. Med. Chem.* 24: 1061–1066.

Al-Munsur, M. A. Z., Haque, M. S., Nasiruddin, K. M., and Hossain, M. S. 2009. *In vitro* propagation of bitter goud (*Momoddica charantia* L.) from nodal and segments. *Plant Tissue Cult. Biotechnol.* 19: 45–52.

Alonso-Castro, A. J. and Salazar-Olivo, L. A. 2008. The anti-diabetic properties of *Guazuma ulmifolia* Lam are mediated by the stimulation of glucose uptake in normal and diabetic adipocytes without inducing adipogenesis. *J. Ethnopharmacol.* 118: 252–256.

Alonso-Castro, A. J., Miranda-Torres, A. C., Gonzalez-Chavez, M. M., and Salazar-Olivo, L. A. 2008. Chlorogenic acid stimulate 2-NBD glucose uptake in both insulin-sensitive and insulin-resistant 3T3 adipocytes. *J. Ethnopharmacol.* 120: 458–464.

Alonoso-Castro, A. J., Zapata-Bustos, R., Gomez-Espinoza, G., and Salazar-Olivo, L. A. 2012. Isoorientin reverts TVF-α-induced insulin resistance in adipocytes activating the insulin signaling pathway. *Endocrinology* 153: 5222–5230.

Alonso-Castro, A. J., Zapata-Bustos, R., Romo-Yañez, J., Camarillo-Ledesma, P., Gomez-Sanchez, M., and Salazar-Olivo, L. A. 2010. The antidiabetic plants *Tecoma stans* (L.) Juss. ex Kunth (Bignoniaceae) and *Teucrium cubense* Jacq (Lamiaceae) induce the incorporation of glucose in insulin-sensitive and insulin-resistant murine and human adipocytes. *J. Ethnopharmacol.* 127: 1–6.

Al-Romaiyan, A., Jayasri, M. A., Mathew, T. L., Huang, G. C., Amiel, S., Jones, P. M., et al. 2010. *Costus pictus* extracts stimulate insulin secretion from mouse and human islets of Langerhans *in vitro*. *Cell. Physiol. Biochem.* 26: 1051–1058.

Al-Snafi, A. E. 2013. The pharmaceutical importance of *Althaea officinalis* and *Althaea rosea*: A review. *Int. J. PharmTech. Res.* 5: 1378–1385.

Al-Sulaiman, M. A. 2010. Clonal propagation of *Ziziphus spina-christi* by shoot tip culture: 1. Improved inorganic and organic media constituents for *in vitro* shoot multiplication. *JKAU: Met. Ecv. Arid. Land Agric. Sci.* 21: 3–17.

Al-Sulaiman, M. A. and Barakat, M. N. 2010. *In vitro* shoot multiplication of *Ziziphus spina-christi* by shoot tip culture. *Afr. J. Biotechnol.* 9: 850–857.

Al-Youssef, H. M. and Hassan, W. H. B. 2014. Phytochemical and pharmacological aspects of *Carissa edulis* Vahl: A review. *Int. J. Curr. Res. Chem. Pharm. Sci.* 1: 12–24.

Amarachinta, P. R. and Jamil, K. 2012. Preclinical evaluation of polyherbal formulations: Hypoglycemic activity in rats. *Int. J. Ayurvedic Herb. Med.* 2: 218–228.

American Diabetes Association 2013. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 36: 1033–1046.

Amezqueta, S., Galan, E., Vila-Fernandez, I., Pumarola, S., Carrascal, M., Abian, J., et al. 2013. The presence of D-fagomine in the human diet from buckwheat-based foodstuffs. *Food Chem.* 136: 1316–1321.

Amudhan, M. S., Begum, H. V., and Hebbar, K. B. 2012. A review on phytochemical and pharmacological potential of *Areca catechu* L. seed. *Int. J. Pharm. Sci. Res.* 3: 4151–4157.

An, G. Y. 1985. Treatment of 102 cases of non-insulin dependent diabetes mellitus with Gan Lu Xiao Ke capsule. *J. Trad. Chin. Med.* 26: 431–432.

An, H. J., Kim, I. T., Park, H. J., Kim, H. M., Choi, J. H. Lee, K. T. 2011. Tormentic acid, a triterpenoid saponin, isolated from Rosa rugosa, inhibited LPS-induced iNOS, COX-2, and TNF-α expression through inactivation of the nuclear factor-κb pathway in RAW 264.7 macrophages. *Int. Immunopharmacol.* 11: 504–510.

Anand, P., Murali, K. Y., Tandon, V., Murthy, P. S., and Chandra, R. 2009. Insulinotropic effect of aqueous extract of *Brassica nigra* improves glucose homeostasis in streptozotocin induced diabetic rats. *Exp. Clin. Endocrinol. Diabetes* 117: 151–156.

Anandharajan, R., Jaiganesh, S., Shankernarayanan, N. P., Viswakarma, R. A., and Balakrishnan, A. 2006. *In vitro* glucose uptake activity of *Aegles marmelos* and *Syzygium cumini* by activation of Glut4, PIP3 kinase and PPARgamma in L6 myocytes. *Phytomedicine* 13: 434–441.

Anandharajan, R., Pathmanathan, K., Shankernarayanan, N. P., Vishwakarma, R. A., and Balakrishnan, A. 2005. Upregulation of Glut-4 and PPAR gamma by an isoflavone from *Pterocarpus marsupium* on L6 myotubes: A possible mechanism of action. *J. Ethnopharmocol.* 97: 253–260.

Anbu, N., Musthafa, M. D., and Velpandian, V. 2012. Anti-diabetic activity of polyherbal formulation Aavaraiyathi churnum in alloxan induced diabetic rats. *Int. J. Toxicol. Pharmacol. Res.* 4: 77–80.

Anderson, R. A. and Polansky, M. M. 2002. Tea enhances insulin activity. *J. Agric. Food Chem.* 50: 7182–7186.

Anderson, R. A., Broadhurst, C. L., Polansky, M. M., Schmidt, W. E., Khan, A., Flanagan, V. P., et al. 2004. Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity. *J. Agric. Food Chem.* 52: 65–70.

Andrade-Cetto, A. and Vazquez, R. C. 2010. Gluconeogenesis inhibition and phytochemical composition of two Cecropia species. *J. Ethnopharmacol.* 130: 93–97.

Andrade-Cetto, A. and Wiedenfeld, H. 2001. Hypoglycemic effect *Cecropia obtusifolia* on streptozotocin diabetic rats. *J. Ethnopharmacol.* 78: 145–149.

Andrade-Cetto, A., Becerra-Jimenez, J., and Cardenas-Vazquez, R. 2008b. Alfa-glucosidase-inhibiting activity of some Mexican plants used in the treatment of type 2 diabetes. *J. Ethnopharmacol.* 116: 27–32.

Andrade-Cetto, A., Martinez-Zurita, E., Soto-Constantino, A., Revilla-Monsalve, C., and Wiedenfeld, H. 2008a. Chronic hypoglycemic effect of *Malmea depressa* root on n5-streptozotocin diabetic rats. *J. Ethnopharmacol.* 116: 358–362.

Angel de la Fuente, J. and Manzanaro, S. 2003. Aldose reductase inhibitors from natural sources. *Nat. Prod. Rep.* 20: 243–251.

Anis, E., Anis, I., Ahmed, S., Mustafa, G., Malik, A., Afza, N., Hal, S. M., Shahzad-ul-hussan, S., and Choudhary, M. I. 2002. Alpha glucosidase inhibitory constituents from *Cuscuta reflexa*. *Chem. Pharm. Bull.* 50: 112–114.

Anis, M., Faisal, M., and Singh, S. K. 2003. Micropropagation of mulberry (*Morus alba*) through *in vitro* culture of shoot tip and nodal explants. *Plant Tissue Cult.* 13: 47–51.

Anis, M., Husan, M. K., and Shahzad, A. 2005. *In vitro* plantlet regeneration of *Pterocarpus marsupium* Roxb., an endangered leguminous tree. *Curr. Sci.* 88: 861–863.

Anisuzzaman, M., Kabir, A. H., Sarker, K. K., Jarin, S., and Alam, M. F. 2010. Micropropagation of *Abelmoschus esculentus* L. (Moench.) for disease free plantlets through meristem culture. *Arch. Phytopathol. Plant Protect.* 43: 460–466.

Antonisamy, P., Subash-Babu, P., Alshatwi, A. A., Aravinthan, A., Ignacimuthu, S., Choi, K. C., et al. 2014. Gastroprotective effect of nymphayol isolated from Nymphaea stellata (Willd.) flowers: Contribution of antioxidant, anti-inflammatory and anti-apoptotic activities. *Chem. Biol. Interat.* 224: 157–163.

Antu, K. A., Riya, M. P., Mishra, A., Anilkumar, K. S., Chandrakanth, C. K., Tamrakar, A. K., et al. 2014. Antidiabetic property of *Symplocos cochinchinensis* is mediated by inhibition of alpha glucosidase and enhanced insulin sensitivity. *PLoS One* 9: e105829.

Anuja Patil, A., Nirmal, S., Pattan, S., Tambe, V. And Tare, M. 2012. Antidiabetic effect of polyherbal combinations in streptozotocin-induced diabetes involve inhibition of α-amylase and α-glucosidase with amelioration of lipid profile. *Phytopharmacology* 2: 46–57.

Anwar, J., Spanevello, R. M., Thome, G., Stefanello, N., Schmatz, R., Gutierres, J., et al. 2012. Effects of caffeic acid on behavioral parameters and on the activity of acetylcholinesterase in different tissues from adult rats. *Pharmacol. Biochem. Behav.* 103: 386–394.

Arai, H., Hirasawa, Y., Rahman, A., Kusumawati, I., Zaini, N. C., Sato, S., et al. 2010. Alstiphyllanines E-H, picraline and ajmaline-type alkaloids from *Alstonia macrophylla* inhibiting sodium glucose cotransporter. *Bioorg. Med. Chem.* 18: 2152–2158.

Arai, M., Hayashi, A., Sobou, M., Ishida, S., Kawachi, T., Kotoku, N., et al. 2011. Anti-angiogenic effect of triterpenoidal saponins from *Polygala senega*. *J. Nat. Med.* 65: 149–156.

Arakawa, K., Ishihara, T., Aoto, M., Inamasu, M., Saito, A., and Ikezawa, K. 1998. Actions of a novel antidiabetic thiazolidinedione, T-174 in animal models of non-insulin dependent diabetes mellitus (NIDDM) and in cultured muscle cells. *Br. J. Pharmacol.* 125: 429–436.

Arawwawala, M., Thabrew, I., and Arambewela, L. 2009. Anti-diabetic activity of *Trichosanthes cucumerina* in normal and streptozotocin-induced diabetic rats. *Int. J. Biol. Chem. Sci.* 3: 287–296.

Ardiles, A. E., Gonzalez-Rodriguez, A., Nunez, M. J., Perestelo, N. R., Pardo, V., Jimenez, I. A., et al. 2012. Studies on naturally occurring friedelane triterpinoids as insulin sensitizers in the treatment of type 2 diabetes mellitus. *Phytochemistry*. 84: 116–124.

Arif, T., Sharma, B., Gahlauit, A., Kumar,V., and Dabur, R. 2014. Antidiabetic agents from medicinal plants: A review. *Chem. Biol. Lett.* 1: 1–13.

Arockiasami, S., Ignacimuthu, S., and Melchias, G. 2000. Influence of growth regulators and explants type on in vitro shoot propagation and rooting of red sandalwood (*Pterocarpus santalinus* L.). *Indian J. Exp. Bot*. 38: 1270–1273.

Arora, S., Singh, S., Piazza, G. A., Contreras, C. M., Panyam, J., and Singh, A. P. 2012. Honokiol: A novel natural agent for cancer prevention and therapy. *Curr. Mol. Med*. 12: 1244–1252.

Arulmozhi, D. K., Veeranjaneyulu, A., and Bodhankar, S. L. 2004. Neonatal streptozotocin-induced rat model of type 2 diabetes mellitus: A glance. *Indian J. Pharmacol*. 36: 217–221.

Arumugam, B., Manaharan, T., Heng, C. K., Kuppusamy, U. R., and Palanisamy, U. D. 2014. Antioxidant and antiglycemic potentials of a standardized extract of *Syzygium malaccense*. *Food Sci. Technol*. 59: 707–712.

Arun, N. and Nalini, N. 2002 Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. *Plant Food Hum. Nutr.* 57: 41–52.

Aruna, A., Vijayalakshmi, K., and Karthikeyan, V. 2014. Anti-diabetic screening of methanolic extract of *Citrullus lanatus* leaves. *Am. J. PharmTech Res*. 4: 295–323.

Arunakumara, K. K. I. U., Walpola, B. C., and Yoon, M. -H. 2013. Mass multiplication of important medicinal plant *Gymnema sylvestre* R. Br.: A review. *Int. J. Med. Plants* 105: 250–259.

Arya, A., Abdullah, M. A., Haerian, B. S., and Mohd, M. A. 2012. Screening for hypoglycemic activity on the leaf extracts of nine medicinal plants: *In vivo* evaluation. *J. Chem*. 9: 1196–1205.

Asaka, I., Li, I., Hirotani, M., Asada, Y., and Furuya, T. 1993. Production of ginsenoside saponins by culturing ginseng (*Panax ginseng*) embryogenic tissues in bioreactors. *Biotechnol. Lett*. 15: 1259–1264.

Asaka, I., Li, I., Hirotani, M. Asada, Y., Yoshokawa, T., and Furuya, T. 1994. Mass production of Ginseng (Panax ginseng) embryoids on media containing high concentrations of sugar. *Planta Med*. 60: 146–148.

Asano, N., Kato, A., Matsui, K., Watson, A. A., Nash, R. J., Molyneux, R. J., et al. 1997. The effects of calystegines isolated from edible fruits and vegetables on mammalian liver glycosidases. *Glycobiology* 7: 1085–1088.

Asgarpanah, J. and Haghighat. E. 2012. Phytochemistry and pharmacological properties of *Ziziphus spina christi* (L.) Willd. *Afr. J. Pharm. Pharmacol*. 6: 2332–2339.

Ashok, P. and Meenakshi, B. 2004. Contraceptive effect of *Curcuma longa* L. in male albino rats. *Asian J. Androl*. 6: 71–74.

Ashokkumar, B. S., Lakshman, L., Nandeesh, R., Arunkumar, P. A., Manoj, B., Kumar, V., et al. 2011. *In vitro* alpha-amylase inhibition and *in vivo* antioxidant potential of *Amaranthus spinosus* in alloxan-induced oxidative stress in diabetic rats. *Saudi J. Biol. Sci*. 18: 1–5.

Assareh, M. H. and Sardabi, H. 2005. Macropropagation and micropropagation of *Ziziphus spina-christi*. *Pesq. Agropec. Bras. Brasilia* 40: 459–465.

Atanasov, A. G., Wang, J. N., Gu, S. P., Bu, J., Kramer, M. P., Baumgartner, L., et al. 2013. Honokiol: A non-adipogenic PPARγ agonist from nature. *Biochem. Biophys Acta* 1830: 4813–4819.

Atolani, O., Olatunji, G. A., and Fabyk, O. A. 2009. *Blighia sapida*: The plant and its hypoglycins, an overview. *J. Sci. Res*. 39: 15–25.

Attele, A. S., Zhou, Y. P., Xie, J. T., Wu, J. A., Zhang, L., Dey, L., et al. 2002. Antidiabetic effects of *Panax ginseng* berry extract and the identification of an effective component. *Diabetes* 51: 1851–1858.

Attia, A. O., Sdessoky, E., El-Hallous, E. I., and Shaaban, H. F. 2014. Micropropagation of mulberry (*Morus alba*) cv. al-taify. *Int. J. Bio-Technol*. 4: 15–22.

Augusti, K. T. and Sheela, C. G. 1996. Antiperoxide effect of S-allyl cysteine sulfoxide, an insulin secretagogue in diabetic rats. *Experientia* 52: 115–120.

Augusti, K. T., Daniel, R. S., Cherian, S., Sheela, C. G., and Nair, C. R. 1994. Effect of leucopelargonin derivative from *Ficus bengalensis* L. on diabetic dogs. *Indian J. Med. Res.* 99: 82–86.

Augusti, K. T., Joseph, P., and Babu, T. D. 1995. Biologically active principles isolated from *Salacia oblonga* Wall. *Indian J. Physiol. Pharmocol.* 39: 415–417.

Austin, A. 2008. A review on Indian sarsaparilla, *Hemidesmus indicus* (L.) R. Br. *J. Biol. Sci*. 8: 1–12.

Auwerx, J. 1999. PPARγ, the ultimate thrifty gene. *Diabetologia* 42: 1033–1049.

Auzanneau, C., Montaudon, D., Puyo, S., Jacquet, R., Elkaoukabi-Chaibi, A., Quideau, S., et al. 2011. Vescalagin, a polyphenolic ellagitanin specifically inhibiting the alpha isoform of human DNA topoisomerase II. In: *Proceedings of the 102nd Annual Meeting of the American Association for Cancer Research*. 2011 Apr 2–6; Orlando, FL. Philadelphia (PA): AACR; *Cancer Res.* 71(8 Suppl): Abstract No. 2531. doi:10.1158/1538-7445.AM2011-2531.

Awad, N. E., Seida, A. A., Shaffie, Z. E. N., and El-Aziz, A. M. A. 2012. Hypoglycemic activity of *Artemisia herba-alba* (Asso.) used in Egyptian traditional medicine as hypoglycemic remedy. *J. Appl. Pharm. Sci.* 2: 30–39.

Azay-Milhau, J., Ferrare, K., Leroy, J., Aubaterre, J., Tournier, M., Lajoix, A. D., et al. 2013. Antihyperglycemic effect of a natural chicoric acid extract of chicory (*Cichorium intybus* L.): A comparative *in vitro* study with the effects of caffeic and ferulic acids. *J. Ethnopharmacol*. 150: 755–760.

Azizeh, B. Y., Shenderovich, M. D., Trivedi, D., Li, G., Sturm, N. S., and Hruby, V. J. 1996. Topographical aminoacid substitution in position 10 of glucagon leads to antagonists / partial agonists with greater binding differences. *J. Med. Chem*. 39: 2449–2455.

Babri, S., Azami, S. H., Mohaddes, G. 2013. Effect of acute administration of loganin on spatial memory in diabetic male rats. *Adv. Pharm. Bull*. 3: 91–95.

Babu, P. S. and Prince, S. M. P. 2004. Antihyperglycaemic and antioxidant effect of hyponidd, an Ayurvedic herbomineral formulation in streptozotocin-induced diabetic rats. *J. Pharm. Pharmacol*. 56: 1435–1442.

Babuji, S. S. H, Sahu, D., Bahadur, V., and Kassim, T. 2010. Evaluation of safety and efficacy of a polyherbal antidiabetic formulation Diasol. *AsPac. J. Mol. Biol. Biotechnol*. 18: 59–61.

Bachri, M. S., Jang, H. W., Choi, J., and Park, J. 2010. Protective effect of white-skinned sweet potato (*Ipomoea batatas* L.) from Indonesia on streptozotocin-induced oxidative stress in rats. *J. Life Sci*. 20: 1569–1576.

Badole, S. L. and Bodhankar, S. L. 2009a. Investigation of antihyperglycaemic activity of aqueous and petroleum ether extract of stem bark of *Pongamia pinnata* on serum glucose level in diabetic mice. *J Ethnopharmacol*. 123: 115–120.

Badole, S. L. and Bodhankar, S. L. 2010. Antidiabetic activity of cycloart-23-ene-3beta, 25-diol (B2) isolated from *Pongamia pinnata* (L. Pierre) in streptozotocin-nicotinamide induced diabetic mice. *Eur. J. Pharmacol*. 632: 103–109.

Bajracharya, G. B. 2015. Diversity, pharmacology and synthesis of bergenin and its derivatives: Potential materials for therapeutic usages. *Fitoterapia* 101: 133–152.

Bakrudeen, A. A. A. and Arun, K. R. 2009. *In vitro* propagation of Monocot (*Costus pictus* D. Don)—An antidiabetic medicinal plant. *J. Agric. Technol*. 5: 361–369.

Bakrudeen, A. A. A., Shanthi, G. S., Gouthaman, T., Kavitha, M. S., and Rao, M. V. 2011. *In vitro* micropropagation of *Catharanthus roseus*—An anticancer medicinal plant. *Acta Botanica Hungarica* 53: 197–209.

Bakrudeen, A. A. A., Rao, A. S., Rao, M. V., and Taha, R. M. 2012. Different wave lengths light to induce physiological changes in callus for the bio-synthesis of gymnemic acid in *Gymnema sylvestre*. *Agro. Food Industry Hi Tech*. 23: 31–34.

Balakrishnan, V., Latha, M. R., Ravindran, K. C., and Robinson, J. P. 2009. Clonal propagation of *Morus alba* L. through nodal and axillary bud explants. *Bot. Res. Int*. 2: 42–49.

Balamurugan, R., Duraipandiyan, V., and Ignacimuthu, S. 2011. Antidiabetic activity of γ-sitosterol isolated from *Lippianodi flora* L. in streptozotocin induced diabetic rats. *Eur. J. Pharmacol*. 667: 410–418.

Balaraju, K., Agastian, P., Ignacimuthu, S., and Park, K. 2011. A rapid in vitro propagation of red sanders (*Pterocarpus santalinus* L.) using shoot tip explants. *Acta Physiologiae Plantarum* 33: 2501–2510.

Balasubramanyam, M. and Mohan, V. 2000. Current concept of PPAR-signaling in diabetes mellitus. *Curr. Sci*. 79: 1440–1445.

Balasubramanyam, M. and Mohan, V. 2004. Insulin signaling in diabetes: Cascades and complexities. *Advanced Biotech*. 2: 24–27.

Balasubramanyam, M., Sampathkumar, R., and Mohan, V. 2005. Is insulin signaling molecules misguided in diabetes for ubiquitin-proteasome mediated degradation? *Mol. Cell Biochem*. 275: 117–125.

Baldi, A. and Goyal, S. 2011. Hypoglycemic effect of polyherbal formulation in alloxan-induced diabetic rats. *Pharmacologyonline* 3: 764–773.

Ball, S. W., Bailey, J. R., Stewart, J. M., Vogels, C. M., and Westcott, S. A. 2002. A fluorescent compound for glucose uptake measurements in isolated ratmyocytes. *Can. J. Physiol. Pharmacol*. 80: 205–209.

Bandara, T., Uluwaduge, I., and Jansz, E. R. 2012. Bioactivity of cinnamon with special emphasis on diabetes mellitus: A review. *Int. J. Food Sci. Nutr.* 63: 380–386.

Bandekar, H. and Lele, S. S. 2014. Production of flavonol quercetin from cultured plant cells of Banyan (*Ficus benghalensis* L.). *Int. J. Innovative Res. Sci. Eng. Technol*. 3: 12150–12159.

Banerjee, P., Maity, S., and Banerjee, N. 2012. High frequency somatic embryogenesis and plantlet regeneration of *Bauhinia variegata*, a multipurpose tree legume. *Indian J. Fundamental Appl. Life Sci*. 2: 87–95.

Bangar, O. P., Jarald, E. E., Asghar, S., and Ahmad, S. 2009. Antidiabetic activity of a polyherbal formulation (Karnim plus). *Int. J. Green Pharm*. 3: 211–214.

Bansal, M., Gupta, S. K., and Singhvi, I. J. 2012. Screening of phloroglucinol as a potent antidiabesity. *Asian J. Pharm. Sci. Clin. Res*. 2: 21–25.

Banu, L. A. and Bari, M. A. 2007. Protocol establishment for multiplication and regeneration of *Ocimum sanctum* Linn. An important medicinal plant with high religious value in Bangladesh. *J. Plant Sci*. 2: 530–537.

Bao, H. and Chen, L. 2011. Icariin reduces mitochondrial oxidative stress injury in diabetic rat hearts. *Zhongguo Zhong Yao Za Zhi* 36: 1503–1507.

Barad, A., Malashetty, V. B., and Seetharam, Y. N. 2014. *In vitro* epiphyllous buds formation in *Enicostemma hyssopifolium* (Willd.) Ver. induction and cellular origin. *Int. J. Herbal Med*. 2: 505–506.

Barampuram, S., Anjaneyulu, C., and Giri, C. C. 2003. Multiple shoot induction from cotyledonary node explants of *Terminalia chebula*. *Biol. Plant*. 47: 585–588.

Bardy, G., Virsolvy, A., Quignard, J. F., Ravier, M. A., Bertrand, G., Dalle, S., et al. 2013. Quercetin induces insulin secreation by direct activation of L-type calcium channels in pancreatic β-cells. *Br. J. Pharmacol*. 169: 1102–1113.

Barham, D. and Trinder, P. 1972. An improved colour reagent for the determination of blood glucose by the oxidase system. *Analyst* 97: 142–145.

Barik, C. S., Kanungo, S. K., Tripathy, N. K., Panda, J. R., and Padhi, M. 2015. A review on therapeutic potential of polyherbal formulations. *Int. J. Pharm. Sci. Drug Res*. 7: 211–228.

Barman, S. and Das, S. 2012. Hypoglycemic effect of ethanolic extract of bark of *Terminalia arjuna* Linn. in normal and alloxan-induced noninsulin-dependent diabetes mellitus albino rats. *Int. J. Green Pharm*. 6: 279–284.

Baskaran,P., Velayutham, P., and Jayabalan, N. 2008a. *In vitro* regeneration of *Melothria maderaspatana via* indirect organogenesis. *In Vitro Cell. Dev. Biol. Plant* 45: 407–413.

Baskaran, P., Velayutham, P., Rajadurai, D. M., and Jayabalan, N. 2008b. Micropropagation of *Melothria maderaspatana* (L.) Cong through apical buds derived from mature plants. *J. Biol. Res*. 9: 83–88.

Basnet, P., Kadota, S., Shimizu, M., and Namba, T. 1994. Bellidifolin: A potent hypogycemic agent in streptozotocin (STZ)-induced diabetic rats from *Swertia japonica*. *Planta Med*. 60: 507–511.

Basnet, P., Kadota, S., Shimizu, M., Takata, Y., Kobayashi, M., and Namba, T. 1995. Bellidifolin stimulates glucose uptake in rat fibroblasts and ameliorates hyperglycemia in streptozotocin-induced diabetic rats. *Planta Med*. 61: 402–405.

Basnet, P., Kadota, S., Terashima, S., Shimizu, M., Namba, T. 1993. Two new 2-arylbenzofuran derivatives from hypoglycemic activity-bearing fractions of *Morus insignis*. *Chem. Pharm. Bull*. 41: 1238–1243.

Bates, S. H., Jones, R. B., and Bailey, C. J. 2000. Insulin-like effect of pinitol. *Br. J. Pharmocol*. 130: 1944–1948.

Bauer, J., Kuehnl, S., Rollinger, J. M., Scherer, O., Northoff, H., Werz, O., et al. 2012. Carnosol and carnosic acids from *Salvia officinalis* inhibit microsomal prostaglandin E2 synthase-1. *J. Pharmacol. Exp. Ther.* 342: 169–176.

Baumgartner, R. R., Steinmann, D., Heiss, E. H., Atanasov, A. G., Ganzera, M., Stuppner, H., et al. 2010. Bioactivity-guided isolation of 1,2,3,4,6-Penta-O-galloyl-D-glucopyranose from *Paeonia lactiflora* roots as a PTP1B inhibitor. *J. Nat. Prod*. 73: 1578–1581.

Baur, J., Kuehnl, S., Rollinger, J. M., Scherer, O., Northoff, H., Stuppner, H., et al. 2012. Carnosol andcCarnosic acids from *Salvia officinalis* inhibit microsomal prostaglandin E_2 synthase-1. *J. Pharmacol. Exp. Ther.* 342: 169–176.

Beg, M., Chauhan, P., Varshney, S., Shankar, K., Rajan, S., Saini, D., et al, 2014. A withanolide coagulin-L inhibits adipogenesis modulating Wnt/β-catenin pathway and cell cycle in mitotic clonal expansion. *Phytomedicine* 21: 406–414.

Behera, B. and Yadav, D. 2013. Current researches on plants having antidiabetic potential: An overview. *Res. Rev. J. Bot. Sci*. 2: 4–17.

Bekheet, S. A., Taha, H. S., and Gabr, A. M. M. 2013. Protocol for *in vitro* morphogenesis and hairy root cultures of milk thistle (*Silybum marianum* L. Gaertn). *J. Appl. Sci*. Res. 9: 860–866.

Belemkar, S., Dhameliya, K., and Pata, M. K. 2013. Comparative study of garlic species (*Allium sativum* and *Allium porrum*) on glucose uptake in diabetic rats. *J. Talibah Uni. Med. Sci*. 8: 80–85.

Belfiore, A. and Malaguarnera, R. 2011. Insulin receptor and cancer. *Endocr. Related Cancer* 18: R125–R147.

Borniquel, S., Jansson, E. A., Cole, M. P., Freeman, B. A., and Lundberg, J. O. 2010. Nitrated oleic acid up-regulates PPAR-gamma and attenuates experimental inflammatory bowel disease. *Free Radic. Biol. Med*. 48: 499–505.

Bello, A., Aliero, A. A., Saidu, Y., and Muhammad, S. 2011b. Phytochemical screening, polyphenolic content and alpha-glycosidase inhibitory potential of *Leptadenia hastata* (Pers.) Decne. *Nigerian J. Basic Appl. Sci*. 19: 181–186.

Bera, T. K., De, D., Chatterjee, K., Ali, K. M., and Ghosh, D. 2010. Effect of *Diashis*, a polyherbal formulation, in streptozotocin-induced diabetic male albino rats. *Int J Ayurveda Res*. 1: 18–24.

Berger, J. and Moller, D. E. 2002. The mechanisms of action of PPARs. *Annu. Rev. Med*. 53: 409–435.

Bergmeyer, H. and Bernt, E. 1963. D-glucose determination with glucose oxidase and peroxidase. In: *Methods of Enzymatic Analysis*. 1st ed. Bergmeyer, H. (Ed.). New York: Academic Press, 123–130.

Bernfeld, P. 1955. Amylase-α and -β. In: *Methods in Enzymology*, Vol. 1. Colowick, S. P. and Kaplan, N. O. (Eds). New York: Academic Press, 141–158.

Berry, M. and Friend, D. 1969. High-yield preparation of isolated rat liver parenchyma cells. A biochemical and fine structure study. *J. Cell Biol*. 43: 506–520.

Bertoglio, J. C., Calvo, M., Hancke, J. L., Burgos, R. A., Riva, A., and Morazzoni, P. 2011. Hypoglycemic effect of lupin seed γ-conglutin in experimental animals and healthy human subjects. *Fitoterapia* 82: 933–938.

BGCI 2001. Summary of the international review of the *ex situ* plant collections of the botanic gardens of the world. *BGCI News* 7: 1–5.

Bhalerao, B. M., Kishor, S., Vishwakarma, K. S., and Maheshwar, V. J. 2013. *Tinospora cordifolia* (Willd.) Miers ex Hook.f. & Thoms.- plant tissue culture and comparative chemo-profiling study as a function of different supporting trees. *Indian J. Nat. Prod. Resources* 4: 380–386.

Bhandari, M. R., Anurakkun, N. J., Gao, H., Kawabata, J. 2008. α-Glucosidase and α-amylase inhibitory activities of Nepalese medicinal herb Pakhanbhed (*Bergenia ciliata*, Haw.). *Food Chem*. 106: 247–252.

Bharti, S. K., Kumar, A., Prakash, O., Krishnan, S., and Gupta, A. K. 2013. Essential oil of *Cymbopogon citratus* against diabetes: Validation by *in vivo* experiments and computational studies. *J. Bioanal. Biomed*. 5: 194–203.

Bhaskaran, S., Dileep, K. V., Deepa, S. S., Sadasivan, C., Klausner, M., Krishnegowda, N. K., et al. 2013. Gossypin as a novel selective dual Inhibitor of v-raf murine sarcoma viral oncogene homolog B1 and cyclin-dependent kinase 4 for melanoma. *Mol. Cancer Ther.* 12: 361–372.

Bhat, B. M., Raghuveer, C. V., D'Souza, V., and Manj, P. A. 2012. Antidiabetic and hypolipidemic effect of *Salacia oblonga* in streptozotocin-induced diabetic rats. *Clin. Diagn. Res.* 6: 1685–1687.

Bhat, M., Kothiwale, S. K., Tirmale, A. R., Bhargava, S. Y., and Joshi, B. N. 2011a. Antidiabetic properties of *Azardiracta indica* and *Bougainvillea spectabilis in vivo* studies in murine diabetes model. *Evid. Based Complement. Alternat. Med*. 2011: 561625.

Bhat, M., Zinjarde, S. S., Bhargava, S. Y., Kumar, A. R., and Joshi, B. N. 2011b. Anti-diabetic Indian plants: A good source of potent amylase inhibitors. *Evid. Based Complement. Alternat. Med*. 2011: 810207.

Bhat, M. Z. A., Ali, M., and Mir, S. R. 2013. Anti-diabetic activity of *Ficus carica* L. stem barks and isolation of two new flavonol esters from the plant by using spectroscopical techniques. *Asian J. Biomed. Pharm. Sci*. 3: 22–28.

Bhattacharyya, R. and Bhattacharya, S. 2001. High frequency in vitro propagation of *Phyllanthus amarus* Schum. & Thom. by shoot tip culture. *Indian J. Exp. Biol*. 39: 1184–1187.

Bhattacharya, S., Rasmussen, M. K., Christensen, L. P., Young, J. F., Kristiansen, K., and Oksbjerg, N. 2014. Naringenin and falcarinol stimulate glucose uptake and TBC1D1 phosphorylation in porcine myotube cultures. *J. Biochem. Pharmacol. Res*. 2: 91–98.

Bhoumik, A., Ali Khan, L., Akhter, M., and Rokeya, B. 2009. Studies on the anti-diabetes effects of *Mangifera indica* stem barks and leaves on type 1 and type 2 diabetic models of rats. *Bangladesh J. Pharmacol.* 4: 110–114.

Bierer, D. E., Fort, D. M., Mendez, C. D., Luo, J., Imbach, P. A., Dubenko, L. G., et al. 1998. Ethnobotanical-directed discovery of the antihyperglycemic properties of cryptolepine: Its isolation from *Cryptolepis sanguinolenta*, synthesis, and *in vitro* and *in vivo* activities. *J. Med. Chem.* 41: 894–901.

Bino Kingsley, Arun, K.P., Stalin, S. and Brindha, P. 2014b. *Stereospermum tetragonam* as an antidiabetic agent by activating PPARγ and GLUT4. *Bangladesh J. Pharmacol.* 9: 250-256.

Bino Kingsley, R. 2014. Studies on the Anti-diabetic Potentials of Selected Ethnomedicinal Plants. Ph. D. Thesis, SASTRA Deemed University, Thanjavur, India.

Bino Kingsley, R., Manisha, M., Brindha. P., and Subramoniam, A. 2013. Anti-diabetes mellitus activity of active fraction of *Stereospermum tetragonum* DC. and isolation of active principles. *J. Young Pharm.* 5: 7–12.

Bisht, S. and Sisodia, S. S. 2010. *Coffea arabica*: A wonder gift to medical science. *J. Nat. Pharm.* 1: 58–65.

Biswas, M., Kar, B., Bhattacharya, S., Kumar, R. B., Ghosh, A. K., Haldar, P. K. 2011. Antihyperglycemic activity and antioxidant role of *Terminalia arjuna* leaf in streptozotocin-induced diabetic rats. *Pharm. Biol.* 49: 335–340.

Bland, J. S., Minich, D., Lerman, R., Darland, G., Lamb, S., Tripp, M., et al. 2015. Isohumulones from hops (*Humulus lupulus*) and their potential role in medical nutrition therapy. *Pharma Nutr.* 3: 46–52.

Bodhipadma, K., Noichinda, S., and Kludnin, S. 2005. Eugenol production from holy basil (*Ocimum sanctum* L. cv. Dang) tissue culture. *J. Appl. Sci.* 4: 57–66.

Bolkent, S., Yanardag, R., Tabakoglu-Oguz, A., and Ozsov-Sacan, O. 2000. Effects of chard (*Beta vulgaris* L. var. cicla) extract on pancreatic β-cells in streptozotocin-diabetic rats: A morphological and biochemical study. *J. Ethnopharmacol.* 73: 251–259.

Bonyanpour, A. and Khosh-Khui, M. 2013. Callus induction and plant regeneration in *Punica granatum* L. 'Nana' from leaf explants. *J. Central Eur. Agric.* 14: 928–936.

Bopana, N. and Saxena, S. 2008. *In vitro* propagation of a high value medicinal plant: *Asparagus racemosus* Willd. *In Vitro Cell. Dev. Biol. Plant* 44: 525–532.

Bordoloi, R. and Dutta, K. N. 2014. A review on herbs used in the treatment of diabetes mellitus. *J. Pharm. Chem. Biol. Sci.* 2: 86–92.

Borlinghaus, J., Albrecht, F., Gruhlke, M. C. H., Nwachukwu, I. D., and Slusarenko, A. J. 2014. Allicin: Chemistry and biological properties. *Molecules* 19: 12591–12618.

Borniquel, S., Jansson, E. A., Cole, M. P., et al. 2010. Nitrated oleic acid up-regulates PPARgamma and attenuates experimental inflammatory bowel disease. *Free Radic. Biol. Med.* 48: 499–505.

Bos F., Lynn, K. and Robert, C. 2002. Commonly used Chinese medicinal formulas in diabetes. In: *The Treatment of Diabetes Mellitus with Chinese Medicine*. Boulder: Blue Poppy Press, CO80301, 43–51.

Bothon, F. T. D., Debiton, E., Avlessi, F., Forestier, C., Teulade, J. -C., and Sohounhloue, D. K. C. 2013. *In vitro* biological effects of two anti-diabetic medicinal plants used in Benin as folk medicine. *BMC Complement. Altern. Med.* 13: 51.

Brasnyo, P., Molnar, G. A., Mohas, M., Marko, L., Laczy, B., Cseh, J., et al. 2011. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. *Br. J. Nutr.* 106: 383–388.

Breen, D. M., Rasmussen, B. A., Kokorovic, A., Wang, R., Cheung, G. W., and Lam, T. K. 2012. Jejunal nutrient sensing is required for duodenal-jejunal bypass surgery to rapidly lower glucose concentrations in uncontrolled diabetes. *Nat. Med.* 18: 950–955.

Bresciani, L. F. V., Yunes, R. A., Burger, C., Oliveira, L. E. D., Bof, K. L., and Cechinel-Filho, V. 2004. Seasonal variation of kaurenoic acid, a hypoglycemic diterpene in *Wedelia paludosa* (*Acmela brasiliensis*) (Asteraceae). *Z. Naturforsch C.* 59: 229–232.

Brierley, D. I. and Davidson, C. 2012. Developments in harmine pharmacology—Implications for ayahuasca use and drug-dependence treatment. *Prog. Neuro Psychopharmacol. Biol. Psychiatry* 39: 263–272.

Brijwal, L. and Tamta, S. 2015. *Agrobacterium rhizogenes* mediated hairy root induction in endangered *Berberis aristata* DC. *Springer Plus* 4: 443–449.

Broadhurst, C. L., Polansky, M. M., Anderson, R. A. 2000. Insulin-like biological activity of culinary and medicinal plant aqueous extracts *in vitro. J Agric Food Chem.* 48: 849–852.

Brown, P. N. and Roman, M. C. 2008. Determination of hydrastine and berberine in goldenseal raw materials, extracts, and dietary supplements by high-performance liquid chromatography with UV: Collaborative Study. *J AOAC Int*. 91: 694–701.

Buitrago-Hurtado, G., Bustamante-Rodriguez, S., Ramos-Duarte, A., and Perea-Dallos, M. 2014. Efficient *in vitro* propagation of yacon (*Smallanthus sonchifolius*) as support of seeds production in Colombia. *International Association for Plant Biotechnology Congress*, 2014, abstract, 256.

Burant, C. F., Flink, S., DePoali, A. M., Chen, J., Lee, W. S., Hediger, M. A., et al. 1994. Small intestine hexose transport in experimental diabetes. Increased transporter mRNA and protein expression in enterocytes. *J. Clin. Invest*. 93: 578–585.

Bustanji, Y., Taha, M. O., Al-Masri, I. M., and Mohammad, M. K. 2009. Docking simulations and *in vitro* assay unveil potent inhibitory action of papaverine against protein tyrosine phosphatase 1B. *Biol. Pharm. Bull*. 32: 640–645.

Calabrese, F. J., Matton, M. P., and Calabrese, V. 2010. Resveratrol commonly displays hormesis: Occurance and biomedical significance. *Human Exp. Toxicol*. 29: 980–1015.

Calderon-Montano, J. M., Burgos-Moron, F., Perez-Guerrero, C., and Lopez-Lazaro, M. 2011. A review on the dietary flavonoid kaempferol. *Mini Rev. Med. Chem*. 11: 298–344.

Carney, J. R., Krenisky, J. M., Williamson, R. T., and Luo, J. 2002. Achyrofuran, a new antihyperglycemic dibenzofuran from the South American medicinal plant *Achyrocline satureioides. J. Nat. Prod*. 65: 203–205.

Campbell-Tofte, J. I. A., Molgaard, P., and Winther, K. 2012. Harnessing the potential clinical use of medicinal plants as anti-diabetic agents. *Botanics Targets and Ther* 2012: 7–19.

Campos, M. G., Oropeza, M., Torres-Sosa, C., Jimenez-Estrada, M., and Reyes-Chilpa, R. 2009. Sesquiterpenoids from antidiabetic *Psacalium decompositum* block ATP sensitive potassium channels. *J. Ethanopharmacol*. 123: 489–493.

Candasamy, M., Kammili, N., Varikutti, S. M. K., Pamarthi, B., Chennu, R., and Alla, M. 2011. Hypoglycemic and anti-hyperglycemic effect of Jamboola, a poly herbal Ayurvedic formulation in normal and alloxan induced diabetic rats. *Eur. J. Exp. Biol*. 1: 109–114.

Cao, H., Graves, D. J., and Anderson, R. A. 2010. Cinnamon extract regulates glucose transporter and inslin-signalling gene expression in mouse adipocytes. *Phytomedicine* 17: 1027–1032.

Capuana, M. 2013. *In vitro* propagation of ash (*Fraxinus excelsior* L.) by somatic embryogenesis. *Methods Mol. Biol*. 11013: 213–221.

Casanova, L. M., da Silva, D., Sola-Penna, M., Camargo, L. M., Celestrini, D. M., Tinoco, L. W., et al. 2014. Identification of chicoric acid as a hypoglycemic agent from *Ocimum gratissmum* leaf extract in a biomonitoring *in vivo* study. *Fitoterapia* 93: 132–141.

Castellano, J. M., Guinda, A., Delgado, T., Rada, M., and Cayuela, J. A. 2013. Biochemical basis of the antidiabetic activity of oleanolic acid and related pentacyclic triterpenes. *Diabetes* 62: 1791–1799.

Castro, A., Frederico, M. J., Cazarolli, L. H., Mendes, C. P., Bretanha, L. C., Schmidt, E. C. 2015. The mechanism of action of ursolic acid as insulin secretagogue and insulinomimetic is mediated by cross-talk between calcium and kinases to regulate glucose balance. *Biochim. Biophys. Acta* 1850: 51–61.

Cazarolli, L. D., Folador, P., Moresco, H. H., Brighente, I. M., Pizzolatti, M. G. and Silva, F.R. 2009. Stimulatory effect of apigenin-6-C-β-L-fucopyranoside on insulin secretion and glycogen synthesis. *Eur. J. Med. Chem*. 44: 4668–4673.

Cazarolli, L., Zanatta, L., Jorge, A. P., de Sousa, E., Woehl, V. M., Pizzolatti, M. G., et al. 2006. Follow-up studies on glycosylated flavonoids and their complexes with vanadium: Their anti-hyperglycemic potential role in diabetes. *Chem. Biol. Interact*. 163: 177–191.

Cechinel-Filho, V., Vaz, Z. R., Zunino, L., Calixto, J. B., and Yunes, R. A. 2000. Antinociceptive and anti-oedematogenic properties of astilbin, taxifolin and some related compounds. *Arzneimittelforschung* 50: 281–285.

Cetto, A. A. and Heinrich. M. 2005. Mexican plants with hypoglycaemic effect used in the treatment of diabetes. *J. Ethnopharmacol*. 99: 325–348.

Ch, B., Rao, K., Gandi, S., and Giri, A. 2012. Abiotic elicitation of gymnemic acid in the suspension cultures of *Gymnema sylvestre*. *World J. Microbiol. Biotechnol*. 28: 741–747.

Chaari Rkhis, A., Maalej, M., Drira, N., and Standardi, A. 2011. Micropropagation of olive tree *Olea europaea* L. 'oueslati'. *Turk J. Agric. For.* 35: 403–412.

Chakrabarthi, S., Biswas, T. K., Seal, T., Rokeya, B., Ali, L., AzadKhan, A. K., et al. 2005. Antidiabetic activity of *Caesalpinia bonducella* F. in chronic type 2 diabetic model in Long Evans rats and evaluation of insulin secretagogue property of its fraction on isolated islets. *J. Ethnopharmacol.* 97: 117–122.

Chakraborty, U. and Das, H. 2010. Anti-diabetic and anti-oxidant activities of *Cinnamomum tamala* leaf extracts in streptozotocin-treated diabetic rats. *Global J. Biotechnol. Biochem.* 5: 12–18.

Chan, H. -H., Sun, H. -D., Reddy, M. V. B., and Wu, T. -S. 2010. Potent α-glucosidase inhibitors from the roots of *Panax japonicas* C. A. Meyer var. major. *Phytochemistry* 71: 1360–1364.

Chan, J. C., Lau, C. B., Chan, J. Y., Fung, K. P., Leung, P. C., Liu, J. Q., et al. 2015. The anti-guconeogenic activity of cucurbitacins from *Momordica charantia*. *Planta Med.* 81: 327–332.

Chan, J. Y., Lam, F. C., Leung, P. C., Che, C. T., and Fung, K. P. 2009. Antihyperglycemic and antioxidative effects of a herbal formulation of Radix Astragali, Radix Codonopsis and Cortex Lycii in a mouse model of type 2 diabetes mellitus. *Phytother. Res.* 23: 658–665.

Chand, S. and Singh, A. K. 2004. *In vitro* shoot generation from cotyledonary node explants of a multipurpose leguminous tree *Pterocarpus marsupium* Roxb. *In Vitro Cell. Dev. Biol. Plant* 40: 464–466.

Chandra, R., Pati, R., and Mishra, M. 2011. Mango. In: *Advances in Horticulture Biotechnology—Regeneration Systems—Fruit Crops, Plantation Crops and Spices*, Vol. 1. Singh, H. P., Parthasarathy, V. A. and Babu, K. N. (Eds). New Delhi: Westville Publishing House, 73–90.

Chandra, S. J., Ekambaram, S. P., and Subramanian, V. 2007. Hypoglycemic and anti-lipidperoxidative effects of a polyherbal formulation, Diakyur, in experimental animal models. *J. Health Sci.* 53: 734–739.

Chandramohan, G., Al-Numair, K. S., Sridevi, M., and Pugalendi, K. V. 2010. Antihyperlipidemic activity of 3-hydroxymethyl xylitol, a novel antidiabetic compound isolated from *Casearia esculenta* (Roxb.) root, in streptozotocin-diabetic rats. *J. Biochem. Mol. Toxicol.* 24: 95–101.

Chandramohan, G., Ignacimuthu, S., and Pugalendi, K. V. 2008. A novel compound from *Casearia esculenta* (Roxb.) root and its effect on carbohydrate metabolism in streptozotocin-diabetic rats. *Eur. J. Pharmacol.* 590: 437–443.

Chandramohan, G., Ignacimuthu, S., and Pugalendi, K. V. 2007. A novel compound 3-hydroxymethyl xylitol and process for preparing the compound having antidiabetic activity. Indian Patent No: 243139 (Application No: 268/CHE/2007).

Chandrashekhar, V. M., Ganapathy, S., Ramkrishnan, A., and Narsu, M. L. 2013. Neuroprotective activity of gossypin from *Hibiscus vitifolius* against global cerebral ischemia model in rats. *Indian J. Pharmacol.* 45: 575–580.

Chang, C. L., Chang, S. L., Lee, Y. M., Chiang, Y. M., Chuang, D. Y., Kuo, H. K. et al. 2007. Cytopiloyne, a polyacetylenic glucoside, prevents type 1 diabetes in nonobese diabetic mice. *J. Immunol.* 178: 6984–6993.

Chang, C. L. T., Lin, Y., Bartolome, A. P., Chen, Y. -C. Chiu, S. -C., and Yang, W. -C. 2013a. Herbal therapies for type 2 diabetes mellitus: Chemistry, biology and potential application of selected plants and compounds. *Evid. Based Complement. Altern. Med.* 2013(378657): 33.

Chang, M. S., Oh, M. S., Kimdo, R., Jung, K. J., Park, S., Choi, S. B., et al. 2006. Effects of okchun-san, a herbal formulation, on blood glucose levels and body weight in a model of type 2 diabetes. *J. Ethnopharmacol.* 103: 491–495.

Chang, S. H., Liu, C. J., Kuo, C. H. Chen, H., Lin, W. Y., Teng, K. Y., et al. 2011. Garlic oil alleviates MAPKs- and IL-6-mediated diabetes-related cardiac hypertrophy in STZ-induced DM rats. *Evid. Based Complement. Altern. Med.* 950150: 1–11.

Chang, S. L., Chang, C. L., Chiang, Y. M., Hsieh, R. H., Czeng, C. R., Wu, T. K. et al. 2004. Polyacetylenic compounds and butanol fraction from *Bidens pilosa* can modulate the differentiation of helper T cells and prevent autoimmune diabetes in non-obese diabetic mice. *Planta Med.* 70: 1045–1051.

Chang, W. C., Shen, S. C., and Wu, J. S. 2013b. Protective effects of vescalagin from pink wax apple [*Syzygium samarangense* (Blume) Merrill and Perry] fruit against methylglyoxal-induced inflammation and carbohydrate metabolic disorder in rats. *J. Agric. Food Chem.* 61: 7102–7109.

Chattopadhyay, R. R. 1999. A comparative evaluation of some blood sugar lowering agents of plant origin. *J. Ethnopharmacol.* 67: 367–372.

Chauhan, H., Bais, S., and Reddy, Y. N. 2012. *Antidiabetic, Antihyperlipidemic and Antioxidant Activities of Lawsone: Study on Antidiabetic, Antihyperlipidemic, and Antioxidant Activity of Lawsone and Its O-Alkyl Derivatives.* Germany: LAP Lambert Academic Publishing, 100.

Chauhan, H., Bais, S., and Reddy, Y. N. 2013. *Antidiabetic, Antihyperlipidemic and Antioxidant Activity of Lawsone: Study on Antidiabetic, Antihyperlipidemic, and Antioxidant Activity of Lawsone and Its O-Alkyl Derivatives.* Germany: LAP Lambert Academic Publishing, Südwestdeutscher Verlag für Hochschulschriften, 100.

Chaurasia, B., Dhakad, R. S., Dhakar, V. K., and Jain, P. K. 2011. Preliminary phytochemical and pharmacological (antidiabetic) screening of *Cassia tora* Linn. *Int. J. Pharm. Life Sci.* 2: 759–766.

Chee, R. P., Schultheis, J. R., Cantliffe, D. J. 1992. Micropropagation of sweet potato (*Ipomoea batatas* L.). *Biotechnol. Agric. Forestry* 19: 107–117.

Chempakam. B. 1993. Hypoglycaemic activity of arecoline in betel nut, *Areca catechu* L. *Indian J. Exp. Biol.* 31: 474–475.

Chen, C., Zhang, Y., and Huang, C. 2010. Berberine inhibits PTP1B activity and mimics insulin action. *Biochem. Biophys. Res. Commun.* 397: 543–547.

Chen, C. -Y., Chiu, F. -Y., Lin, Y., Huang, W. -J., Hsieh, P. -S., and Hsu, F. -L. 2015. Chemical constituents analysis and anti-diabetic activity validation of four fern species from Taiwan. *Int. J. Mol. Sci.* 16: 2497–2516.

Chen, D., Wang, M. W., 2005. Development and application of rodent models for type 2 diabetes. *Diabetes Obes. Metab.* 7, 307–317.

Chen, L., He, T., Han, Y., Sheng, J. -Z., Jin, S., and Jin, M. -W. 2011. Pentamethylquercetin improves adiponectin expression in differentiated 3T3-L1 cells *via* a mechanism that implicates PPARγ together with TNF-α and IL-6. *Molecules* 16: 5754–5768.

Chen, Q. M., Xie, M. Z. 1986. Studies on the hypoglycaemic effect of *Coptis chinensis* and berberine. *Acta Pharmaceutica Sinica* 21: 401–406.

Chen, S. K., Zhao, P., Shao, Y. X., Li, Z., Zhang, C., Liu, P., et al. 2012. Moracin M from *Morus alba* L. is a natural phosphodiesterase-4 inhibitor. *Borg. Med. Chem. Lett.* 22: 3261–3264.

Chen, T. H., Chen, S. C., Chan, P., Chu, Y. L., Yang, H. Y., and Cheng, J. T. 2005. Mechanism of hypoglycemic effect of Stevioside, a glycoside of *Stevia rebaudiana*. *Planta Med.* 71: 108–113.

Chen, X., Bao, J., Guo, J., Ding, Q., Lu, J., Huang, M., and Wang, Y. 2012. Biological activities and potential molecular targets of cucurbitacins: A focus on cancer. *Anticancer Drugs* 23: 777–787.

Chen, X., Liu, Y., Bai, X., Wen, L., Fang, J., Ye, M., and Chen, J. 2009. Hypoglycemic polysaccharides from the tuberous root of *Liriope spicata*. *J. Nat. Prod.* 72: 1988–1992.

Chen, X., Yang, L., Zhang, N., Turpin, J., Buckheit, R. W., Osterling, C., et al. 2003. Shikonin, a component of chinese herbal medicine, inhibits chemokine receptor function and suppresses human immunodeficiency virus type 1. *Antimicrob. Agents Chemother.* 47: 2810–2816.

Chen, X. B., Zhuang, J. J., Liu, J. H., Lei, M., Ma, L., Chen, J., et al. 2011a. Potential AMPK activators of cucurbitane triterpenoids from *Siraitia grosvenorii* Swingle. *Bioorg. Med. Chem.* 19: 5776–5781.

Chen, X. L., Li, J. H., Xin, X., Zhang, Z. E., Xin, P. P., and Lu, X. X. 2011c. Cryopreservation of *in vitro* -grown apical meristems of *Lilium* by droplet-vitrification. *S. Afr. J. Bot.* 77: 397–403.

Chen, Y., Huang, P., Lin, F., Chen, W., Chen, Y., Yin, W., et al. 2011b. Magnolol: A multifunctional compound isolated from the Chinese medicinal plant *Magnolia officinalis*. *Eur. J. Integr. Med.* 3: 317–324.

Chen, Z., Jin, K., Gao, L., Lou, G., Jin, Y., Yu, Y., et al. 2010. Anti-tumor effects of bakuchiol, an analogue of resveratrol, on human lung adenocarcinoma A549 cell line. *Eur. J. Pharmacol.* 643: 170–179.

Cherian, S. and Augusti, K. T. 1993. Antidiabetic effects of a glycoside of leucopelargonidin isolated from *Ficus bengalensis* Linn. *Indian J. Exp. Biol.* 31: 26–29.

Cheruvathur, M. K., Britto, J., and Thomas, T. D. 2010. Callus induction and shoot regeneration from epicotyls explants of ethnomedicinally important *Caesalpinia bonduc* (L.) Roxb. *Iranian J. Biotechnol.* 8: 263–269.

Chi, L., Na, M., Oh, H., Bae, E. Y., Jeong, D. G., Ryu, S. E. 2006. Protein tyrosine phosphatase 1B inhibitors from *Morus* root bark. *Bioorg. Med. Chem. Lett.* 16: 1426–1429.

Chiang, Y. -M., Chang, C. L. -T., Chang, S. -L., Yang, W. -C., and Shyur, L. -F. 2007. Cytopiloyne, a novel polyacetylenic glucoside from Bidens pilosa, functions as a T helper cell modulator. *J. Ethnopharmacol.* 110: 532–538.

Chigozie, I. J. and Chidinma, I. C. 2012. Hypoglycemic, hypocholesterolemic and ocular-protective effects of an aqueous extract of the rhizomes of *Sansevieria senegambica* Baker(Agavaceae) on alloxan-induced diabetic Wistar rats. *Am. J. Biochem. Mol. Biol.* 2: 48–66.

Chitra, R., Rajamani, K., and Vadivel, E. 2009. Regeneration of plantlets from leaf and internode explants of *Phyllanthus amarus* Schum and Thonn. *Afr. J. Biotechnol.* 8: 2209–2211.

Chittora, M. and Tiwari, K. 2013. Biology and biotechnology of cumin. *Int. J. Bioassys* 2: 1066–1068.

Cho, H., Mu, J., Kim, J. K., et al. 2001. Insulin resistance and a diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKB beta). *Science* 292: 1728–1731.

Cho, J. Y., Moon, J. H., Seong, K. Y., and Park, K. H. 1998. Antimicrobial activity of 4-hydroxybenzoic acid and trans 4-hydroxycinnamic acid isolated and identified from rice hull. *Biosci. Biotechnol. Biochem.* 62: 2273–2276.

Cho, W. C., Chung, W. S., Lee, S. K., Leung, A. W., Cheng, C. H., and Yue, K. K. 2006. Gingenoside Re of *Panax ginseng* possesses significant anti-oxidant and anti-hyperlipidemic effects in streptozotocin-induced diabetic rats. *Eur. J. Pharmacol.* 550: 173–179.

Chohachi, K., Yusuka, S., Kajna, S., Eiko, M., and Hiroshi, S. 1985. Hypoglycemic activity of Glycan A, B, C, D and E from *Saccharum officinarum*. *Planta Med.* 51: 113–115.

Choi, E. -K., Kim, K. -S., Yang, H. J., Shin, M. H., Suh, H. -W., Lee, K. -B., et al. 2012a. Hexane fraction of *Citrus aurantium* L. stimulates glucagon-like peptide-1 (GLP-1) secretion *via* membrane depolarization in NCI-H716 cells. *BioChip J.* 6: 41–47.

Choi, J., Shin, M. H., Park, K. Y., Lee, K. T. Jung, H. J., Lee, M. S., et al. 2004a. Effect of kaikasaponin III obtained from *Pueraria thunbergiana* flowers on serum and hepatic lipid peroxides and tissue factor activity in the streptozotocin-induced diabetic rat. *J. Med. Food.* 7: 31–37.

Choi, J. G., Kang, O. H., Lee, Y. S., Oh, Y. C., Chae, H. S., Obiang-Obounou, B., et al. 2010. Antimicrobial activity of the constituents of *Smallanthus sonchifolius* leaves against methicillin-resistant *Staphylococcus aureus*. *Eur. Rev. Med. Pharmacol. Sci.* 14: 1005–1009.

Choi, J. S., Yokozawa, T., and Oura, H. 1991. Improvement of hyperglycemia and hyperlipemia in streptozotocin-diabetic rats by a methanolic extract of *Prunus davidiana* stems and its main component, prunin. *Planta Med.* 57: 208–211.

Choi, J. Y., Na, M., Hwang, I. H., Lee, S. H. Bae, E. Y., Kim, B. Y., and Ahn, J. S. 2009. Isolation of betulinic acid, its methyl ester and guaiane sesquiterpenoids with protein tyrosine phosphatase 1B inhibitory activity from the roots of *Saussurea lappa* C.B. Clarke. *Molecules* 14: 266–272.

Choi, R., Kim, B. H., Naowaboot, J., Lee, M. Y., Hyun, M. R., Choi, E. J., et al. 2011. Effects of ferulic acid on diabetic nephropathy in a rat model of type 2 diabetes. *Exp. Mol. Med.* 43: 676–683.

Choi, S. B., Park, C. H., Choi, M. K., Jun, D. W., Park, S. 2004b. Improvement of insulin resistance and insulin secretion by water extracts of *Cordyceps militaris*, *Phellinus linteus*, and *Paecilomyces tenuipes* in 90% pancreatectomized rats. *Biosci. Biotechnol. Biochem.* 68: 2257–2264.

Choi, S. E., Shin, H. C., Kim, H. E., Lee, S. J., Jang, H. J., Lee, K. W., et al. 2007. Involvement of Ca^{2+}, CaMK II and PKA in EGb761-induced insulin secretion in INS-1 cells. *J. Ethnopharmacol.* 110: 49–55.

Choi, Y. H., Zhou, W., Oh, J., Choe, S., Lim, D. W., and Lee, S. H. 2012b. Rhododendric acid A, a new ursane-type PTP1B inhibitor from the endangered plant *Rhododendron brachycarpum* G. Don. *Bioorg. Med. Chem. Lett.* 22: 6116–6119.

Choo, M. K., Park, E. K., Yoon, H. K., and Kim, D. H. 2002. Antithrombotic and antiallergic activities of daidzein, a metabolite of puerarin and daidzin produced by human intestinal microflora. *Biol. Pharm. Bull.* 25: 1328–1332.

Chou, T. -H., Chen, I. -S., Peng, C. -F., Sung, P. -J., and Chen, J. -J. 2008. A new dihydroagarofuranoid sesquiterpene and antituberculosis constituents from the root of *Microtropis japonica*. *Chem. Biodivers.* 5: 1412–1418.

Choudhary, M., Jaiswal, S., Singh, R., Arya, I. D., and Arya, S. 2015. A micropropagation protocol for mass multiplication of *Terminalia arjuna*—A valuable medicinal tree. *Adv. For. Sci. Cuiaba* 2: 1–6.

Chua, L. S. 2013. A review on plant-based rutin extraction methods and its pharmacological activities. *J. Ethnopharmacol.* 150: 805–817.

Chucla, M. T., Lamela, M., Gata, A., and Cadavid, I. 1998. *Centaurea corcubionensis:* A study of its hypoglycemic activity in rats. *Planta Med.* 54: 107–109.

Chung, M. J., Cho, S. Y., Bhuiyan, M. J., Kim, K. H., and Lee, S. J. 2010. Anti-diabetic effects of lemon balm (*Melissa officinalis*) essential oil on glucose- and lipid-regulating enzymes in type 2 diabetic mice. *Br. J. Nutr.* 104: 180–188.

Chung, S. H. and Choi, C. G. 2001. Comparison between white ginseng radix and rootlet for anti-diabetic mechanism in KKAy mice. *Arch. Pharm. Res.* 24: 214–218.

Chuthamat, P., Montri, N., and Sukumolanandana, C. 1999. Tissue culture of *Phyllanthus emblica* Linn. *AGRIS*, FAO (International Information System for the Agricultural Science and Technology), Thai National AGRIS Centre.

Clark, R. B. 2002. The role of PPARs in inflammation and immunity. *J. Leukoc. Biol.* 71: 388–400.

Cleasby, M. E., Dzamko, N., Hegarty, B. D., Cooney, G. J., Kraegen, E. W., and Ye, J. M. 2004. Metformin prevents the development of acute lipid-induced insulin resistance in the rat through altered hepatic signaling mechanisms. *Diabetes* 53: 3258–3266.

Compbell, W. W., Haub, M. D., Fluckery, J. D., Ostlund, R. E. Jr., Thyfault, J. P., Morse-Carrithers, H., et al. 2004. Pinitol supplementation does not affect insulin-mediated glucosemetabolism and muscle insulin receptor content and phosphorylation in older humans. *J. Nutr.* 134: 2998–3003.

Connel, R. D. 1999. Glucagon antagonists for the treatment of type 2 diabetes. *Expert Opin. Therapeutic Patents* 9: 701–709.

Cooper, E. J., Hudson, A. L., Parker, C. A., and Morgan, N. G. 2003. Effects of the beta-carbolines, harmane and pinoline, on insulin secretion from isolated human islets of Langerhans. *Eur. J. Pharmacol.* 482: 189–196.

Cooper, M. E., White, M. F., Zick, Y., and Zimmet, P. 2012. Type 2 diabetes mellitus. *Nature Publishing Group*. Novo Nordisk, Denmark. http://www.Nature.com/nrendo/posters/type2diabetesmellitus/.

Coskun, O., Kanter, M., Korkmaz, A., and Oter, S. 2005. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and β-cell damage in rat pancreas. *Pharmacol. Res.* 51: 117–123.

Costantino, L., Raimondi, L., Pirisino, R., Brunetti, T., Pessotto, P., Giannessi, F., Lins, A. P., Barlocco, D., Antolini, L., and Abady, S. A. E. 2003. Isolation and pharmacological activities of the *Tecoma stans* alkaloids. *Farmaco.* 58: 781–785.

Cristians, S., Guerrero-Analco, J. A., Perez-Vasquez, A., Palacios-Espinosa, F., Ciangherotti, C., Bye, R., et al. 2009. Hypoglycemic activity of extracts and compounds from the leaves of *Hintonia standleyana* and *H. latiflora*: Potential alternatives to the use of the stem bark of these Species. *J. Nat. Prod.* 72: 408–413.

Cummings, D. E. 2006. Ghrelin and the short and long-term regulation of appetite and body weight. *Physiol. Behav.* 89: 71–84.

Cunha, W. R., Arantes, G. M., Ferreira, D. S., Lucarini, R., Silva, M. L. A., Furtado, N. A. J. C., et al. 2008. Hypoglycemic effect of *Leandra lacunosa* in normal and alloxan-induced diabetic rats. *Fitoterapia* 79: 356–60.

D'Silva, I. and D'Souza, L. 1992. *In vitro* propagation of *Anacardium occidentale* L. *Plant Cell Tiss. Org. Cult.* 29: 1–6.

Daisy, P., Eliza, J., and Farook, K. A. M. 2009b. A novel dihydroxygymnemic triacetate isolated from *Gymnema sylvestre* possessing normoglycemic and hypolipidemic activity on streptozotocin-induced diabetic rats. *J. Ethnopharmacol.* 126: 339–344.

Daisy, P., Jasmine, R., Ignacimuthu, S., and Murugan, E. 2009a. A novel steroid from *Elephantopus scaber* L. an ethnomedicinal plant with antidiabetic activity. *Phytomedicine* 16: 252–257.

Daisy, P., Lizzy, J. A., and Rajalakshmy, M. 2012. Identification of dual agonistic ligands for insulin receptor and PPARγ through molecular docking. *Int. J. Pharm. Pharm. Sci.* 4: 142–147.

Daisy, P., Priya, C. E., and Vargese, L. 2011. A study on the regenerative potential of the root and leaf extracts of *Elephantopus scaber* L.: An anti-diabetic approach. *Afr. J. Pharm. Pharmacol.* 5: 1832–1837.

Dandin, V. S. and Murthy, H. N. 2012. Regeneration of *Andrographis paniculata* Nees: Analysis of genetic fidelity and andrographolide content in micropropagated plants. *Afr. J. Biotechnol.* 11: 12464–12471.

Danial, G. H., Ibrahim, D. A., Brkat, S. A., and Khalil, B. M. 2014. Multiple shoots production from shoot tips of fig tree (Ficus carica L.) and callus induction from leaf segments. *Int. J. Pure Appl. Sci. Technol.* 20: 117–124.

Das, A., Mukherjee, P., and Jha, T. B. 2010. High frequency micropropagation of *Aloe vera* L. Burm.f. as a low cost option towards commercialization. *Plant Tiss. Cult. Biotechnol.* 20: 29–35.

Das, S., Choudhury, M. D., and Mazumber, P. B. 2013. *In vitro* propagation of genus *Dioscorea*—A critical review. *Asian J. Pharm. Clin. Res.* 6: 26–30.

Day, C. and Bailey, C. J. 2005. Preclinical and clinical methods for evacuating anti-diabetic activity of plants. In: *Traditional Medicines for Modern Times: Antidiabetic Plants*. Soumyanath, A. (Ed.). Boca Raton, FL: CRC Press, Taylor & Francis.

De, A. U. and Saha, B. P. 1975. Indolizines II: Search for potential oral hypoglycemic agents. *J. Pharm. Sci.* 64: 49–55.

de Paulis, T., Commers, P., Farah, A., Zhao, J., McDonald, M. P., Galici, R., et al. 2004. R. 4-Caffeoyl-1,5-quinide in roasted coffee inhibits [^{3}H] naloxone binding and reverses anti-nociceptive effects of morphine in mice. *Psychopharmacology* 176: 146–153.

Deb, M. S., Jamir, N. S., and Deb, C. R. 2014. *In vitro* culture of immature embryos of *Cinnamomum tamala* Nees—The role of different factors. *Indian J. Exp. Biol*. 52: 1003–1010.

Debnath, S. C. 2004. *In vitro* culture of lowbush blueberry (*Vaccinium angustifolium* Ait.). *Small Fruits Review* 3: 393–408.

Debnath, S. C. 2009. A scale-up system for lowbush blueberry micropropagation using a bioreactor. *HortScience* 44: 1962–1966.

Dechandt, C. R. P., Siqueire, J. T., de Souze, D. L. P., Araujo, L. C. J., da Silva, V. C., de Sousa Junior, P. T., et al. 2013. *Combretum lanceolatum* flowers extract shows antidiabetic activity through activation of AMPK by quercetin. *Revista Brasileira de Farmacognosia* 23: 291–300.

Dedov, V. N., Tran, V. H., Duke, C. C., Connor, M., Christie, M. J., Mandadi, S., et al. 2002. Gingerols: A novel class of vanilloid receptor (VR1) agonists. *Br. J. Pharmacol*. 137: 793–798.

Deepak, K. G. K., Suneetha, G., and Surekha, C. 2015. A simple and effective method for vegetative propagation of an endangered medicinal plant *Salacia oblonga* Wall. *J. Nat. Med*. 70: 115–119.

Deepralard, K., Kawanishi, K., Moriyasu, M., Pengsuparp, T., and Suttisri, R. 2009. Flavonoid glucosides from the leaves of *Uvaria rufa* with advanced glycation end-products inhibitory activity. *Thai. J. Pharm. Sci*. 33: 84–90.

DeFronzo, R. A. 2004. Pathogenesis of type 2 diabetes mellitus. *Med. Clin. North Am*. 88: 787–835.

De Gouveia, N. M., Albuquerque, C. L., Espindola, L. S., and Espindola, F. S. 2013. *Pouteria ramiflora* extract inhibits activity of human salivary alpha-amylase and decreases glycemic level in mice. *An. Acad. Bras. Cienc*. 85: 1141–1148.

Dejkhamron, P., Menon, R. K., et al. 2007. Childhood diabetes mellitus: Recent advances and future prospects. *Indian J. Med. Res*. 125: 231–250.

Deng, Y., He, K., Ye, X., Chen, X., Huang, J., Li, X., et al. 2012. Saponin rich fractions from *Polygonatum odoratum* (Mill.) Druce with more potential hypoglycemic effects. *J. Ethnopharmacol*. 141: 228–233.

De-Oliveira, A. C., Silva, I. B., Manhaes-Rocha, D. A., and Paumgartten, F. J. 2003. Induction of liver monooxygenases by annatto and bixin in female rats. *Braz. J. Med. Biol. Res*. 36: 113–118.

DePaula, A. C. C. F. F., Sousa, R. V., Figueiredo-Ribeiro, R. C. L., and Buckeridge, M. S. 2005. Hypoglycemic activity of polysaccharide fractions containing ß-glucans from extracts of *Rhynchelytrum repens* (Willd.) C.E. Hubb., Poaceae. *Braz. J. Med. Biol. Res*. 38: 885–893.

Desai, S. and Tatke, P. 2015. Charantin: An important lead compound from *Momordica charantia* for the treatment of diabetes. *J. Pharmacog. Phytochem*. 3: 163–166.

Deshpande, H. A. and Bhalsing, S. R. 2015. *Helicteres isora*: Regeneration through meristem culture. *Acta Biologica Szegediensis* 59: 55–58.

Deshpande, P. K., Pathak, A. K., and Gothalwa, R. 2014. Pharmacological properties of *Andrographis paniculata*. *Int. J. Recent Adv. Multidiscip. Res*. 1: 105–110.

Deutschlander, M. S., Lall, N., van de Venter, M., and Hussein, A. A. 2011. Hypoglycaemic evaluation of a new triterpene and other compounds isolated from *Euclea undulata* Thunb. var. *myrtina* (Ebenaceae) root bark. *J. Ethnopharmacol*. 16: 1091–1095.

Deutschlander, M. S., van de Venter, M., Roux, S., Louw, J., and Lall, N. 2009. Hypoglycaemic activity of four plant extracts traditionally used in South Africa for diabetes. *J. Ethnopharmacol*. 124: 619–624.

Devani, U., Pandita, N., and Kachwala, Y. 2013. Evaluation of inhibitory activity of Vitex negundo and Terminalia chebula by alpha amylase inhibition assay in management of diabetes. *Asian J. Plant Sci. Res*. 3: 6–14.

Devi, B., Sharma, N., Kumar, D., and Jeet, K. 2013. *Morus alba* L.: A phytopharmocological review. *Int. J. Pharm. Pharmaceut. Sci*. 5: 14–18.

Devi, C. S., Murugesh, S., and Srinivasan, V. M. 2006. Gymnemic acid production in suspention cell cultures of *Gymnema sylvestre*. *J. Appl. Sci*. 6: 2263–2268.

Dey, B. and Mitra, A. 2013. Chemo-profiling of eucalyptus and study of its hypoglycemic potential. *World J. Diabetes* 4: 170–176.

Dhanabal, S. P., Kokate, C. K., Ramanathan, M., Kumar, E. P., and Suresh B. 2006. Hypoglycaemic activity of *Pterocarpus marsupium* Roxb. *Phytother Res*. 20: 4–8.

Dhanasri, G., Reddy, M. S., Naresh, B., and Devi, P. 2013. Micropropagation of *Salacia reticulata*—An endangered medicinal plant. *Plant Tissue Cult. Biotechnol*. 23: 221–229.

Diao, H., Kang, Z., Han, F., and Jiang, W. 2014. Astilbin protects diabetic rat hear against ischemia-reperfusion injury *via* blockage of HMGB1-dependent NF-κB signaling pathway. *Food Chem. Toxicol*. 63: 104–110.

Dias, A. S., Porwski, M., Alonso, M., Marroni, N., Collado, P. S., and Gonzalez-Gallego, J. 2005. Quercetin decreases oxidative stress, NF-κB activation and iNOS overexpression in liver of streptozotocin-induced diabetic rats. *J. Nutr.* 135: 2299–2304.

Dias, M. I., Cardoso, S., Martins, A., and Sousa, M. J. 2011. *In vitro* culture of *Coriandrum sativum* L. *Acta Hortic*. 925: 271–274.

Dineshkumar, B., Mithra, A., and Mahadevappa, M. 2010. Antidiabetic and hypolipidemic effects of mahanimbine (carbazole alkaloid) from *Murraya koenigii* (Rutaceae) leaves. *Int. J. Phytomed*. 2: 22–30.

Dipankar, C. R., Shital, K. B., and Shaik, M. M. 2013, Current updates on *Centella asiatica*: Phytochemistry, pharmacology and traditional uses. *Medicinal Plant Res*. 3: 20–36.

Doliński, R. and Olek, A. 2013. Micropropagation of sweet potato (*Ipomoea batatas* (L.) Lam.) from node explants. *Acta Sci. Pol. Hortorum Cultus* 12: 117–127.

Dong, H. -Q., Li, M., Zhu, F., Liu, F. -L., and Huang, J. -B. 2012. Inhibitory potential of trilobatin from *Lithocarpus polystachyus* Rehd against α-glucosidase and α-amylase linked to type 2 diabetes. *Food. Chem*. 130: 261–266.

Dong, L., Liu, M., Song, G. Y., and Wang, J. 2009. Protective effects of *Ginkgo biloba* extract on apoptosis of pancreatic β-cells in insulin resistance rats induced by high fat diet. *J. Pract. Med*. 25: 3761–3763.

Drucker, D. J. 2006. The biology of incretin hormones. *Cell Metab*. 3: 153–165.

D'Sinva, I. and D'Souza, L. 1992. *In vitro* propagation of *Anacardium occidentale* L. *Plant Cell Tiss. Org.* 29: 1–6.

Duan, S. Z., Ivashchenko, C. Y., Usher, M. G., and Mortensen, R. M. 2008. PPAR-γ in the cardiovascular system. *PPAR Res.* 2008: 745–804.

Dugasani, S., Pichika, M. R., Nadarajah, V. D., Balijepalli, M. K., Tandra, S., and Korlakunta, J. N. 2010. Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *J. Ethnopharmacol*. 127: 515–520.

Dwivedi, C. and Daspaul, S. 2013. Anti-diabetic herbal drugs and poilyherbal formulations used for diabetes: A review. *J. Phytopharmacol*. 2: 44–51.

Ebrahim, N., Shibli, R., Makhadmeh, I., Shatnawi, S., and Abu-Ein, A. 2007. *In vitro* propagation and *in vivo* acclimatization of three coffee cultivars (*Coffea arabica* L.) from Yeman. *World Appl. Sci. J.* 2: 142–150.

Eddouks, M. and Maghrani, M. 2004. Phlorizin-like effect of *Fraxinus excelsior* in normal and diabetic rats. *J. Ethnopharmacol*. 94: 149–154.

Eddouks, M. and Maghrani, M. 2008. Effect of *Lipidium sativam* L. on renal glucose reabsorption and urinary TGF-beta 1 levels in diabetic rats. *Phytother. Res.* 22: 1–5.

Eddouks, M., Chattopadhyay, D., and Zeggwagh, N. A. 2012. Animal models as tools to investigate antidiabetic and anti-inflammatory plants. *Evid. Based Complement. Alternat. Med*. 2012: 142087.

Edens, N. K., Reaves, L. A., Bergana, M. S., Reyzer, I. L., O'Mara, P., Baxter, J. H., et al. 2002. Yeast extract stimulates glucose metabolism and inhibits lipolysis in rat adipocytes *in vitro*. *J. Nutr.* 132: 1141–1148.

Eid, H. M. and Haddad, P. S. 2014. Mechanisms of action of indigenous anti-diabetic plants from the Boreal forest of Northeastern Canada. *Adv. Endocrinol*. 2014(272968): 11.

El-Abhar, H. S. and Schaalan, M. F. 2014. Phytotherapy in diabetes: Review of potential mechanistic perspectives. *World J. Diabetes* 5: 176–197.

Elaleem, K. G. A., Ahmed, M. M., and Saeed, B. E. A. E. 2014. Study of the in vitro callus induction *Trigonella foenum-graecum* L. from cotyledons and hypocotyls explants supplemented with various plant hormones. *Int. J. Curr. Microbiol. Appl. Sci*. 3: 486–493.

El-Badry, H., Shalaby, G. I., Kandeel. N. M., and Aboul-Nasr, M. H. 1998. *In vitro* propagation of garlic (*Allium sativum* L.). *HortSci*. 33: 461–468.

Elendran, S., Wang, L. W., Prankerd, R., and Palanisamy, U. D. 2015. The physicochemical properties of geraniin, a potential antihyperglycemic agent. *Pharm. Biol*. 53: 1719–1726.

El-Hawaz, R. F., Bridges, W. C., and Adelberg, J. W. 2015. *In vitro* growth of *Curcuma longa* L. in response to five mineral elements and plant density in fed-batch culture systems. *PLoS One* 10: e0118912.

El-Houri, R. B., Kotowska, D., Kristiansen, K., and Wolber, G. 2014. Isomeric C12-alkamides from purple coneflower (Echinacea purpurea) exhibit characteristics of a PPARγ partial agonist. *Planta Med*. 80: SL31. Conference: At Braga—Portugal. doi:10.1055/s-0034-1394519.

Eliza, J., Daisy, P., and Ignacimuthu, S. 2009a. Antidiabetic and anti-lipidemic effect of eramanthin from *Costus speciosus* (Koen) Sm., in streptozotocin-induced diabetic rats. *Chem. Biol. Interact*. 182: 67–72.

Eliza, J., Daisy, P., and Ignacimuthu, S. 2010. Antioxidant activity of costunolide and eremanthin isolated from *Costus speciosus* (Koen ex. Retz) Sm. *Chem. Biol. Interact*. 188: 467–472.

Eliza, J., Daisy, P., Ignacimuthu, S., and Duraipandiyan, V. 2009b. Normo-glycemic and hypolipidemic effect of costunolide isolated from *Costus speciosus* (Koen) Sm., in streptozotocin-induced diabetic rats. *Chem. Biol. Interact*. 179: 329–334.

El-Khayat, Z., Hussein, J., Ramzy, T., and Ashour, M. 2011. Antidiabetic antioxidant effect of *Panax ginseng*. *J. Med. Plants Res*. 5: 4616–4620.

El-Kordy, E. and Alshahrani, A. M. 2015. Effect of genistein, a natural soy isoflavone, on pancreatic β-cells of streptozotocin-induced diabetic rats: Histological and immunohistochemical study. *J. Microsc Ultrastructure* 3: 108–119.

Ellis, L., Clauser, E., Morgan, D. O., Edery, M., Roth, R. A., and Rutter, W. J. 1986. Replacement of insulin receptor tyrosine residues 1162 and 1163 compromises insulin stimulated kinase activity and up take of 2-deoxy glucose. *Cell* 45: 721–732.

El-Mostafa, K., kharrassi, Y. E., Badreddline, A., Andreoletti, P., Vamecq, J. Kebbaj, M. S. E., et al. 2014. Nopal cactus (*Opuntia ficus-indica*) as a source of bioactive compounds for nutrition, health and disease. *Molecules* 19: 14879–14881.

El-Nour, M. E. M., Mohammed, L. S., and Saeed, B. E. A. 2013. *In vitro* callus induction of Fenugreek (*Trigonella foenum graecum)* using different media with different auxins concentration. *Agric. Biol. J. N. Am*. 4: 243–251.

El-Shobaki, F. A., El-Bahay, A. M., Esmail, R. S. A., Abd-El-Megeid, A. A., and Esmail, N. S. 2010. Effects of figs fruit (*Ficus carica* L.) and its leaves on hyperglycemia in alloxan-diabetic rats. *World J. Dairy Food Sci*. 5: 47–57.

El-Wahab, A. E. A., Ghareeb, D. A., Sarhan, E. E., Abu-Serie, M. M., and Demellawy, M. A. E. 2013. *In vitro* biological assessment of *Berberis vulgaris* and its active constituent, berberine: Antioxidants, anti-acetylcholinesterase, anti-diabetic and anticancer effects. *BMC Complement. Altern. Med.* 13: 218.

Emerole, G., Thabrew, M. I., Anosa, V., and Okorie, D. A. 1981. Structure-activity relationship in the toxicity of some naturally occurring coumarins-chalepin, imperatorin and oxypeucedanine. *Toxicology* 20: 71–80.

Encina, C. L., Martin, E. C., Lopez, A. A., and Padilla, I. M. G. 2014. Biotechnology applied to *Annona* species: A review. *Rev. Bras. Frutic.* 36: 17–21.

Erdogan-Orhan, I., Altun, M. L., Sever-Yilmaz, B., and Saltan, G. 2011. Anti-acetylcholinesterase and anti-oxidant assets of the major components (salicin, amentoflavone, and chlorogenic acid) and the extracts of *Viburnum opulus* and *Viburnum lantana* and their total phenol and flavonoid contents. *J. Med. Food* 14: 434–440.

Estrada, O., Hasegawa, M., Gonzalez-Mujica, F., Motta, N., Ferdomo, E., Solorzano, A., et al. 2005. Evaluation of flavonoids from *Bauhinia megalandra* leaves as inhibitors of glucose-6-phosphatase system. *Phytother. Res.* 19: 859–863.

Estrada-Luna, A. A., Lopez-Perata, C., and Cardenas-Soriano, E. 2002. *In vitro* micrografting and the histology of graft union formation of selected species of prickly pear cactus (*Opuntia* spp.). *Sci. Hortic*. 92: 317–327.

Fai, Y. M. and Tao, C. C. 2009. A review of oleanoic acid in natural products. *Nat. Prod. Med*. 28: 277–290.

Fan, X., Zhang, Y., Dong, H., Wang, B., Ji, H., and Liu, X. 2015. Trilobatin attenuates the LPS-mediated inflammatory response by suppressing the NF-κB signaling pathway. *Food Chem*. 166: 609–615.

Fang, X. K., Gao, J., and Zhu, D. N. 2008a. Kaempferol and quercetin isolated from *Euonymus alatus* improve glucose uptake of 3T3-L1 cells without adipogenesis activity. *Life Sci*. 82: 615–622.

Fang, X. K., Gao, Y., Yang, H. Y., Lang, S. M., Wang, O. J., Yu, B. Y., et al. 2008b. Alleviating effects of active fraction of *Euonymus alatus* abundant in flavonoids on diabetic mice. *Am. J. Chin. Med*. 36: 125–140.

Farahanikia, B., Akbarzadeh, T., Jahangirzadeh, A., Yassa, N., Shams, A. M. R., Mirnezami, T., et al. 2011. Phytochemical investigation of *Vinca minor* cultivated in Iran. *Iranian J. Pharm. Res.* 10: 777–785.

Farias, R. A. F., Rao, V. S. N., Viana, G. S. B., Silveira, E. R., Maciel, M. A. M., and Pinto, A. C. 1997. Hypoglycaemic effect of trans-Dehydrocrotonin, a Nor-clerodane diterpenes from *Croton cajucara*. *Planta Med*. 63: 558–560.

Farooq, S. A. and Farooq, T. T. 2003. Rapid clonal propagation of *Tamarindus indica* (L) using explants from adult trees. *Pakistan J. Biol. Sci*. 6: 1591–1592.

Farswan, M., Mazumder, P. M., Parcha, V., and Upaganlawar, V. 2009. Modulatory effect of *Syzygium cumini* seeds and its isolated compound on biochemical parameters in diabetic rats. *Int. J. Green Pharm*. 5: 127–133.

Febrinda, A. E., Yuliana, N. D., Ridwan, E., Wresdiyati, T., and Astawan, M. 2014. Hyperglycemic control and diabetes complication preventive activities of Bawang Dayak (*Eleutherine palmifolia* L. Merr.) bulbs extracts in alloxan-diabetic rats. *Int. Food Res. J.* 21: 1405–1411.

Fernandes, A. C., Almeida, C. A., Albano, F., Laranja, G. A., Felzenszwalb, I., Lage, C. L., et al. 2002. Norbixin ingestion did not induce any detectable DNA breakage in liver and kidney but caused a considerable impairment in plasma glucose levels of rats and mice. *J. Nutr. Biochem*. 13: 411–420.

Fernandez-Lizarazo, J. C. and Mosquera-Vasquez, T. 2012. Efficient micropropagation of French tarragon (*Artemisia dracunculus* L.). *Agronomia Columbiana* 30: 335–343.

Ferreira da Cruz, A. C., Roche, D. I., Iarema, L., Ventrella, M. C., Costa, M. G. C., Neta, V. B. P., et al. 2014. In vitro organogenesis from root culture segments of *Bixa orellana* L. (Bixaceae). *In Vitro Cell. Dev. Biol. Plant* 50: 76–83.

Ferreres, F., Gil-Izquierdo, A., Vinholes, J., Silva, S. T., Valentao, P., and Andrade, P. B. 2012. *Bauhinia forficata* Link authenticity using flavonoids profile: Relation with their biological properties. *Food Chem*. 134: 894–904.

Feyissa, T. and Dugassa, G. 2011. *In vitro* production of virus-free sweet potato [*Ipomoea batatas* (L.) Lam] by meristem culture and thermotherapy. *Ethiopian J. Sci*. 34: 17–28

Firdous, S. M. 2014. Phyto-chemicals for the treatment of diabetes. *EXCLI J.* 13: 451–453.

Fisman, E. Z. and Tenenbaum, A. 2015. Antidiabetic treatment with gliptins: Focus on cardiovascular effects and outcome. *Cardiovasc. Diabetol*. 14: 129–132.

Fisman, E. Z., Motro, M., and Tenenbaum, A. 2008. Non-insulin antidiabetic therapy in cardiac patients: Current problems and future prospects. *Adv. Cardiol*. 45: 154–170.

Forsyth, C. and Staden, J. V. 1981. An improved method of in vitro propagation of *Dioscorea bulbifera*. *Plant Cell. Tiss. Org. Cult*. 1: 275–281.

Fotso, E., Bikay, V. B., and Derek, A. F. 2002. Callogenesis and micropropagation of *Bidens pilosa* Linn.*Cahiers Agricultures* 11: 399–402.

Fraguas, C. B., Pasqual, M., Dutra, L. F., and Caserta, J. O. 2004. Micropropagation of fig (*Ficus carica* L.) 'roxo de valinhos' plants. *In vitro Cell. Dev. Biol. Plant*. 40: 471–474.

Frank, F. M., Ulloa, J., Cazorla, S. I., Maravilla, G., Malchiodi, E. L., Garu, A., et al. 2013. Trypanocidal activity of *Smallanthus sonchifolius*: Identification of active sesquiterpene lactones by bioassay-guided fractionation. *Evid. Based Complement. Altern. Med*. 2013(627898): 8.

Frankish, N., de Sousa, F., Mills, C., and Sheridan, H. 2010. Enhancement of insulin release from the beta-cell line INS-1 by an ethanolic extract of *Bauhinia variegata* and its major constituent roseoside. *Planta Med*. 76: 995–997.

Frias, A. D. and Sgarbieri, V. C. 1998. Guar gum effect on blood serum lipids and glucose concentration of Wistar diabetic rats. *Ciencia Techno De Alimentos* 18: 1–10.

Frode, T. S. and Medeiros, Y. S. 2008. Animal models to test drugs with potential anti-diabetic activity. *J. Ethnopharmacol*. 115: 173–183.

Fuentes, N. L., Sagua, H., Morales, G., Borquez, J., San Martin, A., Soto, J., and Loyola, L. A. 2005. Experimental anti-hyperglycemic effect of diterpenoids of *Illareta azorella* compacta (Umbelliferae) Phil in rats. *Phytother. Res*. 19: 713–716.

Fuhr, L., Rousseau, M., Plauth, A., Schroeder, F. C., and Sauer, S. 2015. Amorfrutins are natural PPARγ agonists with potent anti-inflammatory properties. *J. Nat. Prod*. 78: 1160–1164.

Fujij, M., Takei, I., and Umezawa, K. 2009. Antidiabetic effect of orally administered conophylline-containing plant extract on streptozotocin-treated and Goto-Kakizaki rats. *Biomed. Pharmacother.* 63: 710–716.

Fukuda, T., Ito, H., and Yoshida, T. 2004. Effect of the walnut polyphenol fraction on oxidative stress in type 2 diabetic mice. *Biofactors* 2: 251–253.

Gaikwad, S. B., Mohan, G. K., and Rani, M. S. 2014. Phytochemicals for diabetes management. *Pharm. Crops* 5: 11–28.

Gajalakshmi, S., Vijayalakshmi, S. and Rajeswari, D. V. 2013. Pharmocological activities of *Balanites aegyptiaca* (I.)- a perspective review. *Int. J. Pharm. Sci. Rev. Res.* 22: 117–120.

Galal, A. 2012. Improving effect of salicylic acid on the multipurpose tree, *Ziziphus spina-christi* (L.) Willd tissue culture. *Am. J. Plant Sci.* 3: 947–952.

Gallagher, A. M., Flatt, P. R., Duffy, G., and Abdel-Wahab, Y. H. 2003. The effects of traditional antidiabetic plants on *in vitro* glucose diffusion. *Nutr. Res.* 23: 413–424.

Gallo, M. B. C. and Sarachine, M. J. 2009. Biological activities of lupeol. *Int. J. Biomed. Pharm. Sci.* 3(Special Issue 1): 46–66.

Gandhi, G. R., Vanlalhruaia, P., Stalin, A., Irudayaraj, S., Ignacimuthu, S., and Paulraj, M. G. 2014. Polyphenols rich *Cyamopsios tetragonoloba* (L.) Taub. beans show hypoglycemic and β-cell protective effects in type 2 diabetic rats. *Food Chem. Toxicol.* 66: 358–365.

Gao, D., Li, Q., Li, Y., Liu, Z., Fan, Y., Liu, Z., et al. 2009. Antidiabetic and antioxidant effects of oleanolic acid from *Ligustrum lucidum* Ait in alloxan-induced diabetic rats. *Phytother. Res.* 23: 1257–1262.

Gao, H., Huang, Y. -N., Xu, P. -Y., and Kawabata, J. 2007. Inhibitory effect of α-glucosidase by the fruit of *Terminalia chebula* Retz. *Food Chem.* 105: 628–634.

Gao, H., Nishioka, T., Kawabata, J., and Kasai, T. 2004. Structure-activity relationships for alpha-glucosidase inhibition of baicalein, 5,6,7-trihydroxyflavone: The effect of A-ring substitution. *Biosci. Biotechnol. Biochem.* 68: 369–375.

Gao, Q. H., Wu, C. S., and Wang, M. 2013. The jujube (*Ziziphus jujuba* Mill.) fruit: A review of current knowledge of fruit composition and health benefits. *J. Agric. Food Chem.* 61: 3351–3363.

Gao, Y., Yong, M. F., Su, Y. P., Jiang, H. M., You, X. J., Yang, Y. L., et al. 2013. Gingenoside reduces insulin resistance through activation of PPARγ pathway and inhibition of TNF-α production. *J. Ethnopharmacol.* 147: 509–516.

Gao, Y., Yong, M. F., Su, Y. P., Jiang, H. M., You, X. J., Yang, Y. L., et al. 2013a. Gingenoside reduces insulin resistance through activation of PPARγ pathway and inhibition of TNF-α production. *J. Ethnopharmacol.* 147: 509–516.

Gara, R. K., Srivastava, V. K., Duggal, S., Bagga, J. K., Bhatt, M. L. B., Sanyal, S., et al. 2015. Shikonin selectively induces apoptosis in human prostate cancer cells through the endoplasmic reticulum stress and mitochondrial apoptotic pathway. *J. Biomed. Sci.* 22: 26–33.

García López, P. M., de la Mora, P. G., Wysocka, W., Maiztegui, B., Alzugaray, M. E., Del Zotto, H., and Borelli, M. I. 2004. Quinolizidine alkaloids isolated from *Lupinus* species enhance insulin secretion. *Eur. J. Pharmacol.* 504: 139–142.

Garg, A., Garg, S., Zaneveld, L. J., and Singla, A. K. 2001. Chemistry and pharmacology of the Citrus bioflavonoid hesperidin. *Phytother. Res.* 15: 655–669.

Garg, M., Garg, C., Dhar, V. J., and Kalia, A. N. 2010. Standardized alcoholic extract of *Phyllanthus fraternus* exerts potential action against disturbed biochemical parameters in diabetic animals. *Afr. J. Biochem. Res.* 4: 186–190.

Gauttam, V. K. and Kalia, A. N. 2013. Development of polyherbal anti-diabetic formulation encapsulated in the phospholipids vesicle system. *J. Adv. Pharm. Technol. Res.* 4: 108–117.

Gayathri, M. and Kannabiran, K. 2009. Antidiabetic activity of 2-hydroxy 4-methoxy benzoic acid isolated from the roots of *Hemidesmus indicus* on streptozotocin-induced diabetic rats. *Int. J. Diabetes Metabol.* 17: 53–57.

Gayathri, M. and Kannabiran, K. 2010. 2-hydroxy-4-methoxy benzoic acid isolated isolated from *Hemidesmus indicus* ameliorates liver, kidney and pancreas injury due to streptozotocin-induced diabetes in rats. *Indian J. Exp. Biol.* 48: 159–164.

Gayathri, M. and Kannabiran, K. 2012. Effect of 2-hydroxy-4-methoxy benzoic acid isolated from *Hemidesmus indicus* on erythrocyte membrane bound enzymes and antioxidant status in streptozotocin-induced diabetic rats. *Indian J. Pharm. Sci.* 74: 474–478.

Geetha, B. S., Mathew, B. C., and Augusti, K. T. 1994. Hypoglycemic effects of leucodelphinidin derivative isolated from *Ficus bengalensis* (Linn). *Indian J. Physiol. Pharmacol.* 38: 220–222.

Geetham, P. K. and Prince, P. S. 2008. Anti-hyperglycemic effect of D-pinitol on streptozotocin-induced diabetic Wistar rats. *J. Biochem. Mol. Toxicol.* 22: 220–224.

Gehrke, I. T., Neto, A. T., Pedroso, M., Mostardeiro, C. P., Da Cruz, I. B., Silva, U. F., et al. 2013. Antimicrobial activity of *Schinus lentiscifolius* (Anacardiaceae). *J. Ethnopharmacol.* 148: 486–491.

Gehrke, I. T. S., Neto, A. T., Pedroso, M., Mostardeiro, C. P., Da Cruz, I. B. M., Silva, U. F., et al. 2013. Antimicrobial activity of *Schinus lentiscifolius* (Anacardiacea). *J. Ethnopharmacol.* 148: 486–491.

Gengiah, K., Hari, R., and Anbu, J. 2014. Antidiabetic, anti-hyperlipidemic and hepatoprotective effect of Gluconorm-5: A polyherbal formulation in streptozotocin induced hyperglycemic rats. *Anc. Sci. Life* 34: 23–32.

Genta, S. B., Cabrera, W. M., Mercado, M. I., Grau, A., Catalán, C. A, and Sánchez, S. S. 2010. Hypoglycemic activity of leaf organic extracts from *Smallanthus sonchifolius*: Constituents of the most active fractions. *Chem. Biol. Interact.* 185: 143–152.

George, C., Lochner, A., and Huisamen, B. 2011. The efficacy of *Prosopis glandulosa* as antidiabetic treatment in rat models of diabetes and insulin resistance. *J. Ethnopharmacol.* 137: 298–304.

Gepts, P. 2006. Plant genetic resources conservation and utilization: The accomplishments and future of a societal insurance policy. *Crop Sci.* 46: 2278–2292.

Ghanti, K. S., Govindaraju, B., Venugopal, R. B., Rao, S. R., Kaviraj, C. P., Jabeen, F. T. Z., et al. 2004. High frequency shoot generation from *Phyllanthus amarus* Schum. and Thonn. *Indian J. Biotechnol.* 3: 103–107.

Ghate, M. and Jain, S. V. 2013. Structure based lead optimization approach in discovery of selective DPP4 inhibitors. *Mini Rev. Med. Chem.* 13: 888–914.

Ghazanfar, K., Ganai, B. A., Akbar, S., Mubashir, K., Dar, S. A., Dar, M. Y., and Tantry, M. A. 2014. Antidiabetic activity of *Artimisia amygdalina* Decne in streptozotocin induced diabetic rats. *BioMed. Res. Int.* 2014: 1–10, Article ID 185676. doi: http://dx.doi.org/10.1155/2014/185676.

Ghisalberti, E. L. 2005. Australian and New Zealand plants with anti-diabetic properties. In: *Traditional Medicines for Modern Times: Antidiabetic Plants*, Soumyanath, A. (Ed). Boca Raton, FL: CRC Press, Taylor & Francis, 241–256.

Gholamhoseinian, A., Fallah, H., Sharififar, F., and Mirtajaddini, M. 2008. The inhibitory effect of some Iraian plant extracts on the alpha glucosidase. *Iranian J. Basic Med. Sci.* 11: 1–9.

Gholamhoseinian, A., Fallah, H., and Sharififar, F. 2009. Inhibitory effect of methanol extract of *Rosa damascena* Mill. flowers on alpha-glucosidase activity and postprandial hyperglycemia in normal and diabetic rats. *Phytomedicine* 16: 935–941.

Gholap, S. and Kar, A. 2005. Regulation of cortisol and glucose concentration by some plant extract in mice. *J. Med. Aromatic Plant Sci.* 27: 478–482.

Ghorbani, A. 2013. Best herbs for managing diabetes: A review of clinical studies. *Brazilian J. Pharm. Sci.* 49: 413–418.

Ghorbani, A. 2014. Clinical and experimental studies on polyherbal formulations for diabetes: Current status and future prospective. *J. Integrative Med.* 12: 336–345.

Ghosh, S. and Roy, T. 2013. Evaluation of anti-diabetic potential of methanolic extract of *Coccinia indica* leaves in streptozotocin-induced diabetic rats. *Int. J. Pharm. Sci. Res.* 4: 4325–4328.

Ghosh, P. S., Das, N., and Dinda, B. 2014b. Anti-oxidant flavones glycosides and other constituents from *Premna latifolia* leaves. *Indian J. Chem.* 53: 746–749.

Ghosh, S., More, P., Derle, A., Patil, A. B., Markad, P., Asok, A., et al. 2014a. Diosgenin from *Dioscorea bulbifera*: Novel hit for treatment of type 2 diabetes mellitus with inhibitory activity against α-amylase and *α*-glucosidase. *PLoS One* 9: e106039.

Ghosh, T., Maity, T. K., and Singh, J. 2011. Antihyperglycemic activity of bacosine, a triterpene from *Bacopa monnieri*, in alloxan-induced diabetic rats. *Planta Med.* 77: 804–808.

Giaginis, C., Giagini, A., and Theocharis, S. 2009. Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) ligands as potential therapeutic agents to treat arthritis. *Pharmacol. Res.* 60: 160–169.

Giancarlo, S., Rosa, L. M, Nadjafi, F., and Francesco, M. 2006. Hyroglycaemic activity of two spices extracts: *Rhus coriaria* L. and *Bunium persicum* Boiss. *Nat. Prod. Res.* 20: 882–886.

Gilbert, E. R. and Liu, D. 2013. Anti-diabetic functions of soy isoflavone genistein: Mechanisms underlying effects on pancreatic β-cell function. *Food Funct.* 4: 200.

GirGirón, M. D., Sevillano, N., Salto, R., Haidour, A., Manzano, M., Jiménez, M. L., et al. 2009. *Salacia oblonga* extract increases glucose transporter 4-mediated glucose uptake in L6 rat myotubes: Role of mangiferin. *Clin. Nutr.* 28: 565–574.

Gnamien, Y. G., Bi, I. A. Z., Kouadio, Y. J., Brostaux, Y., and Baudoin, J. P. 2013. Medium effects on micropropagation and genetic stability of *Citrullus lanatus* oleaginous type. *Agric. Sci*. 4: 32–44.

Goel, N., Singh, N., and Saini, R. 2009. Efficient *in vitro* multiplication of Syrian Rue (*Peganum harmala* L.) using 6-benzylaminopurine preconditioned seedling explants. *Nat. Sci*. 7: 129–134.

Gomase, P. V. 2012. Sesbania sesban Linn. A review on its ethnobiol, phytochemical and pharmacological profile. *Asian J. Biomed. Pharmaceut. Sci*. 2: 1307–1312.

Gomathy, V., Jayakar, B., Kothai, R., and Ramakrishnan, G. 2010. Anti-diabetic activity of *Spinacia oleracea* Linn. in alloxan-induced diabetic rats. *J. Chem. Pharm. Res*. 2: 266–274.

Gomes, J. A. D., Faria, B. G., Silva, V. D., Zangeronimo, M. G., Miranda, J. R., de Lima, A. R., et al. 2013. Influence of integral and decaffeinated coffee brews on metabolic parameters of rats fed with hiperlipidemic diets. *Braz. Arch. Biol. Technol*. 56: 829–836.

Gomez, L., Molinar-Toribio, E., Calvo-Torras, M. A., Adelantado, C., Juan, M. E., Plans, J. M., et al. 2012. D-Fagomine lowers postprandial blood glucose and modulates bacterial adhesion. *Br. J. Nutr.* 107: 1739–1346.

Gondi, M., Basha, S. A., Bhaskar, J. J., Salimath, P. V., and Prasada Rao, U. J. S. 2015. Anti-diabetic effect of dietary mango (*Mangifera indica* L.) peel in streptozotocin-induced diabetic rats. *J. Sci. Food Agri*. 95: 991–999.

Gonzalez, N. 2014. Effects of epicatechin on glucose transporters in cardiac tissue and peripheral nerves in type 2 diabetes. *FASEB J.* 28(1), Supplement 1086.5.

Goodarzi, M. T., Zal, F., Malakooti, M., Safari, M. R., and Sadeghian, S. 2006. Inhibitary activity of flavonoids on the lens aldose reductase of healthy and diabetic rats. *Acta Medica Iranica* 44: 41–45.

Gopalakrishnan, G. and Dhanapal, C. K. 2015. Evaluation of anti-diabetic activity of ursolic acid acetate isolated from *Coleus vettiveroides* (Jacob) in streptozotocin-induced diabetic rats. *World. J. Pharm. Pharm. Sci*. 4: 1316–1331.

Gopi, C. and Vatsula, T. M. 2006. *In vitro* studies on effect of plant growth regulators on callus and suspension culture biomass yield from *Gymnema sylvestre*. *Afr. J. Biotechnol*. 5: 1215–1219.

Gorelick, J., Kitron, A., Pen, S., Rosenzweig, T., and Mada, Z. 2011. Anti-diabetic activity of *Chiliadenus iphionoides*. *J. Ethnopharmacol*. 137: 1245–9.

Govindarajan, R., Asare-Anane, H., Persaud, S., Jones, P., and Houghton, P. J. 2007. Effect of *Desmodium gangeticum* extract on blood glucose in rats and on insulin secretion *in vitro*. *Planta Med*. 73: 427–432.

Govindarajan, R., Vijayakumar, M., Rao, C. V., Pushpangadan, P., Asare-Anane, H., Persuad, S., et al. 2008. Antidiabetic activity of *Croton klozchianus* in rats and direct stimulation of insulin secretion *in vitro*. *J. Pharm. Pharmacol*. 60: 371–376.

Govorko, D., Logendra, S., Wang, Y., Esposito, D., Komarnytsky, S., Ribnicky, D., et al. 2007. Polyphenolic compounds from *Artemisia dracunculus* L. inhibit PEPCK gene expression and gluconeogenesis in an H4IIE hepatoma cell line. *Am. J. Physiol. Endocrinol. Metab.* 293: E1503–1510.

Goyal, D. and Bhadauria, S. 2008. *In vitro* shoot proliferation in *Emblica officinalis* var. Balwant from nodal explants. *Indian J. Biotechnol*. 7: 394–397.

Grace, M. H., Ribnicky, D. M., Kuhn, P., Poulev, A., Logendra, S., Yousef, G. G., et al. 2009. Hypoglycemic activity of a novel anthocyanin-rich formulation from lowbush blueberry, *Vaccinium angustifolium* Aiton. *Phytomedicine* 16: 406–415.

Gray, A. M. and Flatt, P. R. 1997. Pancreatic and extra-pancreatic effects of the traditional anti-diabetic plant, *Medicago sativa* (lucerne). *Br. J. Nutr.* 78: 325–334.

Gray, A. M. and Flatt, P. R. 1998a. Antihyperglycemic actions of *Eucalyptus globulus* (eucalyptus) are associated with pancreatic and extra-pancreatic effects in mice. *J. Nutr.* 128: 2319–2323.

Gray, A. M. and Flatt, P. 1998b. Insulin releasing and insulin like activity of *Agaricus campestris* (mushroom). *J. Endocrinol*. 157: 259–266.

Gray, A. M. and Flatt, P. R. 1999. Insulin-releasing and insulin-like activity of the traditional anti-diabetic plant *Coriandrum sativum* (coriander). *Br. J. Nutr.* 81: 203–209.

Gray, A. M., Abdel-Wahab, Y. H., and Flatt, P. R. 2000. The traditional plant treatment, *Sambucus nigra* (elder), exhibits insulin-like and insulin-releasing actions *in vitro*. *J. Nutr.* 130: 15–20.

Green, D. E. 2007. New therapies for diabetes. *Clin. Cornerstone* 8: 58–63.

Griffiths, R. C., Watson, A. A., Kizu, H., Asano, N., Sharp, H. J., jones, M. G., et al. 1996. The isolation from *Nicandra physalodes* and identification of the 3-O-(d-glucopyranoside of 1a, 2b, 3a, *6a-tetrahydroxy-nortropane* (Calystegine B2). *Tetrahedron Lett*. 37: 3207–3208.

Grzegorczyk, I. and Wysokinska, H. 2008. Liquid shoot cultureof *Salvia officinalis* L. for micropropagation and production of anti-oxidant compounds: Effect of triacontanol. *Acta Soc. Bot. Pol.* 77: 99–104.

Grzegorczyk, I., Bilichowski, I., Mikiciuk-Olasik, E., and Wysokinska, H. 2005. In vitro cultures of *Salvia officinalis* L as a source of anti-oxidant compounds. *Acta Soc. Bot. Pol.* 74: 17–21.

Gu, M., Zhang, Y., Fan, S., Ding, X., Ji, G., and Huang, C. 2013. Extracts of *rhizoma Polygonati odorati* prevent high-fat diet-induced metabolic disorders in C57BL/6 mice. *PLoS ONE* 8: e81724. doi:10.1371/journal.pone.0081724.

Guerrero-Analco, J., Medina-Campos, O., Brindis, F., Bye, R., Pedraza-Chaverri, J., Navarrete, A., et al. 2007. Anti-diabetic properties of selected Mexican copalchis of the Rubiaceae family. *Phytochemistry* 68: 2087–2095.

Guerrero-Analco, J. A., Hersch-Martinez, P., Pedraza-Chaverri, J., Navarrete, A., and Mata, R. 2005. Antihyperglycemic effect of constituents from *Hintonia standleyana* in streptozotocin-induced diabetic rats. *Planta Med.* 71: 1099–1105.

Guerrero-Analco, J. A., Martineau, L., Saleem, A., Madiraju, P., Muhammad, A., et al. 2010. Bioassay-guided isolation of the antidiabetic principle from *Sorbus decora* (Rosaceae) used traditionally by the Eeyou Istchee Cree First Nations. *J. Nat. Prod.* 73: 1519–1523.

Gulati, V., Harding, I. H., Palombo, E. A. 2012. Enzyme inhibitory and antioxidant activities of traditional medicinal plants: Potential application in the management of hyperglycemia. *BMC Complement. Altern. Med.* 12: 77. doi:10.1186/1472-6882-12-77.

Gulshan, M. D. and Rao, N. R. 2013. An overview on medicinal plants with antidiabetic potential. *Int. J. Pharm. Sci. Rev. Res.* 23: 335–342.

Gunawan-Puteri, M. D. P. T. and Kawabata, J. 2012. Novel α-glucosidase inhibitors from *Macaranga tanarius* leaves. *Food Chem.* 123: 384–389.

Guo, D. -P., Zhu, Z. -J., Hu, X. X., and Zheng, S. J. 2005. Effect of cytokinins on shoot regeneration from cotyledon and leaf segment of stem mustard (*Brassica juncea* var. *Tsatsai*). *Plant Cell Tiss. Org. Cult.* 83: 123–127.

Guo, F., Huang, C., Liao, X., Wang, Y., He, Y., Feng, R., et al. 2011. Beneficial effects of mangiferin on hyperlipidemia in high-fat fed hamsters. *Mol. Nutr. Food Res.* 55: 1809–1818.

Guo, J., Liu, T., Han, L., and Liu, Y. 2009. The effects of corn silk on glycaemic metabolism. *Nutr. Metab.* 6: 47–52.

Gupta, D. and Solanki, A. 2015. *In vitro* response of *Gymnema sylvestre*: A review. *Indian J. Plant Sci.* 4: 52–59.

Gupta, P., Khan, S., Ganguly, S., and Singh, P. 2012. *In vitro* seeds germination and seedling growth of *Gymnema sylvestre* R. Br., an important anti-diabetic medicinal plant. *Researcher* 4: 43–50.

Gupta, R. and Saxena, A. M. 2011. Hypoglycemic and anti-hyperglycemic activitiesof *Syzygium cumini* (Linn.) Skeels whole fruit in normal and streptozotocin-induced diabetic rats. *Asian J. Pharm. Biol. Res.* 267–272.

Gupta, R., Sharma, A. K., Dobhal, M. P., Sharma, M. C., and Gupta, R. S. 2011. Antidiabetic and antioxidant potential of β-sitosterol in streptozotocin induced experimental hyperglycemia. *J. Diabetes* 3: 29–37.

Gupta, S., Dadheech, N., Singh, A., Soni, S. and Bhonde, R.R. 2010. *Enicostemma littorale*: a new therapeutic target for islet neogenesis. *Int. J. Integr. Biol.* 9: 50–56.

Gupta, S., Sahu, P. K., Sen, D. L., and Pandey, P. 2014. *In vitro* propagation of *Aloe vera* (L.) Burm. f. *Br. Biotechnol. J.* 4: 806–816.

Gurrola-Diaz, C. M., Borelli, M. I., Przybyl, A. K., Garcia-Lopez, J. S., de la Mora, P. G., and Garcia-Lopez, P. M. 2008. Insulin secretion effect of 2,17-dioxosparteine, 17-thionosparteine, multiflorine and 17-hydroxylupanine on rat Langerhan's islets. In: *Lupins for Health and Wealth*. Palta, J. A. and Berger, J. (Eds). In: *Proceedings of the 12th International Lupin Conference*. September 14–18 2008, Fremantle, Western Australia. ISBN-086476-153-8.

Gururaj, H. B., Giridar, P., and Ravishankar, G. A. 2007. Micropropagation of *Tinospora cordifolia* (Willd.) Miers ex. Hook. f & Thoms—A multipurpose medicinal plant. *Curr. Sci.* 92: 23–26.

Gutierrez, R. M. P., Juarez, V. A., Sauceda, J. V., and Sosa, I. A. 2014. *In vitro* and *in vivo* antidiabetic and anti-glycation properties of *Apium graveolens* in Type 1 and 2 diabetic rat. *Int. J. Pharmacol.* 10: 368–379.

Guzman, A. and Guerrero, R. O. 2005. Inhibition of aldose reductase by herbs extracts and natural substances and their role in prevention of cataracts. *Revista Cubana de Plantas Medicinales* 10: 3–4.

Guzman-Partida, A. M., Jatomea-Fino, O., Robles-Burgueño, M. R., Ortega-Nieblas, M., and Vazquez-Moreno, L. 2007. Characterization of α-amylase inhibitor from *Palo fierro* seeds. *Plant Physiol. Biochem.* 45: 711–715.

Gwon, S. Y., Jung, C. H., Moon, B. K., and Ha, T. Y. 2013. Shikonin suppresses ERK 1/2 phosphorylation during the early stages of adipocyte differentiation in 3T3-L1 cells. *BMC Complement. Alternat. Med.* 13: 207–214.

Gyes, E. M., Royani, J. I., and Rugini, E. 2007. Efficient method of micropropagation and *in vitro* rooting of teak (*Tectona grandis* L.) focusing on large-scale industrial plantations. *Ann. For. Sci.* 64: 73–78.

Ha, D. T., Phuong, T. T., Oh, J., Bae, K. H, Thuan, N. D., and Na, M. K. 2014. Palbinone from *Paeonia suffruticosa* protects hepatic cells *via* up-regulation of heme oxygenase-1. *Phytother. Res.* 28: 308–311.

Ha, D. T., Tuan, D. T., Thu, N. B., Nhiem, N. X., Ngoc, T. M., Yim, N., et al. 2009. Palbinone and triterpenes from Moutan Cortex (*Paeonia suffruticosa*, Paeoniaceae) stimulate glucose uptake and glycogen synthesis via activation of AMPK in insulin-resistant human HepG2 Cells. *Bioorg. Med. Chem. Lett.* 19: 5556–5559.

Haddad, P. S., Martineau, L. C., Lyoussi, B., and Le. P. M. 2005. Antidiabetic plants of North Africa and the Middle East. In: *Traditional Medicines for Modern Times: Antidiabetic Plants.* Soumyanath, A. (Ed). Boca Raton, FL: CRC Press, Taylor & Francis, 221–224.

Haeri, M. R., Izaddoost, M., Ardekkani, M. R., Nobar, M. R., and White, K. N. 2009. The effect of fenugreek 4-hydroxyisoleucine on liver function biomarkers and glucose in diabetic and fructose-fed rats. *Phytother. Res.* 23: 61–64.

Hailekidan, B., Andargie, M., and Assefa, K. 2013. *In vitro* plantlet regeneration from the bulbs of shallot (*Allium cepa* var. Group Aggregatum). *Res. Plant Sci.* 1: 45–52.

Hajimehdipoor , H., Sadeghi, Z., Elmi, S., Elmi, A., Ghazi-Khansari, M., Amanzadeh, Y., et al. 2006. Protective effects of *Swertia longifolia* Boiss and its active compound, swerchin on paracetamol-induced hepatotoxicity in mice. *J. Pharm. Pharmacol.* 58: 277–280.

Halder, N., Joshi, S., and Gupta, S. K. 2003. Lens aldose reductase inhibiting potential of some indigenous plants. *J. Ethnopharmacol.* 86: 113–116.

Hales, C. N. and Randle, P. J. 1963. Immunoassay of insulin with insulin-antibody precipitates. *Biochem. J.* 88: 137–146.

Hamden, K., Jaouadi, B., Carreau, S., Bejar, S., and Elfeki, A. 2010. Inhibitory effect of fenugreek galactomannan on digestive enzymes related to diabetes, hyperlipidemia, and liver-kidney dysfunctions. *Biotechnol. Bioprocess Eng.* 15: 407–413.

Hamden, K., Mnafgui, K., Amri, Z., Aloulou, A., and Elfeki, A. 2013. Inhibition of key digestive enzymes related to diabetes and hyperlipidemia and protection of liver-kidney functions by trigonelline in diabetic rats. *Sci. Pharm.* 81: 233–246.

Hamidpour, M., Hamidpour, R., and Shahlari, M. 2014. Chemistry, pharmacology and medicinal property of Sage (Salvia) to prevent and cure illnesses such as obesity, diabetes, depression, dementia, lupus, autism, heart disease and cancer. *J. Tradit. Complement. Med.* 4: 82–88.

Hammatt, N. and Ridout, M. S. 1992. Micropropagation of common ash (*Fraxinus excelsior*). *Plant Cell Tiss. Org. Cult.* 31: 67–74.

Hammouda, Y. and Amer, M. S. 1966. Antidiabetic effect of tecomine and tecostanine. *J. Pharm. Sci.* 55: 1452–1454.

Hammouda, Y. and Khalafallah, N. 1971. Stability of tecomine, the major antidiabetic factor of *Tecoma stans* (Juss.) f. Bignoniaceae. *J. Pharm. Sci.* 60: 1142–1145.

Han, J., Yang, N., Zhang, F., Zhang, C., Liang, F., Xie, W., Chen, W., et al. 2015. Rhizoma Anemarrhenae extract ameliorates hyperglycemia and insulin resistance via activation of AMP-activated protein kinase in diabetic rodents. *J. Ethnopharmacol.* 172: 368–376.

Han, L. -K., Zheng, Y. -N., Yoshikawa, M., Okuda, H., and Kimura, Y. 2005. Anti-obesity effects of chikusetsusaponins isolated from *Panax japanicus* rhizomes. *BMC Complement. Altern. Med.* 5: 9–15.

Han, X. Z., Gao, S., Cheng, Y. N., Sun, Y. Z., Liu, W., Tang, L. L., et al. 2012. Protective effect of naringenin-7-O-glucoside against oxidative stress induced by doxorubicin in H9c2 cardiomyocytes. *Biosci. Trends* 6: 19–25.

Han, Y. M., Oh, H., Na, M., Kim, B. S., Oh, W. K., Kim, B. Y., et al. 2005. PTP1B inhibitory effect of abietane diterpenes isolated from *Salvia miltiorrhiza*. *Biol. Pharm. Bull.* 28: 1795–1797.

Handral, H. K., Pandith, A., and Shruthi, S. D. 2012. A review on *Murraya koenigii*: Multipotential medicinal plant. *Asian J. Pharm. Clin. Res*. 5: 5–14.

Hannan, J. M., Ali, L., Khaleque, J.,Akhter, M., Flatt, P. R., and Abdel-Wahab, Y. H. 2012. Antihyperglycaemic activity of Asparagus racemosus roots is partly mediated by inhibition of carbohydrate digestion and absorption, and enhancement of cellular insulin action. *Br. J. Nutr.* 107: 1316–1323.

Hannan, J. M., Marenah, L., Ali, L., Rokeya, B., Flatt, P. R., and Abdel-Wahab, Y. H. 2007. Insulin secretory actions of extracts of Asparagus racemosus root in perfused pancreas, isolated islets and clonal pancreatic beta-cells. *J. Endocrinol*. 192: 159–168.

Hao, L. N., Zhang, Y. Q., Shen, Y. H., Wang, S. Y., Wang, Y. H., Zhang, H. F., and He, S. Z. 2010. Effect of puerarin on retinal pigment epithelial cells apoptosis induced partly by peroxynitrate *via* Fas/Fasl pathway. *Int. J. Ophthalmol*. 3: 283–287.

Haptemariam, S. and Lentini, G. 2015. The therapeutic potential of rutin for diabetes: An update. *Mini. Rev. Med. Chem*. 15: 524–528.

Haque, S. M. and Shosh, B. 2013. High frequency microcloning of *Aloe vera* and their true-to-type conformity by molecular cytogenetic assessment of two years old field growing regenerated plants. *Botanical Studies* 54: 46–55.

Harbilas, D., Vallerand, D., Brault, A., Saleem, A., Arnason, J. T., Musallam, L., et al. 2013. *Populus balsamifera* extract and its active component salicortin reduce obesity and attenuate insulin resistance in a diet-induced obese mouse model. *Evid. Based Complement. Alternat. Med*. 2013: 1–13, Article ID 172537. doi: http://dx.doi.org/10.1155/2013/172537.

Hardie, D. G. 2013. AMPK: A target for drugs and natural products with effects on both diabetes and cancer. *Diabetes* 62: 2164–2172.

Hashim, M. A., Yam, M. F., Hor, S. Y., Lim, C. P., Asmawi, M. Z., and Sadikun, A. 2013. Anti-hyperglycemic activity of *Swietenia macrophylla* King (Meliaceae) in normoglycemic rats undergoing glucose tolerance test. *Chin. Med*. 8: 11–17.

Hashmat, I., Azad, H., and Ahmed, A. 2012. Neem (*Azadirachta indica* A. Juss)—A nature's drug store: An overview. *Int. Res. J. Biol. Sci*. 1: 76–79.

Hassan, A. K. M. S. and Khatun, R. 2010. Regeneration of *Ficus glomerata* Roxb. using shoot tips and nodal explants. *Bangladesh J. Bot*. 39: 47–50.

Hattori, K., Sukenobu, N., Sasaki, S., Takasuga, S., Hayashi, T., Kasai, R., Yamasaki, K., et al. 2003. Activation of insulin receptors by lagerstroemin. *J. Pharmacol. Sci*. 93: 69–73.

He, T., Chen, L., Chen, Y., Han, Y., Yang, W. Q., and Jin, M. W. 2012. *In vivo* and *in vitro* protective effects of pentamethylquercetin on cardiac hypertrophy. *Cardiovasc. Drugs Ther.* 26: 109–120.

Hemalatha, S., Wahi, A. K., Singh, P. N., and Chansouria, J. P. N. 2010. Evaluation of anti-hypergycemic and free radical scavenging activity of *Melothria maderaspatana* Linn. in streptozotocin-induced diabetic rats. *Afr. J. Pharm. Pharmacol.* 4: 817–822.

Hemshekhar, M., Sebastin, S. M., Kemparaju, K., and Girish, K. S. 2012. Emerging roles of anacardic acid and its derivatives: A pharmacological overview. *Basic Clin. Pharmacol. Toxicol.* 110: 122–132.

Heo, S. I., Jin, Y. S., Jung, M. J., and Wang, M. H. 2007. Antidiabetic properties of 2,5-dihydroxy-4,3'-di(beta-D-glucopyranosyloxy)-trans-stilbene from mulberry (*Morus bombycis* Koidzumi) root in streptozotocin-induced diabetic rats. *J. Med. Food* 10: 602–607.

Hepaksoy, S. and Aksoy, U. 2006. Propagation of *Ficus carica* L. clones by *in vitro* culture. *Biologia Plantarum* 50: 433–436.

Hetta, M. H., Aly, H. F., and Arafa, A. 2014. Inhibitary effect of *Eruca sativa* Mill. on carbohydrate metabolizing enzymes *in vitro*. *Int. J. Pharm. Sci. Rev. Res.* 26: 205–208.

Higashino, H., Kinoshita, K., Kurita, T., Hamada, H., Etoh, H., and Hukunaga, Y. 2011. Inhibitory effects of shiso (*Perilla frutescens*) extracts on an increase of blood glucose level in rats. *Nippon Shokuhin Kagaku Kogaku Kaishi* 58: 164–169.

Hii, C. S. and Howell, S. L. 1985. Effects of flavonoids on insulin secretion and Ca handling in rat islets of Langerhans. *J. Endocrinol*. 107: 1–8.

Hikawczuk, V. J., Saad, J. R., Guardia, T., Juarez, A. O., and Giordano, O. S. 1998. Anti-inflammatory activity of compounds isolated from *Cecropia pachystachya*. *Anales des la Asociacion Quimica Argentina* 86: 167–170.

Hikino, H., Konno, C., Takahasi, M., Murakami, M., Kato, Y., and Karikura, M. 1986. Isolation and hypoglycemic activity of dioscorans A, B, C, D, E, and F; glycans of Dioscorea japonica rhizophors. *Planta Med*. 52: 168–171.

Hikino, H., Yoshizawa, M., Suzyki, Y., Oshima, Y., and Konno, C. 1989. Isolation and hypoglycemic activity of trichosans A, B, C, D and E: Glycans of *Trichosanthes kirilowii* roots. *Planta Med*. 55: 349–350.

Hoa, N. K., Phan, D. V., Thuan, N. D., and Ostenson, C. G. 2004. Insulin secretion is stimulated by ethanol extract of *Anemarrhena asphodeloides* in isolated islet of healthy Wistar and diabetic Goto-Kakizaki Rats. *Exp. Clin. Endocrinol. Diabetes* 112: 520–525.

Hong, E. -J., Hong, S. -J., Jung, K. H., Ban, J. Y., Baek, Y. -H., Woo, H. -S., et al. 2008. *Ecommia ulmoides* extract stimulates glucose uptake through PI 3-kinase mediated pathway in L6 rat skeletal muscle cells. *Mol. Cell. Toxicol*. 4: 224–229.

Hong, S. and Yin, M. 2010. Preliminary study on *Anemarrhena asphodeloides* tissue culture. *Chinese Traditional and Herbal Drugs* (article in Chinese). 41: 1886–1889.

Hong, S. R. and Yin, M. H. 2012. High-efficiency encapsulation-vitrification protocols for cryopreservation of embryogenic calli of the oriental medicinal plant *Anemarrhena asphodeloides* Bunge. *Cryo Letters* 33: 191–201.

Honma, A., Koyama, T., and Yazawa, K. 2010. Antihyperglycemic effects of sugar maple *Acer saccharum* and its constituent acertannin. *Food Chem*. 123: 390–394.

Hou, C., Lin, S. J., Cheng, J. T. and Hsu, F. L. 2003. Antidiabetic dimeric guianolides and a lignan glycoside from *Lactuca indica*. *J Nat Prod*. 66: 625–629.

Hou, W., Li, Y., Zhang, Q., Wei, X., Peng, A., Chen, L., and Wei, Y. 2009. Triterpene acids isolated from *Lagerstroemia speciosa* leaves as α-glucosidase inhibitors. *Phytother. Res*. 23: 614–618.

Houghton, P. J. and Raman, A. 1998. *Laboratory Handbook for the Fractionation of Natural Extracts*. London: Chapman and Hall.

Hozayen, W. G. M., Bastawy, M., and Hamed, M. Z. 2011. Biochemical effects of *Cichorium intybus* and *Sonchus oleraceus* infusions and esculetin on streptozotocin-induced diabetic albino rats. *J. Am. Sci*. 7: 1124–1137.

Hsia, S. H., Bazargan, M., and Davidson, M. B. 2004. Effect of Pancreas Tonic (an Ayurvedic herbal supplement) in type 2 diabetes mellitus. *Metabolism* 53: 1166–1173.

Hsu, F. -L., Chen, Y. C., and Cheng, J. T. 2000. Caffeic acid as active principle from the fruit of *xanthium strumarium* to lower plasma glucose in diabetic rats. *Planta Med*. 66: 228–230.

Hsu, F. -L., Huang, C. -F., Chen, Y. -W., Yen, Y. -P., Wu, C. -T., Uang, B. -J., et al. 2013. Anti-diabetic effects of pterosin A, a small molecular-weight natural product, on diabetic mouse models. *Diabetes* 62: 628–638.

Hsu, F. L., Lai, C. W., and Cheng, J. T. 1997. Antihyperglycemic effects of paeoniflorin and 8-debenzoylpaeoniflorin, glucosides from the root of *Paeonia lactiflora*. *Planta Med*. 63: 323–325.

Hsu, Y. -J., Lee, T. -H., Chang, C. L. -T., Huang, Y. -T., and Yang, W. -C. 2009. Anti-hyperglycemic effects and mechanism of *Bidens pilosa* water extract. *J. Ethnopharmacol*. 122: 379–383.

Hsu, Y. S., Kuo, Y. H., Cheng, H. L., Flatt, P. R., and Liu, H. K. 2012. *Schizandra arisanensis* extract attenuates cytokine-mediated cytotoxicity in insulin-secreting cells. *World J. Gastroenterol*. 18: 6809–6818.

Hua, J., Qi, J., and Yu, B. -Y. 2013. Iridoid and phenylpropanoid glycosides from *Scrophularia ningpoensis* Hemsl and their α-glucosidase inhibitory activities. *Fitoterapia* 93: 67–73.

Huang, C. F., Chen, Y. W., Yang, C. Y., Lin, H. Y., Way, T. D., Chiang, W., et al. 2011. Extract of lotus leaf (*Nelumbo nucifera*) and its active constituent catechin with insulin secretagogue activity. *J. Agric. Food Chem*. 59: 1087–1094.

Huang, H., Liu, N., Zhao, K., Zhu, K., Lu, X., Li, S., et al. 2011. Sanggenon C decreases tumor cell viability associated with proteasome inhibition. *Front. Biosci*. (Elite Ed). 3: 1315–1325.

Huang, J., Huang, K., Lan, T., Xie, X., Shen, X., Liu, P., and Huang, H. 2013. Curcumin ameliorates diabetic nephropathy by inhibiting the activation of the SphK1-S1P signaling pathway. *Mol. Cell. Endocrinol*. 365: 231–240.

Huang, T., Peng, G., Li, G., Yamahara, J., Roufogalis, B., and Li, Y. 2006. *Salacia oblonga* root improves postprandial hyperlipidemia and hepatic steatosis in Zucker diabetic fatty rats: Activation of PPAR. *Toxicol. Applied Pharmacol*. 210: 225–235.

Huang, T. H., He, L., Qin, Q., Yang, Q., Peng, G., Harada, M., et al. 2008. *Salacia oblonga* root decreases cardiac hypertrophy in Zucker diabetic fatty rats: Inhibition of cardiac expression of angiotensin II type 1 receptor. *Diabetes Obes. Metab.* 10: 574–585.

Huang, Y. -C., Chang, W. -L., Huang, S. F., Lin, C. -Y., Lin, H. -C., and Chang, T. -C. 2010. Pachymic acid stimulates glucose uptake through enhanced GLUT4 expression and translocation. *Eur. J. Pharmacol.* 648: 39–49.

Hui, C., Like, W., Yan, F., Tian, X., Qiuyan, W., and Lifeng, H. 2010. S-allyl-L-cysteine sulfoxide inhibited tumor necrosis factor-alpha induced monocyte adhesion and intercellular cell adhesion molecule-1 expression in human umbilical vein endothelial cells. *Anat. Rec. (Hoboken)* 293: 421–430.

Husain, G. M., Gingh, P. N., and Kumar, V. 2009. Antidiabetic activity of standardized extract of *Picrorhiza kurroa* in rat model of NIDDM. *Drug Discov. Ther.* 3: 88–92.

Husain, M. K., Anis, M., and Shahzad, A. 2007. In vitro propagation of Indian kino (*Pterocarpus marsupium* Roxb.) using thidiazuron. *In Vitro Cell. Dev. Biol. Plant* 43: 59–64.

Huseini, H. F., Darvishzadeh, F., Heshmat, R., Jafariazar, Z., Raza, M., and Larijani, B. 2009. The clinical investigation of Citrullus colocynthis (L.) schrad fruit in treatment of Type II diabetic patients: A randomized, double blind, placebo-controlled clinical trial. *Phytother Res* 23: 1186–1189.

Hussain, F., Zin, N. N. M., Zullkefli, M. R., Choon, Y. S., Abdullah, N. A., and Lin, T. S. 2013. *Piper sarmentosum* water extract attenuates diabetic complications in streptozotocin-induced Sprague-Dawley rats. *Sains Malaysiana* 42: 1605–1612.

Hussain, Z., Waheed, A., Qureshi, R. A., Burdi, D. K., Verspohl, E. J., Khan, N., et al. 2004. The effect of medicinal plants of Islamabad and Murree region of Pakistan on insulin secretion from INS-1 cells. *Phytother. Res.* 18: 73–77.

Huyssteen, M., Milne, P. J., Campbell, E. E., and van de Venter, M. 2011. Antidiabetic and cytotoxicity screening of five medicinal plants used by traditional African health practitioners in the Nelson Mandela Metropole, South Africa. *Afr. J. Trad. Complement. Altern. Med.* 8: 150–158.

Hwang, J. T., Kim, S. H., Lee, M. S., Kim, S. H., Yang, H. J., Kim, M. J., et al. 2007. Anti-obesity effects of gingenoside Rh2 are associated with the activation of AMPK signaling pathways in 3T3-L1 adipocytes. *Biochem. Biophy. Res. Commun* 364: 1002–1008.

Hwang, J. T., Lee, M. S., and Kim, H. J., Sung, M. J., Kim, H. Y., Kim, M. S., et al. 2009. Anti-obesity effect of gingenoside Rg3 involves the AMPK and PPAR-γ signal pathways. *Phytother. Res.* 23: 262–266.

Hyun, S., Kim, M. S., Song, Y. S. Bak, Y., Ham, S. Y., Lee, D. H., et al. 2015. Peroxisome proliferator-activated receptor-gamma agonist 4-O-methylhonokiol induces apoptosis by triggering the intrinsic apoptosis pathway and inhibiting the PI3K/Akt survival pathway in SiHa human cervical cancer cells. *J. Microbiol. Biotechnol.* 25: 334–342.

IDF 2011. *International Diabetes Federation Diabetes Atlas.* 5th ed. Brussels, Belgium: International Diabetes Federation Bulletin.

IDF. 2012. *International Diabetes Federation Diabetes Atlas*, update 2012. 6th ed. Brussels, Belgium. http://www.idf.org/diabetesatlas/5e/update2012.

IDF 2013. *International Diabetes Federation Diabetes Atlas.* 6th ed. Brussels, Belgium: International Diabetes Federation.

Ignacimuthu, S. and Subash-Babu, P. 2007. A process for nymphayol [17-(hexan-2yl)-10,13-dimethyl hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol] from *Nymphaea stellata* with antidiabetic property. Patent No: 252169 (Indian Patent Application No: 10567/CHE/2007).

Ijaola, T. O., Osunkiyesi, A. A., Taiwo, A. A., Oseni, O. A., Lanreiyanda, Y. A., Ajayi, J. O., et al. 2014. Antidiabetic effect of *Ipomoea batatas* in normal and alloxan-induced diabetic rats. *IOSR J. Appl. Chem.* 7: 16–25.

Ijomone, O. M. and Obi, A. U. 2013. Kolaviron, isolated from *Garcinia kola*, inhibits acetylcholinesterase activities in the hippocampus and striatum of Wistar rats. *Ann. Neurosci.* 20: 42–46.

Inmam, W. D., King, S. R., Evans, J. L., and Luo, J. 1998. Furanoeremophilane and eremophilanolide sesquiterpenes for treatment of diabetes. Patent No: US 5747527.

Inman, W. D., Luo, J., Jolad, S. D., King, S. R., and Cooper, R. 1999. Antihyperglycemic sesquiterpenes from *Psacalium decompositum*. *J. Nat. Prod.* 62: 1088–1092.

Inomoto, Y. and Kitani, Y. 1989. *In vitro* propagation of *Cinnamomum cassia*. *Plant Tiss. Cult. Lett.* 6: 25–27.

Inwanna, O. -U., Samala, S., Chanpradit, C., and van Beem, N. C. 2014. Effects of culture medium and explants types on callus and shoot induction of *Annona muricata* L. *Malaya J. Biosci.* 1: 155–159.

Ip, S. P., Yang, H., Sun, H. D., and Che, C. T. 2002. Dihydroisotanshinone I protects against menadione-induced toxicity in a primary culture of rat hepatocytes. *Planta Med*. 68: 1077–1081.

Ishiki, M. and Klip, A. 2005. Minireview: Recent developments in the regulation of glucose transporter-4 traffic: New signals, locations, and partners. *Endocrinology* 146: 5071–5078.

Ishola, I. O., Chatterjee, M., Tota, S., Tadigopulla, N., Adeyemi, O. O., Palit, G., et al. 2012. Antidepressant and anxiolytic effects of amentoflavone isolated from *Cnestis ferruginea* in mice. *Pharmacol. Biochem. Behav.* 103: 322–331.

Isikalan, C., Akbas, F. A., Namli, S., Tilkat, E., and Basaran, D. 2008. In vitro micropropagation of almond (*Amygdalus communis* L. cv. Nonpareil). *Afr. J. Biotechnol*. 7: 1875–1880.

Islam, T., Rahman, A., and Islam, A. U. 2012. Effects of extracts of fresh leaves of *Abroma augusta* L. on oral absorption of glucose and metformin hydrochloride in experimental rats. *ISRM Pharm*. 2012: 472586.

Ismail, I. S., Ismail, N. A., and Lajis, N. 2010. Ichthyotoxic properties and essential oils of Syzygium malaccense (Myrtaceae). *Pertanika J. Sci. Technol*. 18: 1–6.

Ismail, S., Naqvi, B., Anwar, N., and Zuberi, R. 2003. *In vitro* multiplication of *Coffea arabica. Pak. J. Bot*. 35: 829–834.

Ismail, A. K., Balaji, V., Anne, W. A., Sathish, S., Mayilvanan, C., and Balasubramanian, K. 2012. A novel polyherbal preparation for the management of type-2 diabetes mellitus: A clinical study. *Int. J. Pharm. Pharm. Sci*. 4: 495–500.

Itoh, A., Isoda, K., Kondoh, M., Kawase, M., Watari, A., Kobayashi, M., et al. 2010. Hepatoprotective effect of syringic acid and vanillic acid on CCl_4-induced liver injury. *Biol. Pharm. Bull*. 33: 983–987.

IUCN 2013. IUCN red list of threatened species, version 2013.

Ivorra, M. D., D'Ocan, M. P., Paya, M., and Villar, A. 1998. Antihyperglycemic and insulin-releasing effects of β-sitosterol 3-beta-D-glucoside and its aglycone, β-sitosterol. *Arch. Int. Pharmacodyn. Ther.* 296: 224–231.

Ivorra, M. D., Paya, M., and Villar, A. 1989. Effect of tormentic acid on insulin secretion in isolated rat islets of langerhans. *Phytother. Res*. 3: 145–147.

Ivorra, M. D., Paya, M., and Villar, A. 1990. Effect of β-sitosterol-3-beta-D-glucoside on insulin secretion *in vivo* in diabetic rats and *in vitro* in isolated rat islets of Langerhans. *Pharmazie* 45: 271–273.

Jadhav, A. and Waghmare, V. 2015. Micro propagation studies in insulin plant, *Costus pictus* D. Don. *Int. J. Adv. Res. Comput. Sci. Softw. Eng.* 5: 607–609.

Jain, P. S., Bari, S. B., and Surana, S. J. 2009. Isolation of stigmasterol and γ-sitosterol from petroleum ether extract of woody stem of *Abelmoschus manihot*. *Asian J. Biol. Sci*. 2: 112–117.

Jain, S., Katare, Y., and Patil, U. K. 2011. Effect of n-butanol extract of *Cassia tora* L. seeds on bio-chemical profile and β-cell regeneration in normal and alloxan-induced diabetic rats. *Der. Pharmacia Lettre* 3: 183–193.

Jain, V., Viswanatha, G. L., Manohar, D., and Shivaprasad, H. N. 2012. Isolation of antidiabetic principle from fruit rinds of *Punica granatum*. *Evid. Based Complement. Altern. Med.* 2012: 147202.

Jaiswal, N., Bhatia, V., Srivastava, S. P., Srivastava, A. K., and Tamrakar, A. K. 2012. Antidiabetic effect of *Eclipta alba* associated with the inhibition of α-glucosidase and aldose reductase. *Nat. Prod. Res.* 26: 2363–2367.

Jaiswal, P. K. and Gulati, A. 1991. *In vitro* high frequency plant regeneration of a tree legume *Tamarindus indica* (L.). *Plant Cell Rep.* 10: 569–573.

Jaiswal Sonia, P. K., Gulati, A., and Dahiya, S. 1998. Direct organogenesis in hypocotyl cultures of *Tamarindus indica*. *Biologia Plantarum* 41: 331–337.

Jala, A. 2012. Effect of NAA, BA and sucrose on shoot induction and rapid propagation by trimming shoot of *Curcuma longa* L. *Int. Trans. J. Eng. Manag. Appl. Sci. Technol.* 3: 101–107.

Jan, A., Thomas, G., Shawl, A. S., Jabeen, N., and Kozgar, M. I. 2010. Improved micropropagation protocol of an endangered medicinal plant—*Picrorhiza kurroa* Royle ex Benth. promptly through auxin treatments. *Chiang. Mai J. Sci*. 37: 304–313.

Jang, S. E., Hyam, S. R. Jeong, J. J., Kan, M. J., and Kim, D. H. 2013. Penta-O-galloyl-β-D-glucose ameliorates inflammation by inhibiting MyD88/NF-κB and MyD88/MAPK signalling pathways. *Br. J. Pharmacol*. 170: 1078–1091.

Jarvill-Taylor, K. A., Anderson, R. A., and Graves, D. J. 2001. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. *J. Am. College Nutr.* 20: 327–336.

Javed, M. A., Hassan, S., and Nazir, S. 1996. In vitro propagation of (*Bougainvillea spectabilis*) through shoot apex culture. *Pak. J. Bot.* 28: 207–211.

Jawla, S., Kumar, Y., and Khan, M. S. A. Y. 2013. Isolation of antidiabetic principle from *Bougainvillea spectabilis* willd (Nyctaginaceae) stem bark. *Trop. J. Pharm. Res.* 12: 761–765.

Jay, M. A. and Ren, J. 2007. Peroxisome proliferator-activated receptor (PPAR) in metabolic syndrome and type 2 diabetes mellitus. *Curr. Diabetes Rev.* 3: 33–39.

Jaya, A., Shanthi, P., and Sachdanandam, P. 2010. Hypoglycemic effect of *Semecarpus anacardium* in streptozotocin induced diabetic rats. *Int. J. Pharmacol.* 6: 435–443.

Jaya, A., Shanthi, P., and Sachdanandam, P. 2011. *Semecarpus anacardium* (bhallataka) alters the glucose metabolism and energy production in diabetic rats. *Evid. Based Complement. Alternat. Med.* 2011(142978): 9.

Jaybhaye, A. V. and Deokule, S. S. 2010. Study of *in vitro* seed germination and development of seedlings of *Gymnema sylvestre* (Retz) R. Br. ex Schult. *IUP J. Biotechnol.* 4: 64–68.

Jelodar, G., Mohsen, M., and Shahram, S. 2007. Effect of walnut leaf, coriander, and pomegranate on blood glucose and histo-pathology of pancreas of alloxan diabetic rats. *Afr. J. Trad. CAM.* 43: 299–305.

Jeong, K. J., Kim, G. W., and Chung, S. H. 2014. AMP-activated protein kinase: An emerging target for ginseng. *J. Ginseng Res.* 38: 83–88.

Jeppesen, P. B., Gregersen, S., Alstrup, K. K., and Hermansen, K. 2002. Stevioside induces antihyperglycaemic, insulinotropic and glucagonostatic effects *in vivo*: Studies in the diabetic Goto-Kakizaki (GK) rats. *Phytomedicine* 9: 9–14.

Jessen, N. and Goodyear, L. J. 2005. Contraction signaling to glucose transport in skeletal muscle. *J. Appl. Physiol.* 99: 330–337.

Jette, L., Harvey, L., Eugeni, K., and Levens, N. 2009. 4-Hydroxyisoleucine: A plant-derived treatment for metabolic syndrome. *Curr. Opin. Investig. Drugs* 10: 353–358.

Jianfang, F.,Yuan, L., Li, W., Gao, B., Zhang, N., and Ji, Q. 2009. Paeoniflorin prevents diabetic nephropathy in rats. *Comp. Med.* 59: 557–566.

Jiang, C. -S., Liang, L., and Guo, Y. 2012. Natural products possessing protein tyrosine phosphatase 1B (PTP1B) inhibitory activity found in the last decades. *Acta Pharmacologica Sinica* 33: 1217–1245.

Jiang, W. L., Zhang, S. P., Hou, J., and Zhu, H. B. 2012b. Effect of loganin on experimental diabetic nephropathy. *Phytomedicine* 19: 217–222.

Jimenez-Estrada, M., Merino-Aguilar, H., Lopez-Fernandez, A., Rojano-Vilchis,N. A., Roman-Ramos, R., and Alarcon-Aguilar, F. J. 2011. Chemical characterization and evaluation of the hypoglycemic effect of fructo-oligosaccharides from *Psacalium decompositum*. *J. Complement. Integr. Med.* 8: 1–10.

Jin, C. B., Hamid, M., Ismail, A., and Pei, C. P. 2012. The potential of cocoa extract as a hypoglycemic agent. *J. Trop. Med. Plants* 13: 193–197.

Jin, H. R., Zhao, J., Zhang, Z., Liao, Y., Wang, C. -Z., Huang, W. -H., et al. 2012. The antitumor natural compound falcarindiol promotes cancer cell death by inducing endoplasmic reticulum stress. *Cell Death Dis.* 3: e376.

Jin, H. Y., Cho, Y. S., Baek, H. S., and Park, T. S. 2013. Neuroprotective effects of *Vitis vinifera* extract on prediabetic mice induced by a high-fat diet. *Korean J. Int. Med.* 28: 579–586.

Jing, Y., Nakajo, S., Xia, L., Nakaya, K., Fang, Q., Waxman, S., et al. 1999. Boswellic acid acetate induces differentiation and apoptosis in leukemia cell lines. *Leukemia Res.* 23: 43–50.

Joh, E. -H. and Kim, D. -H. 2011. Kalopanaxsaponin A ameliorates experimental colitis in mice by inhibiting IRAK-1 activation in the NF-κB and MAPK pathways. *Br. J. Pharmacol.* 162: 1731–1742.

Jonnalagadd, V. G. and Selkar, N. 2013. Anti-diabetic herbal products marketed in India: An update. *J. Med. Plant Studies* 1: 24–26.

Jorge, A. P., Horst, H., de Sousa, E., Pizzolatti, M. G., and Silva, F. R. 2004. Insulinomimetic effects of kaempferitrin on glycemia and on ^{14}C-glucose uptake in rat soleus muscle. *Chem Biol. Interact.* 149: 89–96.

Joseph, B. and Jini, D. 2013. Anti-diabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. *Asian Pac. J. Trop. Dis.* 3: 93–102.

Joseph, N., Siril, E. A., and Nair, G. M. 2011. An efficient *in vitro* propagation methodology for annatto (*Bixa orellana* L.). *Physiol. Mol. Biol. Plants* 17: 263–270.

Joshi, B. N., Munot, H., Hardikar, M., and Kulkarni, A. A. 2013. Orally active hypoglycemic protein from *Costus igneus* N. E. Br.: An *in vitro* and *in vivo* study. *Biochem. Biophys. Res. Commun.* 436: 278–282.

Joshi, C. S., Priya, E. S., and Venkataraman, S. 2007. Hypoglycemic and antilipidperoxidative effects of a polyherbal formulation, Diakyur in experimental animal models. *J. Health Sci*. 53: 734–739.

Joshi, P. N., Joshi, E. B., and Jain, B. K. 2012. Ecology and conservation of threatened plants in Tapkeshwari Hill ranges in the Kachchh Island, Gujarat, India. *J. Threatened Taxa* 4: 2390–2397.

Joshi, U. J., Gadge, A. S., D'Mello, P., Sinha, R., Srivastava, S., and Govil, G. 2011. Antiinflammatory, antioxidant and anticancer activity of quercetin and its analogues. *Int. J. Res. Pharm. Biomed. Sci*. 2: 1756–1766.

Jothivel, N., Ponnusamy, S. P., Appachi, M., Singaravel, S., Rasilingam, D., Deivasigamani, K., et al. 2007. Anti-diabetic activity of methanol leaf extract of *Costus pictus* D. Don in alloxan-induced diabetic rats. *J. Health Sci*. 53: 655–663.

Joy, K. and Kuttan, R. 1999. Anti-diabetic activity of *Picrorrhiza kurrooa* extract. *J. Ethnopharmacol*. 67: 143–148.

Judd, P. A. and Ellis, P. R. 2005. Plant polysaccharides in the prevention and treatment of diabetes mellitus. In: *Traditional Medicines for Modern Times: Antidiabetic Plants*. Soumyanath, A. (Ed). Boca Raton, FL: CRC Press, Taylor & Francis, 293–303.

Jung, C. H., Zhou, S., Ding, G. X., Kim, J. H., Hong, M. H., Shin, Y. C., et al. 2006a. Antihyperglycemic activity of herb extracts on streptozotocin-induced diabetic rats. *Biosci. Biotechnol. Biochem*. 70: 2556–2559.

Jung, H. A., Karki, S., Ehom, N. -Y., Yoon, M. -H., Kim, E. J., and Choi, J. S. 2014. Anti-diabetic and antiinflammatory effects of green and red kohlrabi cultivars (*Brassica oleracea* var. *gongylodes*). *Prev. Nutr. Food Sci*. 19: 281–290.

Jung, H. A., Yoon, N. Y., Bae, H. J., Min, B. -S., and Choi, J. S. 2008. Inhibitory activities of the alkaloids from Coptidis Rhizoma against aldose reductase. *Arch. Pharm. Res*. 31: 1405–1412.

Jung, M., Park, M., Lee, H. C., Kang, Y. H., Kang, E. S., and Kim, S. K. 2006. Antidiabetic agent from medicinal plants. *Curr. Med. Chem*. 13: 1203–1218.

Jung, S. H., Ha, Y. J., Shim, E. K., Choi, S. Y., Jin, J. L., Yun-Choi, H. S., et al. 2007. Insulin-mimetic and insulin-sensitizing activities of a pentacyclic triterpinoid insulin receptor activator. *Biochem. J*. 403: 243–250.

Jung, U. J., Lee, M. -K., Jeong, K. -S., and Choi, M. -S. 2004. The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice. *J. Nutr*. 134: 2499–2503.

Jung, U. J., Lee, M. K., Park, Y. B., Kang, M. A., and Choi, M. S. 2006b. Effects of citrus flavonoids on lipid metabolizing and glucose regulating enzymes mRNA levels in type 2 diabetic mice. *Int. J. Biochem. Cell Biol*. 38: 1134–1145.

Kabeer, F. A., Sreedevi, G. B., Nair, M. S., Rajalakshmi, D. S., Gopalakrishnan, L. P., Kunjuraman, S., et al. 2013. Antineoplastic effects of deoxyelephantopin, a sesquiterpene lactone from *Elephantopus scaber*, on lung adenocarcinoma (A549) cells. *J. Integr. Med*. 11: 269–277.

Kabir, A. U., Samad, M. B., D'Costa, N. M., Akhter, F., Ahmed, A., Hannan, J. M. A. 2014. Anti-hyperglycemic activity of *Centella asiatica* is partly mediated by carbohydrase inhibition and glucose-fiber binding. *BMC Complement. Altern. Med*. 14: 31–45.

Kaczmarczyk, A., Turner, S. R., Bunn, E., Mancera, R. L., and Dixon, K. W. 2011. Cryopreservation of threatened native Australian species. *In Vitro Cell. Dev. Biol. Plant* 47: 17–25.

Kadambari, S. and Bhawna, M. 2014. *In vitro* conservation of *Zingiber officinale* through rhizome. *IOSR J. Pharm. Biol. Sci*. 9: 39–40.

Kahane, R., Rancillac, M., and De la Serve, B. T. 1992. Long-term multiplication of onion (*Allium cepa* L.) by cyclic shoot regeneration *in vitro*. *Plant Cell Tiss. Org. Cult*. 28: 281–288.

Kahn, S. E., Cooper, M. E., and Prato, S. D. 2014. Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present and future. *Lancet* 383: 1068–1083.

Kaithwas, G. and Majumdar, D. K. 2012. *In vitro* antioxidant and *in vivo* antidiabetic, antihyperlipidemic activity of linseed oil against streptozotocin-induced toxicity in albino rats. *Eur. J. Lipid Sci. Technol*. 144: 1237–1245.

Kaji, B. V., Ershadi, A., and Tohidfar, M. 2013. *In vitro* propagation of pomegranate (*Punica granatum* L.) Cv. 'Males Yazdi. *Albanian J. Agric. Sci*. 12: 43–48.

Kako, M., Miura, T., Nishiyama, Y., Ichimaru, M., Moriyasu, M., and Kato, A. 1997. Hypoglycemic activity of some triterpenoid glycosides. *J. Nat. Prod*. 60: 604–605.

Kako, M., Miura, T., Usami, M., Nishiyama, Y., Ichimaru, M., Moriyasu, M., and Kato, A. 1995. Effect of senegin-II on blood glucose in normal and NIDDM mice. *Biol. Pharm. Bull.* 18: 1159–1161.

Kamath, J. V., Rahul, N., Ashok Kumar, C. K., and Lakshmi, S. M. 2008. *Psidium guajava* L: A review. *Int. J. Green Pharm.* 2: 9–12.

Kamble, S. M., Kamlakar, P. L., Vaidya, S., and Bambole, V. D. 1998. Influence of *Coccinia indica* on certain enzymes in glycolytic and lipolytic pathway in human diabetes. *Indian J. Med. Sci.* 52: 143–146.

Kamei, R., Kitagawa, Y., Kadokura, M., Hattori, F., Hazeki, O., Ebina, Y., et al. 2002. Shikonin stimulates glucose uptake in 3T3-L1 cells *via* an insulin independent tyrosine kinase pathway. *Biochem. Biophys. Res. Comm.* 292: 642–651.

Kamel, M. S., Ohtani, K., Kurokawa,T., Assaf, M. H., El-Shanawany, M. A., Ali, A. A. et al. 1991. Studies on *Balanites aegyptiaca* fruits, an antidiabetic Egyptian folk medicine. *Chem. Pharmaceut. Bull.* 39: 1229–1233.

Kameswararao, B., Giri, R., Kesavulu, M. M., and Apparao, C. 2001. Effect of oral administration of bark extracts of *Pterocarpus santalinus* L. on blood glucose level in experimental animals. *J. Ethnopharmacol.* 74: 69–74.

Kamstaityte, D. and Stanys, V. 2004. Micropropagation of onion (*Allium cepa* L.). *Acta Universitatis Latviensis Biol.* 673: 173–176.

Kan, C. G., Ko, S. K., Sung, J. H., and Sung, S. H. 2007. Compound K enhances insulin secretion with beneficial metabolic effects in db/db mice. *J. Agric. Food. Chem.* 55: 10641–10648.

Kanai, F., Nishioka, Y., Hayashi, H., Kamohara, S., Todaka, M., and Ebina, Y. 1993. Direct demonstration of insulin-induced GLUT4 translocation to the surface of intact cells by insertion of a c-myc epitope into an exofacial GLUT4 domain. *J. Biol. Chem.* 268: 14523–14526.

Kandhare, A. D., Raygude, K. S., Ghosh, P., Ghule, A., and Bodhankar, S. L. 2012. Neuroprotective ffect of naringin by modulation of endogenous biomarkers in streptozotocin-induced painful diabetic neuropathy. *Fitoterapia* 83: 650–659.

Kanetkar, P., Singhal, R., and Kamat, M. 2007. *Gymnema sylvestre*: A memoir. *J. Clin. Biochem. Nutr.* 41: 77–81.

Kanetkar, P. V., Singhal, R. S., Laddha, K. S., and Kamat, M. Y. 2006. Extraction and quantification of gymnemic acids through gymnemagenin from callus cultures of *Gymnema sylvestre*. *Phytochem. Analysis* 17: 409–413.

Kanfade, H., Rudra, J., Bhowal, M., and Upadhyay, A. 2011. *In-vitro* callus induction and shoot regeneration in *Boerhaavia diffusa* L. *Ann. Biol. Res.* 2: 142–148.

Kang, Y. and Kim, H. Y. 2004. Glucose uptake-stimulatory activity of Amomi Semen in 3T3-L1 adipocytes. *J. Ethnopharmacol.* 92: 103–105.

Kang, J., Lee, J., Kwon, D., and Song, Y. 2013. Effect of *Opuntia humifusa* supplementation and acute exercise on insulin sensitivity and associations with PPAR-γ and PGC-1α protein expression in skeletal muscle of rats. *Int. J. Mol. Sci.* 14: 7140–7154.

Kang, M. -J., Kim, J. -I., Yoon, S. -Y., Kim, J. C., and Cha, I. -J. 2006. Pinitol from soybeans reduces postprandial blood glucose in patients with type 2 diabetes mellitus. *J. Med. Food.* 9: 182–186.

Kang, T. H., Moon, E., Hong, B. N., Choi, S. Z., Son, M., Park, J -H., and Kim, S. Y. 2011. Diosgenin from *Dioscorea nipponica* ameliorates diabetic neuropathy by inducing nerve growth factor. *Biol. Pharmaceut. Bull.* 34: 1493–1498.

Kanmegne, G. and Omokold, N. D. 2008. Germination of *Garcinia kola* (heckle) seeds in response to different hormone treatments. *Fruits* 63: 155–161.

Kant, S., Sahu, M., Sharma, S., and Kulkarni, K. S. 2002. Effect of Diabecon (D-400), an Ayurvedic herbomineral formulation on diabetic retinopathy. *Indian J. Clin. Pract.* 12: 49–56.

Kapoor, R. and Kakkar, P. 2014. Naringenin accords hepatoprotection from streptozotocin induced diabetes *in vivo* by modulating mitochondrial dysfunction and apoptotic signaling cascade. *Toxicol. Rep.* 1: 569–581.

Kappel, V. D., Pereire, D. F., Cazarolli, L. H., Guesser, S. M., da Silva, C. H. B., Schenkel, E. P., et al. 2012. Short and long term effects of *Baccharis articulata* on glucose homeostasis. *Molecules* 17: 6754–6768.

Kar, A., Choudhary, B. K., and Bandyopadhyay. N. G. 2003. Comparative evaluation of hypoglycemic activity of some Indian medicinal plants in alloxan diabetic rats. *J. Ethnopharmacol.* 84: 105–108.

Karan, A., Siril, E. A., Radha, E., and Parthasarathy, V. A. 2004. Somatic embryogenesis and plantlet regeneration from leaf and inflorescence explants of areca nut (*Areca catechu* L.). *Curr. Sci.* 86: 1623–1628.

Karan, S. K., Mondal, A., Mishra, S. K., Pal, D., and Rout, K. K. 2013. Antidiabetic effect of *Streblus asper* in streptozotocin-induced diabetic rats. *Pharmaceut. Biol.* 51: 369–375.

Karawya, M. S., Abde, S. M., EI-Olemy, M. M., and Farrag, N. M. 1984. Diphenylamine, an antihyperglycemic agent from onion and tea. *J. Nat. Prod.* 47: 775–780.

Karthic, R. and Seshadri, S. 2009. Cost effective mass multiplication of *Gymnema sylvestre* in hydroponic system. *Nature Precedings*. http://hdl.handle.net/10101/npre.2009.3770.1.

Karunanayake, E. H., Jeevathayaparan, S., and Tennekoon, K. H. 1990. Effect of *Momordica charantia* fruit juice on streptozotocin-induced diabetes in rats. *J. Ethnopharmacol.* 30: 199–204.

Karuppusamy, A. and Thangaraj, P. 2013. Anti-diabetic of *Ficus amplissima* Smith bark extract in streptozotocin-induced diabetic rats. *J. Ethnopharmacol.* 146: 302–310.

Kasabri, V., Abu-Dahab, R., Afifi, F. U., Naffa, R., and Majdalawi, L. 2012a. Modulation of pancreatic MIN6 insulin secretion and proliferation and extrapancreatic glucose absorption with *Achillea santolina*, *Eryngium creticum* and *Pistacia atlantica* extracts: *In vitro* evaluation. *J. Exp. Integr. Med.* 2: 245–254.

Kasabri, V., Abu-Dahab, R., Afifi, F. U., Naffa, R., Majdalawi, L., and Shawash, H. 2012b. *In vitro* modulation of pancreatic MIN6 insulin secretion and proliferation and extrapancreatic glucose absorption by *Paronychia argentea, Rheum ribes* and *Teucrium polium* extracts. *Jordan J. Pharm. Sci*. 5: 203–219.

Kasabri, V., Afifi,F. U., and Hamdan, I. 2011. Evaluation of the acute antihyperglycemic effects of four selected indigenous plants from Jordan used in traditional medicine. *Pharm. Biol.* 49: 687–695.

Kasabri, V., Flatt, P. R., and Abdel-Wahab, Y. H. A. 2010. *Terminalia bellirica* stimulates the secretion and action of insulin and inhibits starch digestion and protein glycation *in vitro*. *Br. J. Nutr.* 103: 212–217.

Kasagana, V. N. and Karumuri, S. S. 2011. Conservation of medicinal plants (past, present and future trends). *J. Pharm. Sci. Res.* 3: 1378–1386.

Kataeva, N. V. and Popowich, E. A. 1993. Maturation and rejuvenation of *Coriandrum sativum* shoot clones during micropropagation. *Plant Cell Tiss. Org. Cult.* 34: 141–148.

Kataky, A. and Handique, P. J. 2010. Micropropagation and screening of anti-oxidant potential of *Andrographis paniculata* (Burm. f) Nees. *J. Hill Agric.* 1: 13–18.

Katiyar, D. K., Mehrotra, A., and Pant, K. K. 2012. Hypoglycemic and antioxidant effects of a polyherbal formulation in alloxan induced diabetic rats. *Ann. Ayurvedic Med.* 1: 134–139.

Kaur, K. and Kaunt, U. 2000. Clonal propagation of *Acacia catechu* Willd. by shoot tip culture. *Plant Growth Regul.* 31: 143–145.

Kaur, M. and Valecha, V. 2014. Diabetes and anti-diabetic herbal formulations: An alternative to allopathy. *Eur. J. Med.* 6: 226–240.

Kaur, N., Chaudhary, J., Jain, A., and Kishore, L. 2011. Stigmasterol: A comprehensive review. *Int. J. Pharm. Sci. Res.* 2: 2259–2265.

Kavalal, G., Tuncel, H., Goksel, S., and Hatemi, H. H. 2003. Hypoglycemic activity of *Urtica pilulifera* in streptozotocin-diabetic rats. *J. Ethnopharmacol.* 84: 241–245.

Kawabata, J., Mizuhata, K., Sato, E., Nishioka, T., Aoyama, Y., and Kasai, T. 2003. 6-Hydroxyflavonoids as α-glucosidase inhibitors from marjoram (*Origanum majorana*) leaves. *Biosci. Biotechnol. Biochem.* 67: 445–447.

Kawano, A., Nakamura, H., Hata, S., Minakawa, M., Miura, Y., and Yagasaki, K. 2009. Hypoglycemic effect of aspalathin, a rooibos tea component from *Aspalathus linearis*, in type 2 diabetic model db/db mice. *Phytomedicine* 16: 437–443.

Kazeem, M. I., Adamson, J. O., and Ogunwande, I. A. 2013b. Modes of Inhibition of α-amylase and α-glucosidase by aqueous extract of *Morinda lucida* Benth Leaf. *Biomed. Res. Int.* 2013(527570): 6.

Kazeem, M. I., Oyedapa, B. F., Raimi, O. G., and Adu, O. B. 2013a. Evaluation of *Ficus exasperata* Vahl. Leaf extract in the management of diabetes mellitus *in vitro*. *J. Med. Sci.* 13: 269–275.

Ke, M., Hu, X. -Q., Ouyang, J., Dai, B., and Xu, Y. 2012. The effect of astragalin on the VEGF production of cultured Müller cells under high glucose conditions. *Bio-Med. Meter. Eng.* 22: 113–119.

Kelly, M. A., Mijovic, C. H., and Barnett, A. H. 2001. Genetics of type 1 diabetes. *Best Pract. Res. Clin. Endocrinol. Metab.* 15: 279–291.

Kersten, S., Desvergne, B., and Wahli, W. 2000. Roles of PPARs in health and disease. *Nature* 405: 421–424.

Kesavanarayanan, K. S., Sathiya, S., Kalaivani, P., Ranju, V., Sunil, A. G., Saravana Babu, C., et al. 2013. DIA-2, a polyherbal formulation ameliorates hyperglycemia and protein-oxidation without increasing the body weight in type 2 diabetic rats. *Eur. Rev. Med. Pharmacol. Sci.* 17: 356–369.

Keshava, C., Keshava, N., Ong, T. M., and Nath, J. 1998. Protective effect of vanillin on radiation-induced micronuclei and chromosomal aberrations in V79 cells. *Mut. Res.* 397: 149–159.

Kevers, C., Gal, N. L., Monteiro, M., Dommes, J., and Gasper, T. 2000. Somatic embryogenesis of *Panax ginseng* in liquid cultures: A role for polyamines and their metabolic pathways. *Plant Growth Regulation* 31: 209–214.

Kevers, C., Jacques, P., Thonart, P., and Gaspar, T. 1999. *In vitro* root cultures of *Panax ginseng* and *P. quinquefolium*. *Plant Growth Regulation* 27: 173–179.

Khan, A., Ali, S., and Ahmad, J. 2011. Antidiabetic activity of traditional herbal formulation. *Int. J. Drug Formulation Res.* 2: 96–104

Khan, C. R. and White, M. F. 1998. The insulin receptor and the molecular mechanism of insulin action. *J. Clin. Invest*. 82: 1151–1156.

Khan, K. H. 2009. Roles of *Emblica officinalis* in medicine—A review. *Bot. Res. Int.* 2: 218–228.

Khan, M., Ali, M., Ali, A., and Mir, S. R. 2014. Hypoglycemic and hypolipidemic activities of Arabic and Indian origin *Salvadora persica* root extract on diabetic rats with histopathology of their pancreas. *Int. J. Health Sci*. 8: 45–58.

Khan, M., Maryam, A., Qazi, J. I., and Ma, T. 2015. Targeting apoptosis and multiple signaling pathways with icariside II in cancer cells. *Int. J. Biol. Sci.* 11: 1100–1112.

Khan, S. E., Hull, R. l. and Utzschneider 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 444: 840–846.

Khan, V., Najmi, A. K., Akhtar, M., Aqil, M., Mujeeb, M., and Pillai, K. K. 2012. A pharmacological appraisal of medicinal plants with antidiabetic potential. *J. Pharm. Bioallied Sci*. 4: 27–42.

Khanna, P., Jain, S. C., Panagariya, A., and Dixit, V. P. 1981. Hypoglycemic activity of polypeotide-p from a plant source. *J. Nat. Prod*. 44: 648–655.

Khatodia, S. and Biswas, K. 2014. A comparative study of hairy root culture induction efficiency in four medicinally important plants using *Agrobacterium rhizogenes*. *Int. J. Curr. Microbiol. App. Sci*. 3: 625–633.

Khatum, M. M., Hossain, M. S., Haque, M. A., and Khalekuzzaman, M. 2010. *In vitro* propagation of *Citrullus lanatus* Thumb. from nodal explants culture. *J. Bangladesh Agril. Univ.* 8: 203–206.

Khawar, K. M., Ozel, C. A., Calci, S., Ozcan, S., and Arslan, O. 2005. Efficient shoot regeneration in Syrian rue (*Peganum harmala* L.) under *in vitro* conditions. *Int. J. Agri. Biol.* 7: 790–793.

Kho, M. C., Lee, Y. J., Cha, J. D., Choi, K. M., Kang, D. G., and Lee, H. S. 2014. *Gastrodia elata* ameliorates high-fructose diet-induced lipid metabolism and endothelial dysfunction. *Evid. Based Complement. Alternat. Med*. 2014(101624): 10.

Kim, D. -H., Yu, K. -W., Bae, E. -A., Park, H. -J., and Choi, J. -W. 1998. Metabolism of kalopanaxsaponin B and H by human intestinal bacteria and antidiabetic activity of their metabolites. *Bio. Pharm. Bull*. 21: 360–365.

Kim, E. -K., Kwon, K. -B., Han, M. -J., Song, M. -Y., Lee, J. -H., Lv, N., et al. 2007a. Inhibitory effect of *Artemisia capillaris* extract on cytokine-induced nitric oxide formation and cytotoxicity of RINm5F cells. *Int. J. Mol. Med*. 19: 535–540.

Kim, H. J., Kong, M. K., and Kim, Y. C. 2008. Beneficial effects of *Phellodendri Cortex* extract on hyperglycemia and diabetic nephropathy in streptozotocin-induced diabetic rats. *BMB Rep.* 41: 710–715.

Kim, H. -L., Sim, J. -E., Choi, H. -M., Choi, I. -Y., Jeong, M. -Y., Park, J., et al. 2014. The AMPK pathway mediates an anti-adipogenic effect of fruits of *Hovenia dulcis* Thumb. *Food Funct*. 5: 2961–2968.

Kim, H. Y., Moon, B. H., Lee, H. J., and Choi, D. H. 2004. Flavonoid glycosides from the leaves of *Eucommia ulmoides* O. with glycation inhibitory activity. *J Ethnopharmacol.* 93: 227–230.

Kim, J. and Park, Y. 2012. Anti-diabetic effect of sorghum extract on hepatic gluconeogenesis of streptozotocin-induced diabetic rats. *Nutr. Metab.* 9: 106–113.

Kim, J., Kim, C. -S., Lee, Y. M., Sohn, E., Jo, K., Shin, S. D., et al. 2013. Scopoletin inhibits rat aldose reductase activity and cataractogenesis in galactose-fed rats. *Evid. Based Complement. Alternat. Med.* 2013(787138): 8.

Kim, J. D., Kang, S. M., Seo, S. B., Choi, H. Y., Choi, H. S., and Ku, S. K. 2006. Anti-diabetic activity of SMK001, a poly herbal formula in streptozotocin induced diabetic rats: Therapeutic study. *Biol. Pharm. Bull.* 29: 477–482.

Kim, J. -H., Chung, H. -S., Kang, M., Kim, Y., Kim, B. -S., and Kim, Y. -S. 2011c. Anti-diabetic effect of standardized herbal formula PM021 consisting of Mori Folium and Aurantii Fructus on type II diabetic Otsuka Long–Evans Tokushima Fatty (OLETF) rats. *Diabetes Res. Clin. Practice* 93: 198–204.

Kim, J. -I., Kim, J. C., Kang, M. -J., Lee, M. -S., Kim, J. -J., and Cha, I. J. 2005. Effects of pinitol isolated from soybeans on glycaemic control and cardiovascular risk factors in Korean patients with type-2 diabetes mellitus: A randomized controlled study. *Eur. J. Clin. Nutr.* 59: 456–458.

Kim, J. -S., Yang, J., and Kim, M. -J. 2011b. Alpha glucosidase inhibitory effect, anti-microbial activity and UPLC analysis of *Rhus verniciflua* under various extract conditions. *J. Med. Plant Res.* 5: 77–83.

Kim, K. and Kim, H. Y. 2008. Korean red ginseng stimulates insulin release from isolated rat pancreatic islets. *J. Ethnopharmacol*. 120: 190–195.

Kim, K. C., Kang, S. S., Lee, J., Park, D., and Hyn, J. W. 2012. Baicalein attenuates oxidative stress-induced expression of matrix metalloproteinase-1 by regulating the ERK/JNK/AP-1 pathway in human keratinocytes. *Biomol. Ther. (Seoul)* 20: 57–61.

Kim, K. C., Lee, I. K., Kang, K. A., Kim, H. S., Kang, S. S., and Hyun, J. W. 2012. Baicalein (5,6,7-trihydroxyflavone) reduces oxidative stress-induced DNA damage by upregulating the DNA repair system. *Cell Biol. Toxicol*. 28: 421–433.

Kim, K -H., Kim, K -S., Shin, M. H., Jang, E. G., Kim, E. Y., Lee, J. H., et al. 2013. Aqueous extract of *Anemarrhena asphodeloides* stimulate glucagon-like peptide-1 secreation in enteroendocrine NCI-H716 cells. *BioChip J.* 7: 188–193.

Kim, K. J., Lee, M. S., Jo, K., and Hwang, J. K. 2011a. Piperidine alkaloids from *Piper retrofractum* Vahl. protect against high-fat diet-induced obesity by regulating lipid metabolism and activating AMP-activated protein kinase. *Biochem. Biophys. Res. Commun*. 411: 219–225.

Kim, M. -S. and Kim, S. -H. 2011. Inhibitory effect of astragalin on expression of lipopolysaccharide-induced inflammatory mediators through NF-κB in macrophages. *Arch. Pharm. Res*. 34: 2101–2107.

Kim, N. Y., Lee, M. K., Park, M. J., Kim, S. G., Park, H. J., Chow, J. W., et al. 2005. Momordin Ic and oleanolic acid from Kochiae Fructus reduce carbon tetrachloride-induced hepatotoxicity in rats. *J. Med. Food*. 8: 177–183.

Kim, O. S., Kim, Y. S., Jang, D. S., Yoo, N. H., and Kim, J. S. 2009. Cytoprotection against hydrogen peroxide-induced cell death in cultured mouse mesangial cells by erigeroflavanone, a novel compound from the flowers of Erigeron annuus. *Chem. Biol. Interact*. 180: 414–420.

Kim, S., Kang, K., Zhang, R., Piao, M., Ko, D., Wang, Z., et al. 2008. Protective effect of esculetin against oxidative stress-induced cell damage *via* scavenging reactive oxygen species. *Acta Pharmacol. Sinica* 29: 13–19.

Kim, S. J., Kim, M. C., Lee, B. J., Park, D. H., Hong, S. H., and Um, J. Y. 2010. Anti-inflammatory activity of chrysophanol through the suppression of NF-kappaB/caspase-1 activation *in vitro* and *in vivo*. *Molecules* 15: 6436–6451.

Kim, S. M., Kang, K., Jho, E. H., Jung, Y. J., Nho, C. W., Um. B. H., et al. 2011. Hepatoprotective effect of flavonoid glycosides from *Lespedeza cuneata* against oxidative stress induced by tert-butyl hyperoxide. *Phytother. Res*. 25: 1011–1017.

Kim, S. O., Yun, S. -J., and Lee, E. H. 2007b. The water extract of adlay seed (*Coix lachrymajobi* var. *mayuen*) exhibits anti-obesity effects through neuroendocrine modulation. *Am. J. Chin. Med*. 35: 297–308.

Kim, T. H., Kim, J. K., Kang, Y. H., Lee, J. Y., Kang, I. J., and Lim, S. S. 2013a. Aldose reductase inhibitory activity of compounds from *Zea mays* L. *Biomed. Res. Int*. 2013: 727143.

Kim, Y. H., Lee, Y. S., and Choi, E. M. 2010. Chrysoeriol isolated from *Eurya cilliata* leaves protects MC3T3-E1 cells against hydrogen peroxide-induced inhibition of osteoblastic differentiation. *J. Appl. Toxicol*. 30: 666–673.

Kim, Y. M., Kim, S. G, Khil, L. Y., and Moon, C. K. 1995. Brazilin stimulates the glucose transport in 3T3-L1 cells. *Planta Med*. 61: 297–301.

Kimura, M., Waki, I., Chujo, T., Kikuchi, T., Hiyama, C., Yamazaki, K., et al. 1981. Effects of hypoglycemic components in ginseng radix on blood insulin levels in alloxan diabetic mice and on insulin release from perfused rat pancreas. *J. Pharmacobiodyn*. 4: 410–417.

King, A. J. F. 2012. The use of animal models in diabetes research. *Br. J. Pharmacol*. 166: 877–894.

Kingsley, O., Georgina, E. O., Esosa, U. S. and Sunday, J. J. 2010. Evaluation of hypoglycemic and antioxidant properties of *Garcinia kola* seeds in Wister rats. *Curr. Res. J. Biol. Sci*. 3: 326–329.

Kingwell, K. 2014. GIG1 goes long to tackle diabetes. *Nat. Rev. Drug Discov.* 13: 652–653.

Kishi, A., Morikawa, T., Matsuda, H., and Yoshikawam, M. 2003. Structures of new friedelane and norfriedelane-type triterpenes and polyacylated eudesmane-type sesquiterpene from *Salacia chinensis* Linn. (*S. prinoides* DC., Hippocrateaceae) and radical scavenging activities of principal constituents. *Chem. Pharm. Bull*. 51: 1051–1055.

Klein, G., Kim, J., Himmeldirk, K., Cao, Y., and Chen, X. 2007. Antidiabetes and anti-obesity activity of *Lagerstroemia speciosa*. *Evid. Based Complement. Alternative Med. (eCAM)* 4: 401–407.

Klover, P. J. and Mooney, R. A. 2004. Hepatocytes: Critical for glucose homeostasis. *Int. J. Biochem. Cell Biol.* 36: 753–758.

Ko, B. S., Jang, J. S., Hong, S. M., Sung, S. R., Lee, J. E., Lee, M. Y., et al. 2007. Changes in components, glycyrrhizin and glycyrrhetinic acid in raw *Glycyrrhiza uralensis* Fisch, modify insulin sensitizing and insulinotropic actions. *Biosci. Biotechnol. Biochem.* 71: 1452–1461.

Ko, B. S., Kim, H. K., and Park, S. 2002. Insulin sensitizing and insulin like effects of water extract from *Kalopanax pictus* Nakai in 3T3-L1 cells. *J. Korean Soc. Agric. Chem. Biotechnol.* 45: 42–46.

Kobayashi, K., Ishihara, T., Khono, E., Miyase, T., and Yoshizaki, F. 2006. Constituents of stem bark of *Callistemon rigidus* showing inhibitory effects on mouse alpha-amylase activity. *Biol. Pharm. Bull.* 29: 1275–1277.

Kobayashi, T., Song, Q. H., Hong, T., Kitamura, H., and Cyong, J. C. 2002. Preventative effects of the flowers of *Inula britannica* on autoimmune diabetes in C57BL/KsJ mice induced by multiple low doses of streptozotocin. *Phytother. Res.* 16: 377–382.

Kondeti, V. K., Badri, K. R., Maddirala, D. R., Thur, S. K., Fatima, S. S., Kasetti, R. B., et al. 2010. Effect of *Pterocarpus santalinus* bark, on blood glucose, serum lipids, plasma insulin and hepatic carbohydrate metabolic enzymes in streptozotocin-induced diabetic rats. *Food Chem. Toxicol.* 48: 1281–1287.

Kondo, M., Hirano, Y., Nishio, M., Furuya, Y., Nakamura, H., and Watanabe, T. 2013. Xanthine oxidase inhibitory activity and hypouricemic effect of aspalathin from unfermented rooibos. *J. Food Sci.* 78: 1935–1939.

Koneri, R. B., Samaddar, S., and Ramaiah, C. T. 2014a. Antidiabetic activity of a triterpenoid saponin isolated from *Momordica cymbalaria* Fenzl. *Indian J. Exp. Biol.* 52: 46–52.

Koneri, R. B., Samaddar, S., Simi, S. M., and Rao, S. T. 2014b. Neuroprotective effect of a triterpenoid saponin isolated from *Momordica cymbalaria* Fenzl in diabetic peripheral neuropathy. *Indian J. Pharmacol.* 46: 76–81.

Kong, L. D., Tan, R. X., Woo, A. Y., and Cheng, C. H. 2001. Inhibition of rat brain monoamine oxidase activities by psoralen and isopsoralen: Implications for the treatment of affective disorders. *Pharmacol. Toxicol.* 88: 75–80.

Kong, W. -H., Oh, S. -H., Ahn, Y. -R., Kim, K. -W., Kim, J. -H., and Seo, S. -W. 2008. Antiobesity effects and improvement of insulin sensitivity by 1-deoxynojirimycin in animal models. *J. Agric. Food Chem.* 56: 2613–2619.

Konig, G. M., Wright, A. D., Keller, W. J., Judd, R. L., Bates, S., and Day, C. 1998. Hypoglycaemic activity of an HMG-containing flavonoid glucoside, chamaemeloside, from *Chamaemelum nobile*. *Planta Med.* 64: 612–614.

Konno, C., Mizuno, T., and Hikino, H. 1985a. Isolation and hypoglycemic activity of Ephedrans A, B, C, D and E, glycans of *Ephedra distachya* herb. *Planta Med.* 51: 162–163.

Konno, C., Mizuno, T., and Hikino, H. 1985b. Isolation and hypoglycemic activity of lithospermans A, B and C, glycans of *Lithospermum erythrorhizon* roots. *Planta Med.* 2: 157–158.

Konno, C., Murayama, M., Sugiyama, K., Arai, M., Murakami, M., Takahashi, M., et al. 1985c. Antidiabetes drugs. 5. Isolation and hypoglycemic activity of aconitans A, B, C and D, glycans of *Aconitum carmichaeli* roots. *Planta Med.* 51: 160–161.

Konno, C., Sugiyama, K., Kano, M., Takahashi, M., and Hikino, H. 1984. Isolation and hypoglycaemic activity of panaxans A, B, C, D, and E, glycans of *Panaxginseng* roots. *Planta Med* 50: 434–436.

Konno, C., Suzuki, Y., Oishi, K., Munakata, E., and Hikino, H. 1985d. Isolation and hypoglycemic activity of atractans A, B and C, glycans of *Atractylodes japonica* rhizomes. *Planta Med.* 51: 102–103.

Koo, H. J., Kwak, J. H., and Kang, S. C. 2014. Anti-diabetic properties of *Daphniphyllum macropodum* fruit and its active compound. *Biosci. Biotechnol. Biochem.* 78: 1392–1401.

Koopmans, S. J., Moroz, Z., Dekker, R., Corbijin, H., Ackermans, M., and Sauerwein, H. 2006. Association of insulin resistance with hyperglycemia in streptozotocin-diabetic pigs: Effects of metformin at isoenergetic feeding in a type 2-like diabetic pig model. *Metabolism* 55: 960–971.

Korec, R., Sensch, K. H., and Zoukas, T. 2000. Effects of the neoflavonoid coutareagenin, one of the antidiabetic active substances of *Hintonia latiflora*, on streptozotocin-induced diabetes mellitus in rats. *Arzneimittel-Forschung* 50: 189–224.

Kotani, H., Tanabe, H., Mizukami, H., Amagaya, S., and Inoue, M. 2012. A naturally occurring rexinoid, honokiol, can serve as a regulator of various retinoid X receptor heterodimers. *Biol. Pharmaceut. Bull.* 35: 1–9.

Kotowska, D., El-Houri, R. B., Borkowski, K., Petersen, R. K., Frette, X. C., Wolber, G., et al. 2014. Isomeric C_{12}-alkamides from the roots of *Echinacea purpurea* improve basal and insulin-dependent glucose uptake in 3T3-L1 adipocytes. *Planta Med.* 80: 1712–1720.

Kour, K. and Bani, S. 2011. Chicoric acid regulates behavioral and biochemical alterations induced by chronic stress in experimental Swiss albino mice. *Pharmacol. Biochem. Behav.* 99: 342–348.

Kovacic, S., Soltys, C. -L. M., Barr, A. J., Shiojima, I., Walsh, K., and Dyck, J. R. B. 2003. Akt activity negatively regulates phosphorylation of AMP-activated protein kinase in the heart. *J. Biol. Chem.* 278: 39422–39427.

Kozgar, M. I. and Shahzad, A. 2012. An improved protocol for micropropagation of teak tree (*Tectona grandis* L.). *Rend. Fis. Acc. Lincei* 23: 195–202.

Krisanapun, C., Peungvicha, P., Temsiririrkkul, R., and Wongkrajang, Y. 2009. Aqueous extract of *Abutilon indicum* Sweet inhibits glucose absorption and stimulates insulin secretion in rodents. *Nutr. Res.* 29: 579–587.

Krisanapun, C., Wongkrajang, Y., Temsiririkkul, R., Phornchirasilp, S., and Peungvicha, P. 2012. *In vitro* evaluation of anti-diabetic potential of *Piper sarmentosum* Roxb. extract. *FASEB J.* 26: 686–687.

Krishnakumar, K., Augusti, K. T., and Vijayammal, P. L. 1999. Hypoglycemic and anti-oxidant activity of *Salacia oblonga* Wall. extract in streptozotocin-induced diabetic rats. *Indian J. Physiol. Pharmacol.* 43: 510–514.

Krishnan, S. S., Subramanian, I. P., and Subramanian, S. P. 2014. Isolation, characterization of syringin, phenylpropanoid glycoside from *Musa paradisiaca* tepal extract and evaluation of its antidiabetic effect in streptozotocin-induced diabetic rats. *Biomed. Prev. Nutr.* 4: 105–111.

Ku, S. -K., Kwak, S., Kim, Y., and Bae, J. -S. 2015. Aspalathin and nothofagin from rooibos (*Aspalathus linearis*) inhibits high glucose-induced inflammation in vitro and in vivo. *Inflammation* 38: 445–455.

Kubacey, T. M., Haggag, E. G., El-Toumy, S., Ahmed, A. A., El-Ashmawy, I. M., and Youns, M. M. 2012. Biological activity and flavonoids from *Centaurea alexanderina* leaf extract. *J. Pharm. Res.* 5: 3352–3361.

Kukreja, A. and Maclaren, K. 1999. Autoimmunity and diabetes. *J. Clin. Endocrinol. Metab.* 84: 4371–4378.

Kumanan, R., Manimaran, S., Saleemulla, K., Dhanabal, S. P., and Nanjan, M. J. 2010. Screening of bark of *Cinnamomum tamala* (Lauraceae) by using α-amylase inhibition assay for anti-diabetic activity. *Int. J. Pham. Biomed. Res.* 1: 69–72.

Kumar, A. Prakash, K., Sinha, R. K., and Kumar, N. 2013. *In vitro* plant propagation of *Catharanthus roseus* and assessment of genetic fidelity of micropropagated plants by RAPD marker assay. *Appl. Biochem. Biotechnol.* 169: 894–900.

Kumar, B., Gupta, S. K., Nag, T. C., Srivastava, S., and Saxena, R. 2012a. Greentea prevents hyperglycemia-induced retinal oxidative stress and inflammation in streptozotocin-induced diabetic rats. *Ophthalmic Res.* 47: 103–108.

Kumar, C., Kumar, R., and Nehar, S. 2013. Hypoglycemic effect of acetone extract of *Terminalia arjuna* Roxb. stem bark on type 2 diabetic albino rats. *The Bioscan* 8: 709–712.

Kumar, D., Gaonkar, R. H., Ghosh, R., and Pal, B. C. 2012. Bio-assay guided isolation of α-glucosidase inhibitory constituents from *Eclipta alba*. *Nat. Prod. Commun.* 7: 989–990.

Kumar, D., Mitra, A., and Mahadevappa, M. 2010. Antidiabetic and hypolipidemic effects of Mahanimbine (carbazole alkaloid) from *Murraya koenigii* (Rutaceae). *Int. J. Phytomed.* 2: 22–30.

Kumar, K., Mathew, B. C., and Augusti, K. T. 1995. Antidiabetic and hypolipidemic effects of S-methyl cysteine sulfoxide isolated from *Allium cepa* Linn. *Indian J. Biochem. Biophys.* 32: 49–54.

Kumar, R., Patel, D. K., Prasad, S. K., Laloo, D., Krishnamurthy, S., and Hemalatha, S. 2012. Type 2 antidiabetic activity of bergenin from the roots of *Caesalpinia digyna* Rottler. *Fitoterapia* 83: 395–401.

Kumar, R. V. and Augusti, K. T. 1994. Insulin sparing action of a leucocyanidin derivative isolated from *Ficus bengalensis* Linn. *Indian J. Biochem. Biophys.* 31: 71–76.

Kumar, S., Kumar, A., Kaushal, S., Sharma, D. R., and Sharma, S. 2013. *In vitro* micropropagation and to study the effect of different concentrations of growth regulators on *Murraya koenigii* (L.) Spreng. *UJPAH* 2: 4–7.

Kumar, S., Kumar, V., and Prakash, O. 2010. Anti-diabetic and hypolipidemic activities of *Hibiscus tiliaceus* (L.) flowers extract in streptozotocin-induced diabetic rats. *Pharmacologyonline* 2: 1037–1044.

Kumar, S., Sharma, S., and Suman, J. 2011. *In vivo* anti-hyperglycemic and antioxidant potential of *Piper longum* fruit. *J. Pharm. Res.* 4: 471–474.

Kumar, S., Vasudeva, N., and Sharma S. 2012a. GC-MS analysis and screening of antidiabetic, antioxidant and hypolipidemic potential of *Cinnamomum tamala* oil in streptozotocin induced diabetes mellitus in rats. *Cardiovasc. Diabetol.* 11: 95.

Kumar, S., Vasudeva, N., and Sharma, S. 2012b. GC–MS analysis and screening of antidiabetic, antioxidant and hypolipidemic potential of *Cinnamomum tamala* oil in streptozotocin-induced diabetes mellitus in rats. *Cardiovasc. Diabetol.* 10: 1–11.

Kumar, S. R. S., Krishna, V., Venkatesh, P. K., Kumar, K. G., and Gnanesh, A. U. 2012c. Direct and indirect method of plant regeneration from root explants of *Caesalpinia bonduc* (L.) Roxb.—A threatened medicinal plant of Western Ghats. *Indian J. Exp. Biol.* 50: 910–917.

Kumar, V., Khanna, A. K., Khan, M. M., Singh, R., Singh, S., Chander, R., et al. 2009. Hypoglycemic, lipid lowering and anti-oxidant activities in root extract of *Anthocephalus indicus* in alloxan-induced diabetic rats. *Indian J. Clin. Biochem.* 24: 65–69.

Kumar, V., Naidu, M. M., and Ravishankar, G. A. 2006. Developments in coffee biotechnology: *In vitro* plant propagation and crop improvement. *Plant Cell Tiss. Organ Cult.* 87: 49–65.

Kumar, V. R. and Chauhan, S. 2008. Mulberry: Life enhancer. *J. Med. Plant Res.* 2: 271–278.

Kumari, K. and Augusti, K. T. 2002. Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide isolated from onions (*Allium cepa* L.) as compared to standard drugs in alloxan diabetic rats. *Indian J. Exp. Biol.* 40: 1005–1009.

Kumari, S., Wanjari, M., Kumar, P., and Palani, S. 2012. Antidiabetic activity of *Pandanus fascicularis* Lamk—Aerial roots in alloxan-induced hyperglycemic rats. *Int. J. Nutr. Pharmacol. Neurol. Dis.* 2: 105–110.

Kupeli, E., Alsan, M., Gurbuz, I., and Yesilada, E. 2004. Evaluation of *in vivo* biological activity profile of isoorientin. *Z. Naturforsch.* 59: 787–790.

Kurihara, H., Fukami, H., Kusumoto, A., Toyoda, Y., Shibata, H., Matsui, Y., et al. 2003. Hypoglycemic action of *Cyclocarya paliurus* (Batal.) Iljinskaja in normal and diabetic mice. *Biosci. Biotechnol. Biochem.* 67: 877–880.

Kuroda, M., Mimaki, Y., Nishiyama, T., Mae, T., Kishida, H., Tsukagawa, M., et al. 2005. Hypoglycemic effect of turmeric (*Curcuma longa* L. rhizomes) on genitically diabetic KK-Ay mice. *Biol. Pharm. Bull.* 28: 937–939.

Kuroda, M., Mimaki, Y., Sashida, Y., Mae, T., Kishida, H., Nishiyama, H., et al.2004. Phenolics with PPAR-ligand binding activity obtained from licorice (*Glycyrrhiza uralensis* roots) and ameliorative effects of glycyrin on genetically diabetic KK-Ay mice. *Bioorg. Med. Chem. Lett.* 13: 4267–4272.

Kurukulasuriya, R. , Link, J. T., Madar, D. J., Pei, Z., Richards, S. J., Rohde, J. J., et al. 2003. Potential drug target and progress towards pharmacological inhibition of hepatic glucose production. *Curr. Med. Chem.* 10: 123–153.

Kusano, A. and Abe, H. 2000. Antidiabetic activity of white skinned sweet potato (*Ipomoea batatas* L.) in obese Zucker fatty rats. *Biol. Pharm. Bull.* 23: 23–26.

Kusano, S., Abe, H., and Tamura, H. 2001. Isolation of antidiabetic components from white-skinned sweet potato (*Ipomoea batatas* L.). *Biosci. Biotechnol. Biochem.* 65: 109–114.

Kwak, S., Han, M. S., and Bae, J. S. 2015. Aspalathin and nothofagin from rooibos (Aspalathus linearis) inhibit endothelial protein C receptor shedding *in vitro* and *in vivo. Fitoterapia* 100: 179–186.

Kwon, D. Y., Kim, D. S., Yang, H. Y., and Park, S. 2011. The lignan rich fractions of Fructus Schisandrae improve insulin sensitivity via the PPAR-γ pathway in *in vitro* and *in vivo* studies. *J. Ethnopharmacol.* 135: 455–462.

Kwon, D. J., Bae, Y. -S., Ju, S. M., Youn, G. S., Choi, S. Y., and Park, J. 2014. Salicortin suppressed lipopolysaccharide-stimulated inflammatory responses *via* blockade of NF-κB and JNK activation in RAW 264.7 macrophages. *BMB Rep.* 47: 318–323.

Kwon, J. Y., Seo, S. G., Heo, Y. S., Yue, S., Cheng, J. X., et al. 2012. Piceatannol, natural polyphenolic stilbene, inhibits adipogenesis via modulation of mitotic clonal expansion and insulin receptor-dependent insulin signaling in early phase of differentiation. *J. Biol. Chem.* 287: 11566–11578.

Kwon, S. H., Kim, H. C., Lee, S. Y., and Jang, C. G. 2009. Loganin improveed learning and memory impairments induced by scopolamine in mice. *Eur. J. Pharmacol*. 619: 44–49.

Labban, L. 2014. Medicinal and pharmacological properties of turmeric (*Curcuma longa*): A review. *Int. J. Pharm. Biomed. Sci*. 5: 17–23.

Lagarda-Diaz, I., Geiser, D., Guzman-Partida, A. M., Winzerling, J., and Vazquez-Moreno, L. 2014. Recognition and binding of the PF2 lectin to α-amylase from *Zabrotes* subfasciatus (Coleoptera:Bruchidae) larval midgut. *J. Insect Sci*. 14: 1–5.

Lailerd, N., Saengsirisuwan, V., Sloniger, J. A., Toskulkao, C., and Henriksen, E. J. 2004. Effects of stevioside on glucose transport activity in insulin-sensitive and insulin-resistant rat skeletal muscle. *Metabolism* 53: 101–107.

Lala, S., Gupta, S., Sahu, N. P., Mandal, D., Mondal, N. B., Moulik, S. P., et al. 2006. Critical evaluation of the therapeutic potential of bassic acid incorporated in oil-in-water microemulsions and poly-D,L-lactide nanoparticles against experimental leishmaniasis. *Drug Target* 14: 171–179.

Lam, S. H., Ruan, C. T., Hsich, P. H., Su, M. J., and Lee, S. S. 2012. Hypoglycemic diterpenoides from *Tinospora crispa*. *J. Nat. Prod*. 75: 153–159.

Lambardi, M., Ozudogru, E. A., and Roncasaglia, R. 2013. *In vitro* propagation of olive (*Olea europaea* L.) by nodal segmentation of elongated shoots. *Methods Mol. Biol*. 110: 33–44.

Lammi, N., Karvonen, M., and Tuomilehto, J. 2005. Do microbes have a causal role in type 1 diabetes? *Med. Sci. Monitt*. 11: 63–69.

Landete, J. M. 2011. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. *Food Res. Int*. 44: 1150–1160.

Lanjhiyana, S., Garabadu, D., Ahirwar, D., Rana, C. A., Ahirwar, B., and Lanjhiyana, S. K. 2011. Pharmacognostic standardization and hypoglycemic evaluations of novel polyherbal formulations. *Der. Pharm. Lett*. 3: 319–333.

Lata, H., Chandra, S., Mehmedic, Z., Khan, I. A., and El-Sohly, M. A. 2012. *In vitro* germplasm conservation of high D-9-tetrahydrocannabinol yielding elite clones of *Cannabis sativa* L. under slow growth conditions. *Acta Physiol. Plant* 34: 743–750.

Lata, H., Chandra, S., Techen, N., Khan, I. A., and El-Sohly, M. A. 2011. Molecular analysis of genetic fidelity in *Cannabis sativa* L. plants grown from synthetic (encapsulated) seeds following *in vitro* storage. *Biotechnol. Lett*. 33: 2503–2508.

Latha, M. and Pari, L. 2004. Effect of an aqueous extract of *Scoparia dulcis* on blood glucose, plasma insulin and some polyol pathway enzymes in experimental rat diabetes. *Braz. J. Med. Biol. Res*. 37: 577–586.

Latha, M., Pari, L., Ramkumar, K. M., Rajaguru, P., Suresh, T., Dhanabal, T., Sitasawad, S., and Bhonde, R. 2009. Antidiabetic effects of scoparic acid D isolated from *Scoparia dulcis* in rats with streptozotocin induced diabetes. *Nat. Prod. Res*. 23: 1528–1540.

Latha, R. C. R. and Daisy, P. 2010. Influence of *Terminalia bellerica* Roxb. fruit extracts on biochemical parameters in streptozotocin diabetic rats. *Int. J. Pharmacol*. 6: 89–96.

Latha, R. C. R. and Daisy, P. 2011. Insulin-secretagogue, antihyperlipidemic and other protective effects of gallicacid isolated from *Terminalia bellerica* Roxb. in streptozotocin-induced diabetic rats. *Chem. Biol. Interact*. 189: 112–118.

Laurenza, A., Sutkowski, E. M., and Seamon, K. B. 1989. Forskolin: A specific stimulator of adenylyl cyclase or a diterpene with multiple sites of action? *Trends Pharmacol. Sci*. 10: 442–447.

Law, B. Y., Wang, M., Ma, D. L., Al-Mousa, F., Michelangeli, F., Cheng, S. H., et al. 2010. Alisol B, a novel inhibitor of the sarcoplasmic/endoplasmic reticulum Ca(2+) ATPase pump, induces autophagy, endoplasmic reticulum stress, and apoptosis. *Mol. Cancer Ther*. 9: 718–730.

Lawag, I. L., Aguinaldo, A. M., Naheeds, S., and Mosihuzzaman, M. 2012. α-Glucosidase inhibitory activity of selected Philippine plants. *J. Ethnopharmacol*. 144: 217–219.

Laydong, L., Basistha, B. C., Subba, K. B., Gurung, R., and Sharma, N. P. 2012. A reckon on the conservation of sustainability of *Abroma augu*sta L. of Sikkim Himalaya. *J. Med. Sci. Res*. 3: 35–39.

Lee, B., Jung, K., and Kim, D. H. 2010. Timosaponin AIII, a saponin isolated from *Anemarrhena asphodeloides*, ameliorates learning and memory deficits in mice. *Pharmacol. Biochem. Behav*. 93: 121–127.

Lee, H. J., Jeong, S. J., Lee, H. J., Lee, E. O., Bae, H., Lieske, J. C., et al. 2011. 1,2,3,4,6-Penta-O-galloyl-beta-D-glucose reduces renal crystallization and oxidative stress in a hyperoxaluric rat model. *Kidney Int*. 79: 538–545.

Lee, H. N., Cho, H. J., Lim, D. Y., Kang, Y. H., Lee, K. W., and Park, K. H. 2013. Mechanisms by which licochalcone E exhibits potent anti-inflammatory properties: Studies with phorbol ester-treated mouse skin and lipopolysaccharide-stimulated murine macrophages. *Int. J. Mol. Sci.* 14: 10926–10943.

Lee, H. S. 2002. Rat lens aldose reductase inhibitory activities of *Coptis japonica* root derived isoquinoline alkaloids. *J. Agric Food Chem*. 50: 7013–7016.

Lee, H. S. 2005. Cuminaldehyde: Aldose reductase and alpha-glucosidase inhibitor derived from *Cuminum cyminum* L. seeds. *J. Agric. Food Chem*. 53: 2446–2450.

Lee, H. S., Kim, B. S., and Kim, M. K. 2002. Suppression effect of *Cinnamomum cassia* bark-derived component on nitric oxide synthase. *J. Agric. Food Chem*. 50: 7700–7703.

Lee, J., Kim, Y. S., and Park, D. 2007. Rosmarinic acid induces melanogenesis through protein kinase A activation signaling. *Biochem. Pharmacol*. 74: 960–968.

Lee, K. T., Sohn, I. C., Kim, D. H., Choi, J. W., Kwon, S. H., and Park, H. J. 2000. Hypoglycemic and hypolipidemic effects of tectorigenin and kaikasaponin III in the streptozotocin-induced diabetic rat and their antioxidant activity *in vitro. Arch. Pharmacol. Res.* 23: 461–466.

Lee, M. K., Kim, M. J., Cho, S. Y., Park, S. A., Park, K. K., Jung, U. J., et al. 2005. Hypoglycemic effect of Du-zhong (*Eucommia ulmoides* Oliv.) leaves in streptozotocin-induced diabetic rats. *Diabetes Res. Clin. Pract*. 67: 22–28.

Lee, M. S. and Sohn, C. B. 2008. Anti-diabetic properties of chrysophanol and its glucoside from rhubarb rhizome. *Biol. Pharm. Bull*. 31: 2154–2157.

Lee, M. S. and Thuong, P. T. 2010. Stimulation of glucose uptake by triterpenoids from *Weigela subsessilis*. *Phytother. Res*. 24: 49–53.

Lee, N. J., Oh, J. H., Ban, J. O., Shim, J. H., Lee, H. P., Jung, J. K., et al. 2013. 4-O-methylhonokiol, a PPARγ agonist, inhibits prostate tumor growth: p21-mediated suppression of NF-κB activity. *Br. J. Pharmacol*. 168: 1133–1145.

Lee, O. -H., Seo, D. -H., Park, C. -S., and Kim, Y. -C. 2010. Puerarin enhances adipocyte differentiation, adiponectin expression, and antioxidant response in 3T3-L1 cells. *BioFactors* 36: 459–467.

Lee, P. -L. and Che, J. -T. 2014. Plant regeneration via callus culture and subsequent *in vitro* flowering of *Dendrobium houshanense*. *Acta Physiologiae Plantarum* 36: 2619–2625.

Lee, S. H., Lee, J., Jung, M. H., and Lee, Y. M. 2013. Glyceollins, a novel class of soy phytoalexins, inhibit angiogenesis by blocking the VEGF and bFGF signaling pathways. *Mol. Nutr. Food Res*. 57: 556–559.

Lee, S. Y., Eom, S. H., Kim, Y. K., Park, N. I., and Park, S. U. 2009a. Cucurbitane-type triterpenoids in *Momordica charantia* Linn. *J. Med. Plants Res.* 3: 1264–1269.

Lee, W., Ham, J., Kwon, H. C., Yoon, G., Bae, G. U., Kim, Y. K., et al. 2015. Amorphastilbol exerts beneficial effects on glucose and lipid metabolism in mice consuming a high-fat-diet. *Int. J. Mol. Med*. 36: 527–533.

Lee, W. -C., Wang, C. -J., Chen, Y. -H., Hsu, J. -D., Cheng, S. -Y., Chen, H. -C, and Lee, H. -J. 2009. Polyphenol extracts from *Hibiscus sabdariffa* Linn. attenuate nephropathy in experimental type 1 diabetes. *J. Agric. Food Chem*. 57: 2206–2210.

Lee, W. K., Kao, S. T., Liu, I. M., and Cheng, J. T. 2006a. Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in Wister rats. *Clin. Exp. Pharmacol. Physiol*. 33: 27–32.

Lee, Y., Lee, D. E., Lee, H. S., Kim, S. K., Lee, W. S., Kim, S. H., et al. 2011b. Influence of auxins, cytokinins and nitrogen on production of rooting from calus and adventitious roots of the white mulberry tree (*Morus alba*). *Plant Cell Tiss. Org. Cult.* 105: 9–19.

Lee, Y. S., Kim, S. H., Jung, S. H., Kim, J. K,. Pan, C. H., and Lim, S. S. 2010. Aldose reductase inhibitory compounds from *Glycyrrhiza uralensis*. *Biol. Pharm. Bull*. 33: 917–921.

Lee, Y. S., Kim, W. S., Kim, K. H., Yoon, M. J., Cho, H. J., Shen, Y., et al. 2006. Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. *Diabetes*. 55: 2256–2264.

Lehrke, M. and Lazar, M. A. 2005. The many faces of PPAR gamma. *Cell* 123: 993–999.

Lekshmi, P. C., Arimboor, R., Indulekha, P. S., and Menon, A. N. 2012. Turmeric (*Curcuma longa* L.) volatile oil inhibits key enzymes linked to type 2 diabetes. *Int. J. Food Sci. Nutr.* 63: 832–834.

Leong, A. 2015. Tissue culture technique of *Aquilaria sinensis*. Chinese Patent No: CN 104686341 A.

Leshweni, J. L. and Shai, J. 2012. The effects of *Clausena anisata* (Wild) Hook leaf extracts on selected diabetic related metabolizing enzymes. *J. Med. Plant Res*. 6: 4200–4207.

Lestari, K., Hwang, J. K., Kariadi, S. H., Wijaya, A., Ahmad, T., Subarnas, A., et al. 2012. Screening for PPAR γ agonist from *Myristica fragrans* Houtt seeds for the treatment of type 2 diabetes by *in vitro* and *in vivo*. *Med. Health Sci*. J. 12: 7–15.

Li, C., Li, Q., Mei, Q., and Lu, T. 2015. Pharmacological effects and pharmacokinetic properties of icariin, the major bioactive component in *Herba epimedii*. *Life Sci.* 126: 57–68.

Li, C. G., Zhang, S. Q., Wang, S. Y., Cui, M. M., Zhou, M. B., and Qin, Q. 2006. Intervention of litchi nucleus extract fluid in the blood biochemical indexes of model mice with diabetes mellitus induced by alloxan. *J. Zhonguo. Linchuang Kangfu*. 10: 61–63.

Li, G. -S., Jiang, W. -L., Yue, X. -D., Qu, G. -W., Tian, J. -W., Wu, J., et al. 2009. Effect of astilbin on experimental diabetic nephropathy *in vitro* and *in vivo*. *Planta Med*. 75: 1470–1475.

Li, H. M., Kim, J. K., Jang, J. M., Kwon, S. O., Cui, C. B., and Lim, S. S. 2012a. The inhibitory effect of *Prunella vulgaris* L. on aldose reductase and protein glycation. *J. Biomed. Biotechnol*. 2012(928159): 7.

Li, J., Liu, T., Wang, L., Guo, X., Xu, T., Wu, L., et al. 2012. Anti-hyperglycemic and anti-hyperlipidemic actions of Cinnamaldehyde in C57BLKS/J db/db mice. *J. Tradit. Chin. Med*. 32: 446–452.

Li, J. M., Li, Y. C., Kong, L. D., and Hu, Q. H. 2010a. Curcumin inhibits hepatic protein-tyrosine phosphatase 1B and prevents hypertriglyceridemia and hepatic steatosis in fructose-fed rats. *Hepatology* 51: 1555–1566.

Li, N. S., Luo, X. J., Zhang, Y. S., He, L., Liu, Y. Z., and Peng, J. 2011. Phloroglucinol protects gastric mucosa against ethanol-induced injury through regulating myeloperoxidase and catalase activities. *Fundam. Clin. Pharmacol*. 25: 462–468.

Li, Q. and Qu, H. 2012. Study on the hypoglycemic activities and metabolism of alcohol extract of Alismatis Rhizoma. *Fitoterapia* 83: 1046–1053.

Li, Q., Xiao, Y., Gong, H., Shen, D., Zhu, F., Wu, Q., Chen, H., and Zhong, H. 2009. Effect of puerarin on the expression of extracellular matrix in rats with streptozotocin-induced diabetic nephropathy. *Natl. Med. J. India* 22: 9–12.

Li, S., An, T. Y., Li, J., Shen, Q., Lou, F. C., and Hu, L. H. 2006. PTP1B inhibitors from *Saussrurea lappa*. *J. Asian Nat. Prod. Res.* 8: 281–286.

Li, W., Yan, X. T., Sun, Y. N., Ngan, T. H., Shim, S. H., and Kim, Y. H. 2014. Anti-inflammatory and PPAR transactivational effects of oleanane-type triterpenoid saponins from the roots of *Pulsatilla koreana*. *Biomol. Ther. (Seoul)* 22: 334–340.

Li, X., Cui, X., Sun, X., Li, X., Zhu, Q., and Li, W. 2010b. Mangiferin prevents diabetic nephropathy progression in streptozotocin-induced diabetic rats. *Phytother. Res.* 24: 893–899.

Li, Y. and Ding, Y. 2012. Minireview: Therapeutic potential of myricetin in diabetes mellitus. *Food Science Human Wellness* 1: 19–25.

Li, Y., Huang, L., Zeng, X., Zhong, G., Ying, M., Huang, M., et al. 2014. Down-regulation of P-gp expression and function after Mulberroside A treatment: Potential role of protein kinase C and NF-kappa B. *Chem. Biol. Interact*. 213: 44–50.

Li, Y., Peng, G., Li, Q., Wen, S., Huang, T. H., Roufogalis, B. D., et al. 2004. *Salacia oblonga* improves cardiac fibrosis and inhibits postprandial hyperglycemia in obese Zucker rats. *Life Sci*. 75: 1735–1746.

Liang, C. H., Chan, L. P., Chou, T. H., Chiang, F. Y., Yen, C. M., Chen, P. J., et al. 2013. Brazilein from *Caesalpinia sappan* L. antioxidant inhibits adipocyte differentiation and induces apoptosis through caspase-3 activity and anthelmintic activities against *Hymenolepis nana* and *Anisakis simplex*. *Evid. Based Complement. Altern. Med*. 2013: 864892.

Liang, M. L., Da, X. W., He, A. D., Yao, G. Q., Xie, W., Liu, G., et al. 2015. Pentamethylquercetin (PMQ) reduces thrombus formation by inhibiting platelet function. *Sci. Rep*. 5: 11142.

Lieberman, I., Lentz, D. P., Trucco, G. A., Seow, W. K., and Thong, Y. H. 1992. Prevention by tetrandrine of spontaneous development of diabetes mellitus in BB rats. *Diabetes* 41: 616–619.

Lien, D. N., Phuc, D. V., Lien, P. Q., Trang, N. T., Kien, T. T., Lien, T. T. P., et al. 2011. Effect of sweet potato (*Ipomoea batatas* (L.) Lam) leaf extract on hypoglycaemia, blood insulin secretion, and keycarbohydrate metabolic enzymes in experimentally obese and streptozotocin-induced diabetic mice. *VNU J. Sci. Nat. Sci. Technol*. 27: 118–124.

Lim, C. T., Lolli, F., Thomas, J. D., Kola, B., and Korbonits, M. 2012. Measurement of AMP-activated protein kinase activity and expression in response to ghrelin. *Methods Enzymol*. 514: 271–287.

Lim, G. E., Huang, G. J., Flora, N., LeRoith, D., Rhodes, C. J., and Brubaker, P. L. 2009. Insulin regulates glucagon-like peptide-1 secretion from the enteroendocrine L cells. *Endocrinology* 150: 580–591.

Lim, S., Soh, K., and Kuppusamy, U. 2007. Effects of naringenin on lipogenesis, lipolysis and glucose uptake in rat adipocyte primary culture: A natural antidiabetic agent. *Internet J. Altern. Med.* 5: 11–17.

Lima, C. F., Azevedo, M. F., Araujo, R., Fernandes-Ferreira, M., and Pereira-Wilson, C. 2006. Metformin-like effect of Salvia officinalis (common sage): Is it useful in diabetes prevention? *Br. J. Nutr.* 326–333.

Lima, C. R., Vasconcelos, C. F., Costa-Silva, J. H., Maranhao, C. A., Costa, J., Batista, T. M., et al. 2012. Anti-diabetic activity of extract from *Persea americana* Mill. leaf via the activation of protein kinase B (PKB/Akt) in streptozotocin-induced diabetic rats. *J. Ethnopharmacol.* 141: 517–525.

Lim-Ho, C. L. and Lee, S. K. 1985. Micropropagation of *Lagerstroemia speciosa* (L.) Pers. (Lythraceae). *Garden's Bulletin* 38: 175–184.

Lin, Y., Shi, R., Wang, X., and Shen, H. M. 2008. Luteolin, a flavonoid with potential for cancer prevention and therapy. *Curr. Cancer Drug Targets* 8: 634–646.

Ling, H., Yang, H., Tan, S. H., Chui, W. K., and Chew, E. -H. 2010. 6-Shogaol, an active constituent of ginger, inhibits breast cancer cell invasion by reducing matrix metalloproteinase-9 expression via blockade of nuclear factor-κB activation. *Br. J. Pharmacol.* 161: 1763–1777.

Liu, C., Zeng, Y., Dai, L. -H., Cai, T. -Y., Zhu, Y. -M., Dou, D. -Q., et al. 2015. Mogrol represents a novel leukemia therapeutic, via ERK and STAT3 inhibition. *Am. J. Cancer Res.* 5: 1308–1318.

Liu, I. M., Liou, S. S., Lan, T. W., Hsu, F. L., and Cheng, J. T. 2005b. Myricetin as the active principle of *Abelmoschus moschatus* to lower plasma glucose in streptozotocin-induced diabetic rats. *Planta Med.* 71: 617–621.

Liu, I. M., Tzeng, T. F., and Liou, S. S. 2010. *Abelmoschus moschatus* (Malvaceae), an aromatic plant, suitable for medical or food uses to improve insulin sensitivity. *Phytother. Res.* 24: 233–239.

Liu, J. 1995. Pharmacology of oleanolic acid and ursolic acid. *J. Ethnopharmacol.* 49: 57–68.

Liu, J., He, T., Lu, Q., Shang, J., Sun, H., and Zhang, L. 2010. Asiatic acid preserves beta cell mass and mitigates hyperglycemia in streptozotocin-induced diabetic rats. *Diabetes Metab. Res. Rev.* 26: 448–454.

Liu, J., Lu, J. F., Kan, J., Wen, X. Y., and Jin, C. H. 2014. Synthesis, characterization and *in vitro* anti-diabetic activity of catechin grafted inulin. *Int. J. Biol. Macromol.* 64: 76–83.

Liu, J. C. and Chan, P. O. 1999. The antihypertensive effect of the berberine derivative: 6-protoberberine in spontaneously hypertensive rats. *Pharmacology* 59: 283–289.

Liu, K. Y., Wu, Y. C., Liu, I. M., Yu, W. C., and Cheng, J. T. 2008. Release of acetylcholine by syringin, an active principle of *Eleutherococcus senticosus,* to raise insulin secretion in Wistar rats. *Neurosci. Lett.* 434: 195–199.

Liu, T. P., Liu, I. M., and Cheng, J. T. 2005a. Improvement of insulin resistance by *Panax ginseng* in fructose-rich chow-fed rats. *Horm. Metab. Res.* 37: 333–339.

Liu, Z., Liu, W., Li, X., Zhang, M., Li, C., Zheng, Y., et al. 2013a. Anti-diabetic effects of malonyl ginsenosides from *Panax ginseng* on type 2 diabetic rats. *J. Ethnopharmacol.* 145: 233–240.

Liu, Z., Wan, L., Yue, Y., Xiao, Z., Zhang, Y., Wang, Y., et al. 2013b. Hypoglycemic activity and antioxidative stress of extracts and corymbiferin from *Swertia bimaculata in vitro* and *in vivo. Evid. Based Complement. Altern. Med.* 2013(125416): 12.

Liu, Z. L., Liu, Q., Xio, B., Zhou, J., Zhang, J. G., and Li, Y. 2013. The vascular protective properties of kinsenoside isolated from *Anoectochilus roxburghii* under high glucose condition. *Fitoterapia* 86: 163–170.

Logendras, S., Ribnicky, D. M., Yang, H. Poulev, A., Ma, J., Kennelly, E. J., et al. 2006. Bioassay-guided isolation of aldose reductase inhibitors from *Artemisia dracunculus. Phytochemistry* 67: 1539–1546.

Loizou, S., Lekakis, I., Chrousos, G. P., and Moutsatsou, P. 2010. Beta-sitosterol exhibits anti-inflammatory activity in human aortic endothelial cells. *Mol. Nutr. Food Res.* 54: 551–558.

Lokman, E. F., Gu, H. F., Mohamud, W. N. W., and Ostenson, C. -G. 2015. Evaluation of antidiabetic effects of the traditional medicinal plant *Gynostemma pentaphyllum* and the possible mechanisms of insulin release. *Evid. Based Complement. Alternat. Med.* 2015: 120572.

Lokman, E. F., Gu, H. F., Mohamud, W. N. W., Yusoff, M. M., Chia, K. L., and Ostenson, C. -G. 2014. The possible mechanisms by which borapetol B stimulates insulin release from rat islets. *Int. J. Med. Med. Sci.* 47: 1461–1468.

Lokman, F. E., Gu, H. F., Mohamud, W. N. W., Yusoff, M. M., Chia, K. L., and ostenson, C. -G. 2013. Anti-diabetic effect of oral borapetol B compound, isolated from the plant *Tinospora crispa*, by stimulating insulin release. *Evid. Based Complement. Altern. Med.* 2013: 7.

Lomtatidze, N., Zarnadze, N., Alasania, N., and Zarnadz, R. 2009. *In vitro* Morphogenesis of Loquat (*Eriobotria japonica* L.). *Bull. Georgian. Nat. Acad. Sci.* 3: 123–125.

Lopes, A. A. 2009. End-stage renal disease due to diabetes in racial ethnic minorities and disadvantaged populations. *Ethnicity Dis* 19(S1): 47–51.

Lopez, J. L. Jr. 2007. Use of *Opuntia cactus* as a hypoglycemic agent in managing type 2 diabetes mellitus among Mexican American patients. *Nutrition Bytes.* 12: 1–6.

Lopez-Jimenez, A., Garcia-Caballero, M., Medina, M. A., and Quesada, R. 2013. Anti-angiogenic properties of carnosol and carnosic acid, two major dietary compounds from rosemary. *Eur. J. Nutr.* 52: 85–95.

Lovati, M. R., Manzoni, C., Castiglioni, S., Parolari, A., Magni, C., and Duranti, M. 2012. Lupin seed γ-conglutin lowers blood glucose in hyperglycaemic rats and increases glucose consumption of HepG2 cells. *Br. J. Nutr.* 107: 67–73.

Lozano-Mena, G., Sanchez-Gonzalez, M., Juan, E. M., and Planas, J. M. 2014. Maslinic acid, a natural phytoalexn-type triterpene from olives—A promising nutraceutical? *Molecules* 19: 11538–11559.

Lu, H., Zhang, L., Liu, D., Tang, P., and Song, F. 2014. Isolation and purification of psoralen and isopsoralen and their efficacy and safety in the treatment of osteosarcoma in nude rats. *Afr. Health Sci.* 14: 641–647.

Lu, X. Y., Chen, X. M., Fu, D. X., Cong, W., and Ouyang, F. 2002. Effect of *Amorphophallus konjac* oligosaccharides on STZ-induced diabetes model of isolated islets. *Life Sci.* 72: 711–719.

Lu, Y. -F., Wan, X. -L., Xu, Y., and Liu, J. 2013. Repeated oral administration of oleanolic acid produces cholestatic liver injury in mice. *Molecules* 18: 3060–3071.

Ludvik, B., Neuffer, B., and Pacini, G. 2004. Efficacy of *Ipomoea batatas* (Caiapo) on diabetes control in type 2 diabetic subjects treated with diet. *Diabetes Care* 27: 436–440.

Lundqvist, A., Magnusson, L. U., Ullstrom, C., Krasilnikova, G., Dizhbite, T., and Hulten, L. M. 2015. Oregonin reduces lipid accumulation and proinflammatory responses in primary human macrophages. *Biochem. Biophys Res. Commun.* 485: 693–699.

Luo, G., Fort, D. M., Carlson, T. J., Noamesi, B. K., Nii-Amon-Koitei, D., King, S. R., et al. 1998. *Cryptolepis sanguinolenta*: An ethnobotanical approach to drug discovery and the isolation of a potentially useful new anti-hyperglycemic agent. *Diabet. Med.* 15: 367–374.

Luo, J., Chuang, T., Cheung, J., Tsai, J., Sullivan, C., Hector, R. F., et al. 1998. Masoprocol (nordihydroguaiaretic acid): A new antihyperglycemic agent isolated from the creosote bush (*Larrea tridentata*). *Eur. J. Pharmacol.* 346: 77–79.

Luo, Q., Cai, Y., Yan, J., Sun, M., and Corke, H. 2004. Hypohlycemic and hypolipidemic effects and antioxidant activity of fruit extracts from *Lycium barbarum*. *Life Sci.* 76: 137–149.

Lv, L., Wu, S. Y., Wang, G. F., Zhang, J. J., Pang, J. X., Liu, Z. Q., et al. 2010. Effect of astragaloside IV on hepatic glucose-regulating enzymes in diabetic mice induced by a high fat diet and streptozotocin. *Phytother. Res.* 24: 219–224.

Ma, W., Wang, K. -J., Cheng, C. -H., Yan, G., Lu, W. -L., Ge, J. -F., et al. 2014. Bioactive compounds from *Cornus officinalis* fruits and their effects on diabetic nephropathy. *J. Ethnopharmacol.* 153: 840–845.

Ma, X., Egawa, T., Kimura, H., Karaike, K., Masuda, S., Iwanaka, N., et al. 2010. Berberine-induced activation of 5′-adenosine monophosphate-activated protein kinase and glucose transport in rat skeletal muscles. *Metabolism* 59: 1619–1627.

Mackenzie, R. W. A. and Elliott, B. T. 2014. Akt/PKB activation and insulin signaling: A novel insulin signaling pathway in the treatment of type 2 diabetes. *Diabetes Metab. Syndr. Obes. Targets Ther.* 7: 55–64.

Madan, S., Ahmad, S., Singh, J. N., Kohli, K., Kumar, Y., Singh, R., et al. 2010. *Stevia rebaudiana* (Bert.) Bertoni—A review. *Indian J. Nat. Prod. Resour.* 1: 267–286.

Madankumar, A. and Devaki, T. 2015. Geraniol, a component of plant essential oils—A review of its pharmacological activities. *Int. J. Pharm. Pharm. Sci.* 7: 67–70.

Magied, M. M. A., Salama, N. A. R., and Ali, M. R. 2014. Hypoglycemic and hypocholesterolemia effects of intragastric administration of dried red chili pepper (*Capsicum annum*) in alloxan-induced diabetic male albino rats fed with high-fat-diet. *J. Food Nutr. Res.* 2: 850–856.

Magni, C., Sessa, F., Accardo, E., Vanoni, M., Morazzoni, P., Scarafoni, A., and Durant, M. 2004. Conglutin-γ, a lupin seed protein binds insulin in vitro and reduce plasma glucose levels of hyperglycemic rats. *J. Nutr. Biochem.* 15: 646–650.

Mahalingam, G. and Krishnan. K. 2009. Antidiabetic activity of 2-hydroxy 4-methoxy benzoic acid isolated from the roots of *Hemidesmus indicus* on streptozotocin-induced diabetic rats. *Int. J. Diabetes Metab.* 17: 53–57.

Mahavedarao, U. S., Zin, T. Abdurrazak, M., and Ahmad, B. A. 2015. Chemistry and pharmacology of syringing, a novel bioglycoside: A review. *Asian J. Pharm. Clin. Res.* 8: 20–25.

Mahendran, G., Thamotharan, G. Sengottuvelu, S., and Bai, V. N. 2014. Anti-diabetic activity of *Swertia corymbosa* (Griseb.) Wight ex C.B. Clarke aerial parts extract in streptozotocin induced diabetic rats. *J. Ethnopharmacol*. 151: 1175–1183.

Mahli, S. S., Basu, S. P., Sinha, K. P., and Banerjee, N. C. 1989. Pharmacological effects of karanjin and pongamol from seed oil of *Pongamia pinnata*. *Indian J. Anim. Sci.* 59: 657–660.

Mahmad, N., Taha, R. M., Othman, R., Saleh, A., Hasbullah, N. A., and Elias, H. 2014. Effects of NAA and BAP, double-Layered media, and light distance on *in vitro* regeneration of *Nelumbo nucifera* Gaertn. (Lotus), an aquatic edible plant. *Sci. World J.* 2014(745148): 8.

Mahmoud, O. and Arash, M. 2014. Rapid micropropagation of *Cucumis sativas* var. Dastgerdi (Iranian cultivar) by node culture technique. *Br. Biotechnol. J.* 4: 733–739.

Maity, P., Hansda, D., Bandyopadhyay, U., and Mishra, D. K. 2009. Biological activities of crude extracts and chemical constituents of Bael, *Aegle mammelos* (L.) Corr. *Int. J. Exp. Biol.* 47: 849–861.

Majumder, P. and Paridhavi, M. 2013. An ethnophytochemical and pharmacological review on novel Indian medicinal plants used in herbal formulations. *Int. J. Pharm. Pharm. Sci.* 5: 74–83.

Mak, J. C. 2012. Potential role of green tea catechins in various disease therapies: Progress and promise. *Clin. Exp. Pharmacol. Physiol*. 39: 265–273.

Malarvili, A., Selvaraja, P., Ndyeabura, A. W., Akowuah, G. A., and Okechukwu, P. N. 2011. Antidiabetic activity of crude stem extracts of *Coscinium fenestratum* on streptozotocin-induced type-2 diabetic rats. *Asian J. Pharm. Clin. R*es. 4: 47–51.

Malini, P., Kanchana, G., and Rajadurai, M. 2011. Anti-diabetic efficacy of ellagic acid in streptozotocin-induced diabetic mellitus in albino Wistar rats. *Asian J. Pharm. Clin. Res*. 4: 124–128.

Maloney, K. P., Truong, V., and Allen, J. C. 2014. Susceptibility of sweet potato (*Ipomoea batatas*) peel proteins to digestive enzymes. *Food Sci. Nutr.* 2: 351–360.

Mandal, S., Barik, B., Mallick, C., De, D., and Ghosh, D. 2008. Therapeutic effect of ferulic acid, an ethereal fraction of ethanolic extract of seed of *Syzygium cumini* against streptozotocin-induced diabetes in male rat. *Methods Find. Exp. Clin. Pharmacol*. 30: 121–128.

Mandlik, R. V., Desai, S. K., Naik, S. R., Sharma, G., and Kohli, R. K.2008. Antidiabetic activity of a polyherbal formulation (DRF/AY/5001). *Indian J. Exp. Biol*. 46: 599–606.

Mangal, M., Sharma, D., Sharma, M., and Kumar, S. 2014. *In vitro* generation in olive (*Olea europaea* L.) cv, Frontia from nodal segments. *Indian J. Exp. Biol*. 52: 912–916.

Manickam, M., Ramanathan, M., Jahromi, M. A., Chansouria, J. P., and Ray, A. B. 1997. Antihyperglycemic activity of phenolics from *Pterocarpus marsupium*. *J. Nat. Prod.* 60: 609–610.

Manikandan, R., Thiagarajan, R., Beulaia, S., Sivakumar, M. R., Meiyalagan, V., Sundaram, R., et al. 2011. 1, 2 di-substituted idopyranose from *Vitex negundo* L. protects against streptozotocin-induced diabetes by inhibiting nuclear factor-kappa B and inducible nitric oxide synthase expression. *Microsc. Res. Tech.* 74: 301–307.

Mann, R., Agarwal, K., Sing, C., Aeri, V., and Nema, R. K. 2008. Adventious shoot proliferation from aseptically germinated seedlings of *Cuminum cyminum*. *Pharmacogn. Mag.* 4: 132–137.

Manoharan, S., Umadevi, S., Jayanthi, S., and Baskaran, N. 2011. Antihyperglycemic effect of *Coscinium fenestratum* and *Catharanthus roseus* in alloxan-induced diabetic rats. *Int. J. Nutr. Pharmacol. Neurol. Dis.* 1: 189–193.

Manonmani, R. and Francisca, P. 2012. *In vitro* multiplication of *Gymnema sylvestre* R. Br. through nodal explants. *Int. J. Pharma Bio Sci*. 3: 49–53.

Mansour, A. A., Al-Maliky, A. A., Kasem, B., Jabar, A., and Mosbeh, K. A. 2014. Prevalence of diagnosed and undiagnosed diabetes mellitus in adults aged 19 years and older in Basrah, Iraq. *Diabetes Metab. Syndr. Obes. Targets Ther.* 2014: 139–144.

Mantovani, N. C., Grando, M. F., Xavier, A., and Otoni, W. C. 2013. *In vitro* shoot induction and multiplication from nodal segments of adult *Ginkgo biloba* plants. *Horticultura Brasileira* 31: 184–189.

Mapanga, R. P., Tufts, M. A., Shode, F. O., and Musabayane, C. T. 2009. Renal effects of plant derived oleanoic acid in streptozotocin-induced diabetic rats. *Endocr. Abstr.* 19: p124.

Marinangeli, P. 2013. Micropropagation of onion (*Allium cepa* L.) from immature inflorescences. *Methods Mol. Biol.* 11013: 319–327.

Marles, R. J. and Farnsworth, N. R. 1995. Anti-diabetic plants and their active constituents. *Phytomedicine* 2: 137–189.

Maroo, J., Vasu, V. T., and Gupta, S. 2003. Dose dependent hypoglycemic effect of aqueous extract of *Enicostemma littorale* Blume in alloxan-induced diabetic rats. *Phytomedicine* 10: 196–199.

Martineau, L. C., Couture, A., Spoor, D., Benhaddou-Andaloussi, A., Harris, C., Meddah, B., et al. 2006. Anti-diabetic properties of the Canadian lowbush blueberry *Vaccinium angustifolium* Ait. *Phytomedicine* 13: 612–623.

Masiello, P., 2006. Animal models of type-2 diabetes with reduced pancreatic β-cell mass. *Int. J. Biochem. Cell Biol.* 38: 873–893.

Masiello, P., Broca, C., Gross, R., Roye, M., Manteghetti, M., Hillaire-Buys, D., et al. 1998. Experimental NIDDM: Development of a new model in adult rats administered streptozotocin and nicotinamide. *Diabetes* 47: 224–229.

Mathai, M. P., Zachariah, J. C., Samsudeen, K., Rema, J., Babu, K. N., and Ravindran, P. N. 1997. Micropropagation of *Cinnamomum verum* (Bercht & Presl.). *Biotechnol. Spices Med. Aromatic Plants.* 35–38.

Mathew, B. C., Yoseph, B. A., Dessale, T., Daniel, R. S., Alemayehu, A., Campbell, I. W., and Augusti, K. T. 2012. Hypolipidaemic effect of leucodelphinidin derivative from *Ficus bengalensis* Linn on cholesterol fed rats. *Res. J. Chem. Sci.* 2: 54–60.

Mathew, M. M. and Philip, V. J. 2000. *In vitro* adventitious shoot formation from embryos of *Areca catechu* L. *Phytomorphol.* 50: 222–227.

Mathew, P. T. and Augusti. K. T. 1973. Studies on the effect of allicin (diallyldisulphide-oxide) on alloxan diabetes I. Hypoglycaemic action and enhancement of serum insulin effect and glycogen synthesis. *Indian J. Biochem. Biophys.* 10: 209–212.

Mathew, S., Singh, D. Jaiswal, S., Kumar, M., Jayakar, B., and Bhowmik, D. 2013. Anti-diabetic activity of Kalanchoe pinnata (Lam.) Pers. in alloxan induced diabetic rats. *J. Chem. Pharm. Sci.* 6: 1–7.

Mathews, J. N., Flatt, P. R., and Abdel-Wahab, Y. H. 2006. *Asparagus adscendens* (Shweta musali) stimulates insulin secretion, insulin action and inhibits starch digestion. *Br. J. Nutr.* 95: 576–581.

Matsuda, H., Cai, H., Kubo, M., Tosa, H., and Iinuma, M. 1995. Study on anti-cataract drugs from natural sources. Effects of buddlejae flos on *in vitro* ALR2 activity. *Biol. Pharm. Bull.* 18: 463–466.

Matsuda, H., Morikawa, T., Ueda, H., and Yoshikawa, M. 2001. Medicinal foodstuffs. XXVI. Inhibitors of aldose reductase and new triterpene and its oligoglycoside, centellasapogenol A and centellasaponin A, from *Centella asiatica* (Gotu Kola). *Heterocycles.* 55: 1499–1504.

Matsuda, H., Murakami, T., Li, Y., Yamahara, J., and Yoshikawa, M. 1998. Mode of action of escins Ia and IIa and E,Z-senegin II on glucose absorption in gastrointestinal tract. *Bioorg. Med. Chem.* 6: 1019–1023.

Matsuda, H., Murakami, T., Yashiro, K., Yamakara, J., and Yoshikawa, M. 1999. Anti-diabetic principles of natural medicines. IV. Aldose reductase and alpha glucosidase inhibitors from the roots of *Salacia oblonga* Wall. (Celastraceae): Structure of a new friedelane-type triterpene, kotalagenin 16-acetate. *Chem. Pharm. Bull. (Tokyo)* 47: 1725–1729.

Matsuda, H., Nishida, N., and Yoshikawa, M. 2002. Antidiabetic principles of natural medicines. V. Aldose reductase inhibitors from *Myrcia multiflora* DC. (2): Structures of myrciacitrins III, IV, and V. *Chem. Pharm. Bull.* 50: 429–431.

Matsuda, H., Yoshikawa, M., Morikawa, T., Tanabe, G., and Muraoka, O. 2005. Anti-diabetogenic constituents from *Salacia* species. *J. Trad. Med.* 22: 145–153.

Matsumoto, K., Takayama, K., Abesundara, K. J. M., and Matsui, T. 2003. Assay of α-glucosidase inhibitory activity using flow-biosensor system. *Anal. Chim. Acta* 479: 135–141.

Matsumoto, Y., Ishii, M., Hayashi, Y., Miyazaki, S., Sugita, T., Sumiya, E., et al. 2015. Diabetic silkworms for evaluation of therapeutically effective drugs against type 2 diabetes. *Sci. Rep.* 5(10722): 11.

Matsumoto, Y., Sumiya, E., Sugita, T., and Sekimizu, K. 2011. An invertebrate hyperglycemic model for the identification of anti-diabetic drugs. *PLoS One* 6: e18292.

Matsura, T., Yoshikawa, Y., Masui, H., and Sano, M. 2004. Suppression of glucose absorption by various health teas in rats. *Yakugaku Zasshi.* 124: 217–223.

Maurya, R., Srivastava, A., Shah, P., Siddiqi, M. I., Rajendran, S. M., Puri, A., et al. 2012. β-Amyrin acetate and β-amyrin palmitate as antidyslipidemic agents from Wrightia tomentosa leaves. *Phytomedicine* 19: 682–685.

Mawalagedera, S. M. U. P., Perera, G. A. D., and Sooriyapathirana, S. D. S. S. 2014. Prolonged seed dormancy in *Phyllanthus emblica* L. can be overturned by seed scarification and gibberellins pre-treatment. *Open J. Forestry* 4: 38–41.

Mbaka, G. O., Ogbonnia, S. O., and Banjo, A. E. 2011. Antihyperglycaemic and antihyperlidaemic effects of *Raphia hookeri* root extract on alloxan induced diabetic rats. *Planta Med*. 77: PF14. doi:10.1055/s-0031-1282402.

Mbaka, G. O., Ojewale, A. O., Ogbonnia, S. O., and Ota, D. A. 2014. Anti-hyperglycemic and antihyperlipidaemic activities of aqueous ethanol root extract of *Pseudocedrela kotschyi* on alloxan-induced diabetic rats. *Br. J. Med. Medical Res*. 4: 5839–5852.

Mbouangouere, R. N., Tane, P., Ngamga, D., Khan, S. N., Choudhary, M. I., and Ngadjui, B. T. 2007. A new steroid and α-glucosidase inhibitors from *Anthocleista schweinfurthii*. *Res. J. Med. Plant* 1: 106–111.

McCarthy, A. M. and Elmendorf, J. S. 2007. GLUT4's itinerary in health and disease. *Indian J. Med. Res*. 125: 373–388.

McCarty, M. F. 2005. Potential utility of natural polyphenols for reversing fat-induced insulin resistance. *Med. Hypotheses* 64: 628–635.

McCormack, D. and McFadden, D. 2013. A review of pterostilbene antioxidant activity and disease modification. *Oxid. Med. Cell. Longev*. 2013(575482): 15.

McCune, L. M., Owen, P., and Johns, T. 2005. Flavonoids, xanthones and other anti-oxidant polyphenols. In: *Traditional Medicines for Modern Times: Antidiabetic Plants*. Soumyanath, A. (Ed). Boca Raton, FL: CRC Press, Taylor & Francis, 293–303.

McIntosh, C. H., Demuth, H. U., Pospisilik, J. A., et al. 2005. Dipeptidyl peptidase IV inhibitors: how do they work as new antidiabetic agents? *Regul. Pept*. 128: 159–165.

McIntosh, C. H. 2008. Dipeptidyl peptidase IV inhibitors and diabetes therapy. *Front. Biosci*. 13: 1753–1573.

Meena, M. C. and Patni, V. 2007. *In vitro* clonal propagaion of *Citrullus colocynthis* (Linn.) Schrad.—A threatened medicinal plant. *Plant Cell Biotechnol. Mol. Biol*. 8: 147–152.

Meena, M. C., Meena, R., and Patni, V. 2010. High frequency plant regeneration from shoot tip explants of *Citrullus colocynthis* (Linn.) Schrad.—An important medicinal herb. *Afr. J. Biotechnol*. 9: 5037–5041.

Meena, M. C., Meena, R. K., and Patni, V. 2014a. High frequency plant regeneration from shoot tip explants of *Citrullus colocynthis* (Linn.) Schrad.—An important medicinal herb. *J. Pharmacog. Phytochem*. 4: 53–56.

Meena, M. C., Meena, R. K., and Patni, V. 2014b. *In vitro* callus induction and shoot regeneration in *Citrullus colocynthis* (Linn.) Schrad. *World J. Pharm. Pharm. Sci*. 3: 1469–1480.

Mehmood, M. H. and Gilani, A. H. 2010. Pharmacological basis for the medicinal use of black pepper and piperine in gastrointestinal disorders. *J. Food. Med*. 13: 1086–1096.

Mehta, U. J., Barreto, S. M., and Nazra, S. 2004. Effect of thidiazuron in germinating tamarind seedlings. *In Vitro Cell. Dev. Biol. Plant* 40: 279–283.

Melyan, G., Sahakyan, A., and Dangyan, K. 2014. *In vitro* plant regeneration and multiplication of *Ziziphus jujube* Mill. *Acta Hortic*. 1032: 145–150.

Meng, S., Cao, J., Feng, Q., Peng, J., and Hu, Y. 2013. Roles of chlorogenic acid on regulating glucose and lipids metabolism: A review. *Evid. Based Complement. Alternat. Med*. 2013(801457): 11.

Menon, P. V. and Kurup, P. A. 1976. Hypolipidemic action of the polysaccharide from *Phaseolus mungo* (blackgram): Effect on lipid metabolism. *Indian J. Biochem. Biophys*. 13: 46–48.

Merghache, S., Zerriouh, M., Merghache, D., Tabti, B., Djaziri, R., and Ghalem, S. 2013. Evaluation of hypoglycaemic and hypolipidemic activities of Globularin isolated from *Globularia alypum* L. in normal and streptozotocin-induced diabetic rats. *J. Appl. Pharm. Sci*. 3: 1–7.

Metwally, N. S., Mohamed, A. M., and Sharabasy, F. S. E. L. 2012. Chemical constituents of the Egyptian plant *Anabasis articulata* (Forssk) Moq and its anti-diabetic effects on rats with streptozotocin-induced diabetic hepatopathy. *J. Appl. Pharm. Sci*. 2: 54–65.

Mezei, O., Banz, W. J., Steger, R. W., Peluso, M. R., Winters, T. A., and Shay, N. 2003. Soy isoflavones exert hypoglycemic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 246.7 cells. *J. Nutr*. 133: 1238–1243.

Mhammad, H. A., Jubrail, A. M. S., and Najeeb, M. K. 2015. Impact of cinnamon extract on hyperlipidemic and diabetic rats. *Int. J. Chem. Biol. Sci*. 1: 96–106.

Michel, C. G., Nesseem, D. I., and Ismail, M. F. 2011. Anti-diabetic activity and stability study of the formulated leaf extract of *Zizyphus spina-christi* (L.) Willd with the influence of seasonal variation. *J. Ethnopharmacol*. 133: 53–62.

Michel, M. C., Fliers, E., and Van Noorden, C. J. 2008. Dipeptidyl peptidase IV inhibitors in diabetes: More than inhibition of glucagon-like peptide-1 metabolism? *Naunyn Schmiedebergs Arch. Pharmacol*. 377: 205–207.

Michelle de Sales, P., Monteiro de Souza, P., Simeoni, L. A., Magalhaes, P. O., and Silveria, D. 2012. A-amylase inhibitors: A review of raw material and isolated compounds from plant source. *J. Pharm. Pharmaceut. Sci.* 15: 141–147.

Middha, S. K., Usha, T., and Pande, V. 2013. A review on anti-hyperglycemic and hepatoprotective activity of eco-friendly *Punica granatum* peel waste. *Evid. Based Complement. Altern. Med.* 2013(656172): 10.

Mikula, A., Tomiczak, K., and Rybczynski, J. J. 2011. Cryopreservation enhances embryogenic capacity of *Gentiana cruciata* (L.) suspension culture and maintains epigenetic uniformity of regenerants. *Plant Cell Reports* 30: 565–574.

Mingrone, G. and Castagneto-Gissey, L. 2014. A central role of the gut in glucose homeostasis. *Nat. Rev. Endocrinol*. 10: 73–74.

Miranda-Perez, M. E., Escobar-Villanueva, M. D. C., Ortega-Camarillo, C., Sanchez-Munoz, F., Almaza-Perez, J. C., and Alarcon-Aguilar, F. J. 2013. *Cucurbita ficifolia* Bouche fruit acts as an insulin secretagogue RINm5F cells. *Int. Biotechnol. Color J.* 3: 8–14.

Mirza, R. H., Chi, N., and Chi, Y. 2013. Therapeutic potential of the natural product mangiferin in metabolic syndrome. *J. Nutr. Ther.* 2: 74–79.

Misawa, E., Tanaka, M., Nomaguchi, K., Yamada, M., Toida, T., Takase, M., et al. 2008. Administration of phytosterols isolated from *Aloe vera* gel reduce visceral fat mass and improve hyperglycemia in Zucker diabetic fatty (ZDF) rats. *Obes. Res. Clin. Pract.* 2: 239–245.

Mishra, T. 2015. Protocol establishment for multiplication and regeneration of holy basil (*Ocimum sanctum* L.), an important plant with high religious value in India. *J. Med. Plants Studies*. 3: 16–19.

Miura, T., Ichiki, H., Iwamoto, N., Kato, M., Kubo, M., Sasaki, H., Okada, M., Ishida, T., Seino, Y., and Tanigawa, K. 2001. Antidiabetic activity of the rhizoma of *Anemarrhena asphodeloides* and active components, mangiferin and its glucoside. *Biol. Pharm. Bull*. 24: 1009–1011.

Miura, T., Nosaka, K., Ishii, H., and Ishida, T. 2005. Antidiabetic effect of Nitobegiku, the herb *Tithonia diversifolia*, in KK-Ay diabetic mice. *Biol. Pharm. Bull*. 28: 2152–2154.

Miura, Y., Hosono, M., Oyamada, C., Odai, H., Oikawa, S., and Kondo, K. 2005. Dietary, isohumulones, the bitter components of beer, rise plasma HDL-cholesterol levels and reduce liver cholesterol and triglyceride contents similar to PPAR-α activation in C57BL/6 mice. *Br. J. Nutr.* 93: 559–567.

Miyao, H., Arao, T., Udayama, M., Kinjo, J., and Nohara, T. 1998. Kaikasaponin III and soyasaponin I, major triterpene saponins of *Abrus cantoniensis*, act on GOT and GPT: Influence on transaminase elevation of rat liver cells concomitantly exposed to CCl4 for one hour. *Planta Med*. 64: 5–7.

Mizokami, S. S., Arakawa, N. S., Ambrosio, S. R., Zarpelon, A. C., Casagrande, R., Cunha, T. M., et al. 2012. Kaurenoic acid from *Sphagneticola trilobata* inhibits inflammatory pain: Effect on cytokine production and activation of the NO–Cyclic GMP–Protein Kinase G–ATP-Sensitive potassium channels signaling pathway. *J. Nat. Prod*. 75: 896–904.

Mnafgui, K., Hamden, K., Salah, H. B., Kchaou, M., Nasri, M., Slama, S., et al. 2012. Inhibitory activities of *Zygophyllum album*: A natural weight-lowering plant on key enzymes in high-fat diet-fed rats. *Evid. Based Complement. Alternat. Med*. 2012(620384): 9.

Mnafgui, K., Kchaou, M., Hamden, K., Derbali, F., Slama, S., Nasri, M., et al. 2014. Inhibition of carbohydrate and lipid digestive enzymes activities by *Zygophyllum album* extracts: Effect on blood and pancreas inflammatory biomarkers in alloxan-induced diabetic rats. *J. Physiol. Biochem*. 70: 93–106.

Mneney, E. E. and Mantell, S. H. 2001. *In vitro* micro-grafting of cashew. *Plant Cell Tiss. Org. Cul*. 66: 49–58.

Mnonopi, N., Levendal, R. A., Mzilikazi, N., and Frost, C. L. 2012. Murrabiin, a constituent of *Leonotis leonurus*, alleviates diabetic symptoms. *Phytomedicine* 19: 488–493.

Modak, M., Dixit, P., Londhe, J., Ghaskadbi, S., and Devasagayam, T. P. A. 2007. Indian herbs and herbal drugs used for the treatment of diabetes. *J. Clin. Biochem. Nutr.* 40: 163–173.

Mogana, R., Teng-Jin, K., and Wiart, C. 2013. Anti-inflammatory, anticholinesterase, and antioxidant potential of scopoletin isolated from *Canarium patentinervium* Miq. (Burseraceae Kunth). *Evid. Based Complement. Alternat. Med*. 2013(734824): 7.

Moghaddam, M. G., Ahmad, F. B. H., and Samzadeh-Kermani, A. 2012. Biological activity of betulinic acid: A review. *Pharmacol. Pharm*. 3: 119–123.

Mohamed, A. E. H., El-Sayed, M. A., Hegazy, M. E., Helaly, S. E., Esmail, A. M., and Mohamed, N. S. 2010. Chemical constituents and biological activities of *Artemisia herba-alba*. *Rec. Nat. Prod*. 4: 1–25.

Mohamed, E. A., Yam, M. F., Ang, L. F., Mohamed, A. J., and Asmawi, M. Z. 2013. Antidiabetic properties and mechanism of action of *Orthosiphon stamineus* Benth bioactive sub-fraction in streptozotocin-induced diabetic rats. *J. Acupunct. Meridian. Stud.* 6: 31–40.

Mohammadi, A., Gholamhoseinian, A., and Fallah, H. 2014. *Zataria multiflora* increases insulin sensitivity and PPARγ gene expression in high fructose fed insulin resistant rats. *Iranian J. Basic Med. Sci.* 17: 263–270.

Mohammadi, J. and Naik, P. R. 2012. The histopathological effects of Morus alba leaf extract on the pancreas of diabetic rats. *Turk. J. Biol.* 36: 211–216.

Mohan, C. G., Viswanatha, G. L., Savinay, G., Rajendra, C. E., et al. 2013. 1,2,3,4,6 penta-O-galloyl-β-D-glucose, a bioactivity guided isolated compound from *M. indica* inhibits 11-β-HSD-1 and ameliorates high fat diet induced diabetes in C57BL/6 mice. *Phytomedicine* 20: 417–426.

Mokhber-Dezfuli, N., Saeidnia, S., Gohari, A. R., Kurepaz-Mahmoodabadi, M. 2014. Phytochemistry and pharmacology of *Berberis* Species. *Phcog. Rev.* 8: 8–15.

Moloudizargari, M., Mikaili, P., Aghajanshakeri, S., Asghari, M. H., and Shayegh, J. 2013. Pharmacological and therapeutic effects of *Peganum harmala* and its main alkaloids. *Pharmacogn Rev.* 7: 199–212.

Moon, D. O., Kim, M. O., Lee, J. D., Choi, Y. H., and Kim, G. Y. 2010. Rosmarinic acid sensitizes cell death through suppression of TNF-alpha-induced NF-kappaB activation and ROS generation in human leukemia U937 cells. *Cancer Lett.* 288: 183–191.

Moorthy, R., Prabhu, K. M., and Murthy, P. S. 2010a. Anti-hyperglycemic compound GII from fenugreek (*Trigonella foenum-graceum* Linn) seeds, its purification and effect in diabetes mellitus. *Ind. J. Exp. Biol.* 48: 1111–1118.

Moorthy, R., Prabhu, K. M., and Murthy, P. S. 2010b. Mechanism of anti-diabetic action, efficacy and safety profile of GII purified from fenugreek (*Trigonella foenum-graceum* Linn) seeds in diabetic animals. *Ind. J. Exp. Biol.* 48: 1119–1122.

Moradi-Afrapoli, F., Asghari, B., Saeidnia, S., Ajani, Y., Mirjani, M., Malmir, M., et al. 2012. *In vitro* α-glucosidase inhibitory activity of phenolic constituents from aerial parts of *Polygonum hyrcanicum*. *DARU J. Pharm. Sci.* 20: 37–43.

Morikawa, T., Kishi, A., Pongpiriyadacha, Y., Matsuda, H., and Yoshikawa, M. 2003. Structures of new friedelane-type triterpenes and eudesmane-type sesquiterpene and aldose reductase inhibitors from *Salacia chinensis*. *J. Nat. Prod.* 66: 1191–1196.

Moritoh, Y., Takeuchi, K., Asakawa, T., et al. Chronic administration of alogliptin, a novel, potent, and highly selective dipeptidyl peptidase-4 inhibitor, improves glycemic control and beta-cell function in obese diabetic ob/ob mice. *Eur. J. Pharmacol.* 588: 325–332.

Mousinho, N. M., vanTonder, J. J., and Steenkampa, V. 2013. *In vitro* anti-diabetic activity of *Sclerocarya birrea* and *Ziziphus mucronata*. *Nat. Prod. Commun.* 6: 1279–1284.

Mowla, M., Alauddin, M. D., Rahman A., and Ahmed, K. 2009. Antihyperglycemic effect of *Trigonella foenum-graecum* (fenugreek) seed extract in alloxan-induced diabetic rats and its use in diabetes mellitus: A brief qualitative phytochemical and acute toxicity test on the extract. *Afr. J. Tradit. CAM.* 6: 255–261.

Mueller, M., Lukas, B., Novak, J., Simoncini, T., Genazzani, A. R., and Jungbauer, A. 2008. Oregano: A source for peroxisome proliferator-activated receptor gamma antagonists. *J. Agric. Food Chem.* 56: 11621–11630.

Mujeeb, M., Zafar, R., Husain, A., and Ahmad, A. 2012. Antihepatotoxic activity of aqueous extracts of callus culture of *Tephrosia purpurea* (L) pers. *Acta Pol. Pharm.* 69: 545–549.

Muller, C. J., Joubert, E., de Beer, D., Sanderson, M., Malherbe, C. J., Fey, S. J., et al. 2012. Acute assessment of an aspalathin-enriched green rooibos (*Aspalathus linearis*) extract with hypoglycemic potential. *Phytomedicine* 20: 32–39.

Munshi, M. K., Hakim, L., Islam, M. R., and Ahmed, A. 2004. *In vitro* clonal propagation of banyan (*Ficus benghalensis* L.) through axillary bud culture. *Int. J. Agric. Biol.* 6: 321–333.

Murali, B., Upadhyaya, U. M., and Goyal, P. K. 2002. Effect of chronic treatment with *Enicostemma littorale* in non-insulin dependent diabetic (NIDDM) rats. *J. Ethnopharmacol.* 81: 199–204.

Murali, Y. K., Anand, P., Tandon, V., Singh, R., Chandra, R., and Murthy, P. S. 2007. Long-term effects of *Terminalia chebula* Retz. on hyperglycemia and associated hyperlipidemia, tissue glycogen content and *in vitro* release of insulin in streptozotocin induced diabetic rats. *Exp. Clin. Endocrinol. Diabetes* 115: 641–646.

Muruganandan, S., Srinivasan, K., Gupta, S., Gupta, P. K., and Lal, J. 2005. Effect of mangiferin on hyperglycemia and atherogenicity in streptozotocin diabetic rats. *J. Ethnopharmacol*. 97: 497–501.

Muthukumaran, J., Srinivasan, S., Venkatesan, R. S., Ramachandran, V., and Muruganantha n, U. 2013. Syringic acid, a novel natural phenolic acid, normalizes hyperglycemia with special reference to glycoprotein components in experimental diabetic rats. *J. Acute Dis*. 2: 304–309.

Muthusamy, V. S., Anand, S., Sangeetha, K. N., Sujatha, S., Arun, B., and Lakshmi, B. S. 2008. Tannins present in *Cichorium intybus* enhance glucose uptake and inhibit adipogenesis in 3T3-L1 adipocytes through PTP1B inhibition. *Chem. Biol. Interact*. 174: 69–78.

Mvuria, J. M. and Ombori, O. 2014. Low cost micronutrients in the micropropagation of selected sweet potato (*Ipomoea batatas* (L.) Lam) verities. *J. Agric. Environ. Sci*. 3: 89–101.

Mythili, M. D., Vyas, R., Akila, G., Gunasekaran, S., 2004. Effect of streptozotocin on the ultra structure of rat pancreatic islets. *Microsc. Res. Tech*. 63: 274–281.

Na, M. K., Thuong, P. T., Hwang, I. H., Bae, K. H., Kim, B. Y., Osada, H., et al. 2010. Protein tyrosine phosphatase 1 B inhibitory activity of 24-norursane triterpenes isolated from *Weigela subsessilis. Phytother. Res*. 24: 1716–1719.

Nabi, S. A., Kasetti, R. B., Sirasanagandla, S., Tilak, T. K., Kumar, M. V. J., and Rao, C. A. 2013. Antidiabetic and antihyperlipidemic activity of *Piper longum* root aqueous extract in streptozotocin induced diabetic rats. *BMC Complement. Altern. Med*. 13: 37.

Nadolska-Orczyk, A. 1992. Somatic embryogenesis of agriculturally important lupin species (*Lupinus angustifolius*, *L. albus*, *L. mutabilis*). *Plant Cell Tiss. Org. Cult*. 28: 19–25.

Nagahatenna, D. S. K. and Peiris, S. E. 2007. *In vitro* propagation of *Hemidesmus indicus (L.) R. Br. (Iramusu)* through nodal culture. *Trop. Agric. Res*. 19: 181–192.

Nagamine, R., Ueno, S., Tsubata, M., Yamaguchi, K., Takagaki, K., Hira, T., et al. 2014. Dietary sweet potato (*Ipomoea batatas* L.) leaf extract attenuates hyperglycaemia by enhancing the secretion of glucagon-like peptide-1 (GLP-1). *Food Funct*. 5: 2309–2316.

Nagy, M. A. and Mohamed, S. A. 2014. Antidiabetic effect of *Cleome droserifolia* (Cleomaceae). *Am. J. Biochem*. 4: 68–75.

Naik, S. R., Barbosa Filho, J. M., Dhuley, J. N., Deshmukh, V. 1991. Probable mechanism of hypoglycemic activity of bassic acid, a natural product isolated from *Bumelia sartorum*. *J. Ethnopharmacol*. 33: 37–43.

Nain, P., Saini, V., Sharma, S., and Nain, J. 2012. Antidiabetic and antioxidant potential of *Emblica officinalis* Gaertn. leaves extract in streptozotocin-induced type-2 diabetes mellitus (T2DM) rats. *J Ethnopharmacol*. 142: 65–71.

Nakamura, S., Takahira, K., Tanabe, G., Morikawa, T., Sakano, M., Ninomiya, K., Yoshikawa, M., Muraoka, O., and Nakanishi. I. 2010. Docking and SAR studies of Salacinol derivatives as alpha-glucosidase inhibitors. *Bioorg. Med. Chem. Lett*. 20: 4420–4423.

Nakashima, N., Kimura, I., and Kimura, M. 1993. Isolation of pseudoprototimosaponin AIII from rhizomes of *Anemarrhena asphodeloides* and its hypoglycemic activity in streptozotocin-induced diabetic mice. *J. Nat. Prod*. 56: 345–350.

Nalamolu, R. K., Boini, K. M., Nammi, S. 2004. Effect of chronic administration of *Boerhaavia diffusa* Linn. leaf extract on experimental diabetes in rats. *Trop. J. Pharm. Res*. 3: 305–309.

Nalawade, S. M. and Tsay, H. -S. 2004. In vitro propagation of some important Chinese medicinal plants and their sustainable use. *In Vitro Cell Dev. Biol. Plant* 40: 143–154.

Narayan, P., Chakraborty, S., and Subbarao, G. 1989. Regeneration of plantlets from the callus of stem segments of mature plants of *Morus alba* L. *Proc. Indian Natn. Sci. Acad*. B55: 469–472.

Narayanan, R., Joshi, D. D., Mujumdar, A. M., and Dhekne. V. V. 1987. Pinitol, a new antidiabetic compound from the leaves of *Bougainvillea spectabilis. Curr. Sci*. 56, 139–141.

Narender, T., Puri, A., Shweta, S., Khaliq, T., Saxena, R., Bhatia, G., and Chandra, R. 2006. 4-hydroxy isoleucine an unusual amino acid as an anti-dyslipidemic and anti-hyperglycemic agent. *Bioorg. Med. Chem*. 16: 293–296.

Narender, T., Shweta, S., Tiwari, P., Khaliq, T., Prathipati, P., Puri, A., Srivastava, A. K., Chander, R., Agarwal, S. C., and Raj, K. 2007. Antihyperglycemic and antidyslipidemic agent from *Aegle marmelos. Bio org. Med. Chem. Lett*. 17: 1808–1811.

Narendran, M., Deole, S. G., Harkude, S., Shirale, D., Nanote, A., Bihani, P., et al. 2013. Efficient genetic transformation of okra (*Abelmoschus esculentus* (L.) Moench) and generation of insect-resistant transgenic plants expressing the cry1Ac gene. *Plant Cell Rep*. 32: 1191–1198.

Narvaez-Mastache, J. M., Garduno-Ramirez, M. L., Alvarez, L., and Delgado, G. 2006. Antihyperglycemic activity and chemical constituents of *Eysenhardtia platycarpa*. *J. Nat. Prod.* 69: 1687–1691.

Nasirujjaman, K., Uddin, M. S., Zaman, S., and Reza, M. A. 2005. Micropropagation of turmeric (*Curcuma longa* Linn.) through *in vitro* rhizome bud culture. *J. Biol. Sci.* 5: 490–492.

National Medicinal Plant Board. 2008. Agro-techniques of selected medicinal plants. Vol. 1, Ministery of Health and Family Welfare, Government of India, Energy and Resources Institute Press, Innovative Designers and Printers, New Delhi.

Nauck, M. A. 2014. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. *Drug Design Ther.* 8: 1335–1380.

Nayak, A., Mandal, S., Banerji, A., and Banerji, J. 2010b. Review on chemistry and pharmacology of *Murraya koenigii* Spreng (Rutaceae). *J. Chem. Pharm. Res.* 2: 286–299.

Nayak, P., Behera, P. R., and Manikkannan, T. 2007. High frequency plantlet regeneration from cotyledonary node cultures of *Aegle marmelos* (L.) Corr. *In Vitro Cell. Dev. Biol. Plant* 43: 23123–23126.

Nayak, P., Behera, P. R., Thirunavoukkarasu, M., and Chand, P. K. 2010a. High frequency plant regeneration through adventitious multiple shoot organogenesis in epicotyls explants of Indian gooseberry (*Emblica officinalis* Gaertn). *Scientia Horticulturae* 123: 473–478.

Naz, R., Anis, M., and Atta, H. A. E. 2015. Micropropagation of *Cassia occidentalis* L. and the effect of irradiance on photosynthetic pigments and antioxidative enzymes. *Biologia Plantarum* 59: 1–10.

Nazaruk, J. and Borzym-Kluczyk, M. 2015. The role of triterpenes in the management of diabetes mellitus and its complications. *Phytochem. Rev.* 14: 675–690.

Nazreen, S., Kaur, G., Alam, M. M., Shafi, S. Hamid, H., Ali, M., and Alam, M. S. 2012. New flaovones with anti-diabetic activity from *Callistemon lanceolatus* DC. *Fitoterapia* 83: 1623–1627.

Ndiaye, M., Diatta, W, Sy, A. N., Dieye, A. M., Faye, B., and Bassene, E. 2008. Antidiabetic properties of aqueous barks extract of *Parinari excelsa* in alloxan-induced diabetic rats. *Fitoterapia*. 79: 267–270.

Negash, A., Krens, F., Schaart, J., and Visser, B. 2001. *In vitro* conservation of enset under slow-growth condition. *Plant Cell Tiss. Org. Cult.* 66: 107–111.

Negi, R. S., Sharma, K. C., and Sharma, M. 2011. Micropropagation and anatomical comparision of *in vivo* and *in vitro* developed shoot and root in *Cassia auriculata* L.—A medicinally important plant. *Indian J. Fund. Appl. Life Sci.* 1: 21–29.

Nerurkar, P. V., Nishioka, A., Eck, P. O., Johns, L. M., Volper E., and Nerurkar, V. R. 2012. Regulation of glucose metabolism *via* hepatic forkhead transcription factor 1 (FoxO1) by *Morinda citrifolia* (noni) in high-fat diet-induced obese mice. *Br. J. Nutr.* 108: 218–228.

Ng, T. B., Li, W. W., and Yeung, H. W. 1987a. Effect of gingenosides, lectins and *Momordica charantia* insulin-like peptide on corticosterone production by isolated rat adrenal cells. *J. Ethnopharmacol.* 21: 21–29.

Ng, T. B., Wong, C. M., Li, W. W., and Yeung, H. W. 1986. Insulin-like molecules in *Momordica charantia* seeds. *J. Ethnopharmacol.* 15: 107–117.

Ng, T. B., Wong, C. M., Li, W. W., and Yeung, H. W. 1987b. Acid ethanol extractable compounds from fruits and seeds of the bitter gourd, *Momordica charantia*: Effect on lipid metabolism in isolated rat adipocytes. *Am. J. Chin. Med.* 15: 31–42.

Nicasio, P., Anguilar-Santamaria, L., Aranda, E., Ortiz, S., and Gonzalez, M. 2005. Hypoglycemic effect and chlorogenic acid content in two *Cecropia* species. *Phytother. Res.* 9: 661–664.

Nickavar, B. and Amin, G. 2004. Anthocyanins from *Vaccinium arctostaphylos* berries. *Pharm. Biol.* 42: 289–291.

Nickavar, B. and Amin, G. 2010. Bioassay-guided separation of an alpha-amylase inhibiting anthocyanin from *Vaccinium arctostaphylos* berries. *Z. Naturforsch C*. 65: 567–570.

Nickavar, B. and Yousefian, N. 2009. Inhibitory effects of six *Allium* species on α-amylase enzyme activity. *Iranian J. Pharm. Res.* 8: 53–57.

Nidavani, R. B. and Mahalakshmi, A. M. 2014. Pharmacology of *Tectona grandis* Linn.: Short Review. *Int. J. Pharmacogn. Phytochem. Res.* 6: 86–90.

Nimal Christhudas, I. V. S., Kumar, P. P., Christudas, C., Vajravijayan, S., Sundaram, R. L., Siril, S. J., et al. 2013. *In vitro* studies on α-glucosidase inhibition, anti-oxidant and free radical scavenging activities of *Hedyotis biflora* L. *Food Chem.* 138: 1689–1695.

Ninomiya, K., Matsuda, H., Kubo, M., Morikawa, T., Nishida, N., and Yoshikawa, M. 2007. Potent anti-obese principle from *Rosa canina*: Structural requirements and mode of action of trans-tiliroside. *Bioorg. Med. Chem. Lett.* 17: 3059–3064.

Nirmal, N. P., Rajput, M. S., Prasad, R. G. S. V., and Ahmed, M. 2015. Brazilin from *Caesalpinia sappan* heartwood and its pharmacological activities: A review. *Asian Pac. J. Trop. Med.* 5: 421–430.

Nishimura, K., Fukuda, T., Miyase, T., Noguchi, H., and Chen, X. M. 1999. Activity-guided isolation of triterpenoid acyl CoA cholesteryl acyl transferase (ACAT) inhibitors from *Ilex kudincha*. *J. Nat. Prod.* 62: 1061–1064.

Nishioka, T., Kawabata, J., and Aoyama, Y. 1998. Baicalein, an α-glucosidase inhibitor from *Scutellaria baicalensis*. *J. Nat. Prod*. 61: 1413–1415.

Nishiyama, T., Mae, T., Kishida, H., Tsukagawa, M., Mimaki, Y., Kuroda, M., et al. 2005. Curcuminoids and sesquiterpenoids in turmeric (*Curcuma longa* L.) suppress an increase in blood glucose level in type 2 diabetic KK-Ay mice. *J. Agric Food Chem*. 53: 959–563.

Niture, N. T., Ansari, A. A., and Naik, S. R. 2014. Anti-hyperglycemic activity of rutin in streptozotocin-induced diabetic rats: An effect mediated through cytokines, anti-oxidants and lipid biomarkers. *Indian J. Exp. Biol*. 52: 720–727.

Niu, H. S., Liu, I. M., Cheng, J. T., Lin, C. L., and Hsu, F. L. 2008. Hypoglycemic effect of syringin from *Eleutherococcus senticosus* in streptozotocin-induced diabetic rats. *Planta Med.* 74: 109–113.

Niu, Y., Li, S., Na, L., Feng, R., Liu, L., Li, Y., and Sun, C. 2012. Mangiferin decreases plasma free fatty acids through promoting its catabolism in liver by activation of AMPK. *PLoS One* 7: e30782.

Nivedha, R. P., Selvaraj, J., Lalitha, K. G., and Rajalakshmi, M. 2015. Effects of dihydroxy gymnemic triacetate (DGT) on expression of apoptosis associated proteins in human prostate cancer cell lines (PC3). *J. Recept. Signal. Transduct. Res.* 35: 605–612.

Niwa, A., Tajiri, T., and Higashino, H. 2011. *Ipomoea batatas* and *Agarics blazei* ameliorate diabetic disorders with therapeutic antioxidant potential in streptozotocin-induced diabetic rats. *J. Clin. Biochem. Nutr.* 48: 194–202.

Nmila, R., Gross, R., Rchid, H., Roye, M., Manteghetti, M., Petit, P., et al. 2000. Insulinotropic effect of *Citrullus colocynthis* fruit extracts. *Planta Med*. 66: 418–423.

Nojima, H., Kimura, I., Chen, F. J., Sugihara, Y., Haruno, M., Kato, A., and Asano, N. 1998. Antihyperglycemic effects of N-containing sugars from *Xanthocercis zambesiaca*, *Morus bombycis*, *Aglaonema treubii*, and *Castanospermum australe* in streptozotocin-diabetic mice. *J. Nat. Prod*. 61: 397–400.

Noorshahida, A., Wong, T. W., and Choo, C. Y. 2009. Hypoglycemic effect of quassinoids from *Brucea javanica* (L.) Merr (Simaroubaceae) seeds. *J. Ethnopharmacol*. 124: 586–591.

Nualkaew, S., Padee, P., and Talubmook, C. 2015. Hypoglycemic activity in diabetic rats of stigmasterol and sitosterol-3-O-β-D-glucopyranoside isolated from Pseuderanthemum palatiferum (Nees) Radlk. leaf extract. *J. Med. Plants Res*. 90: 629–635.

Nugroho, A. E., Andrie, M., Warditiani, N. K., Siswanto, E., Suwidjivo, P., and Lukitaningsih, E. 2012. Antidiabetic and antihiperlipidemic effect of *Andrographis paniculata* (Burm. f.) Nees and andrographolide in high-fructose-fat-fed rats. *Indian J. Pharmacol*. 44: 377–381.

Nugroho, A. E., Rais, I. R., Setiawan, I., Pratiwi, P. Y., Hadibarata,T., Tegar, M., et al. 2014. Pancreatic effect of andrographolide isolated from *andrographis paniculata* (Burm. F.) Nees. *Pak. J. Biol. Sci.* 17: 22–31.

Nugroho, A. E., Riyanto, S., and Sukari, M. A. 2011. Effects of aegeline, a main alkaloid of *Aegle marmelos* Correa leaves, on the histamine release from mast cells. *Pak. J. Pharm. Sci*. 24: 359–367.

Nyarko, A. K., Ankrah, N. A., Ofosuhene, M., and Sittie, A. A. 1999. Acute and subchronic evaluation of *Indigofera arrecta*: Absence of both toxicity and modulation of selected cytochrome P450 isozymes in ddY mice. *Phytother. Res*. 13: 686–688.

Obae, S. G., Klandorf, H., and West, T. P. 2011. Growth characteristics and ginsenosides production of *in vitro* tissue of American ginseng, *Panax quinquefolius* L. *HortSci*. 46: 1136–1140.

Obanda, D. N., Hernandez, A. Ribnicky, D., Yu, Y., Zhang, X. H., Wang, Z. Q., et al. 2012. Bioactives of *Artemisia dracunculus* L. mitigate the role of ceramide in attenuating insulin signaling in rat skeletal muscle cells. *Diabetes* 61: 597–605.

Oberg, A. I., Yassin, K., Csikasz, R. I., Dehvari, N., Shabalina, I. G., Hutchinson, D. S., Wilcke, M., Ostenson, C. G., and Bengtsson, T. 2011. Shikonin increases glucose uptake in skeletal muscle cells and improves plasma glucose levels in diabetic Goto-Kakizaki rats. *PLoS One*. 6: e22510.

Oboh, G., Akinyemi, A. J., and Ademiluvi, A. O. 2012. Inhibition of α-amylase and α-glucosidase activities by ethanolic extract of *Telfairia occidentalis* (fluted pumpkin) leaf. *Asian Pac. J. Trop. Biomed*. 2: 733–738.

Odoh, U. E., Ezugwu, C. O., and Ezea, C. S. 2013. Antidiabetic and biochemical effect of the different fractions of methanol extract of *Detarium microcarpum* (Fabaceae) Guill and Perr stem bark on normal and alloxan induced diabetic rats. *Planta Med*. 79: 72–78.

Ogata, T., Li, L., Yamada, S., Yamamoto, Y., Tanaka, Y., Takei, I., et al. 2004. Promotion of beta-cell differentiation by conophylline in fetal and neonatal rat pancreas. *Diabetes* 53: 2596–2602.

Oh, J. H., Ban, J. O., Cho, M. C., Jo, M., Jung, J. K., Ahn, B., et al. 2012. 4-O-methylhonokiol inhibits colon tumor growth *via* p21-mediated suppression of NF-κB activity. *J. Nutr. Biochem*. 23: 706–715.

Oh, J. H., Kang, L. L., Ban, J. O., Kim,Y. H., Kim, K. H., Han, S. B., et al. 2009. Anti-inflammatory effect of 4-O-methylhonokiol, compound isolated from *Magnolia officinalis* through inhibition of NF-kappaB. *Chem. Biol. Interact*. 180: 506–514.

Ohan, V., Sandeep, S., Deepa, R., et al. 2007. Epidemiology of type 2 diabetes: Indian scenario. *Indian J. Med. Res*. 125: 217–230.

Ohnishi, M., Matuo, T., Tsuno, T., Hosoda, A., Nomura, E., Taniguchi, H., et al. 2004. Antioxidant activity and hypoglycemic effect of ferulic acid in streptozotocin-induced diabetic mice and KK-Ay mice. *Biofactors* 21: 315–319.

Oki, N., Nonaka, S., and Ozaki, S. 2011. The effects of an arabinogalactan-protein from the white-skinned sweet potato (*Ipomoea batatas* L.) on blood glucose in spontaneous diabetic mice. *Biosci. Biotechnol. Biochem*. 75: 2011–2018.

Okugawa, H., Ueda, R., Matsumota, K., Kawanishi, K., and Kato, A. 1996. Effect of dehydrocostus lactone and costunolide from Saussurea root on the central nervous system in mice. *Phytomedicine* 3: 147–153.

Olajide, O. A., Ajayi, A. M., and Wright, C. W. 2009. Anti-inflammatory properties of cryptolepine. *Phytother. Res*. 23: 1421–1425.

Olaokun, O. O., Mcgaw, L. J., Awouafack, M. D., Eloff, J. N., and Naido, V. 2014. The potential role of GLUT4 transporters and insulin receptors in the hypoglycaemic activity of *Ficus lutea* acetone leaf extract. *BMC Complement. Altern. Med.* 14: 269.

Olaokun, O. O., Mcgaw, L. J., Eloff, J. N., and Naido, V. 2013. Evaluation of the inhibition of carbohydrate hydrolyzing enzymes, anti-oxidant activity and polyphenolic content of extracts of ten African *Ficus* species (Moraceae) used traditionally to treat diabetes. *BMC Complement. Altern. Med.* 13: 94–99.

Olubunmi, A., Ademola, O. G., and Adenike, F. O. 2009. *Blighia sapida*: The plant and its hypoglycins: An overview. *J. Sci. Res.* 39: 15–25.

Onakpoya, J. J., Spencer, E. A., Thompson, M. J., and Heneghan, C. J. 2015. The effect of chlorogenic acid on blood pressure: A systematic review and meta-analysis of randomized clinical trials. *J. Hum. Hypertens.* 29: 77–81.

Ong, K. W., Hsu, A., and Tan, B. K. H. 2012. Chlorogenic acid stimulates glucose transport in skeletal muscle *via* AMPK activation: A contributor to the beneficial effects of coffee on diabetes. *PLoS ONE* 7: e32718.

Ong, K. W., Hsu, A., Song, L., Huang, D., and Tan, B. K. 2011. Polyphenols-rich *Vernonia amygdalina* shows anti-diabetic effects in streptozotocin-induced diabetic rats. *J. Ethnopharmacol.* 133: 598–607.

Orhan, N., Hocbac, S., Orhan, D. D., Asian, M., and Ergun, F. 2014. Enzyme inhibitory and radical scavenging effects of some antidiabetic plants of Turkey. *Iran J. Basic Med. Sci*. 17: 426–432.

Ortiz-Andrade, R. R., Garcia-Jimenez, S., Castillo-Espana, P., Ramirez-Avila, G., Villalobos-Molina, R., and Estrada-Soto, S. 2007. Alpha-glucosidase inhibitory activity of the methanolic extract from *Tournefortia hartwegiana*: An anti-hyperglycemic agent. *J. Ethnopharmacol.* 109: 48–53.

Ortiz-Andrade, R. R., Sanchez-Salgado, J. C., Navarrete-Vazquez, G., Webster, S. P., Binnie, M., Garcia-Jimenez, S., et al. 2008. Antidiabetic and toxicological evaluations of naringenin in normoglycaemic and NIDDM rat models and its implications on extra-pancreatic glucose regulation. *Diabetes Obes. Metab.* 10: 1097–1104.

Oshima, Y., Sato, K., and Hikino, H. 1987. Isolation and hypoglycemic activity of quinquefolans A, B, and C, glycans of Panax quinquefolium roots. *J. Nat. Prod*. 50: 188–190.

Otuki, M. F., Ferreira, J., Lima, F. V., Meyre-Silva, C., Malheiros, A., Muller, L. A., et al. 2005. Antinociceptive properties of mixture of alpha-amyrin and beta-amyrin triterpenes: Evidence for participation of protein kinase C and protein kinase A pathways. *J. Pharmacol. Exp. Ther.* 313: 310–318.

Oyunbileg, Y., Altanzul, K., Oyunsuren, T., and Bayarlkhagva, D. 2005. Tissue culture and micropropagation of Mongolian licorice (*Glycyrrhiza uralensis* Fisch.). *Mongolian J. Biol. Sci.* 3: 21–24.

Ozaki, S., Oe, H., and Kitamura, S. 2008. Alpha-glucosidase inhibitor from Kothala-himbutu (*Salacia reticulata* Wight). *J Nat Prod*. 71: 981–984.

Paarakh, P. M. 2009. *Coriandrum sativum* Linn.—A review. *Pharmacologyonline* 3: 561–573.

Padhan, B. 2015. Regeneration of *Piper longum* L. through *in vitro* culture from nodal segments. *J. Appl. Biol. Biotechnol.* 3: 35–39.

Paek, J. H., Shin, K. H., Kang, Y. -H., Lee, J. -Y., and Lim, S. S. 2013. Rapid identification of aldose reductase inhibitory compounds from *Perilla frutescens*. *Bio Med. Res. Int.* 2013(679463): 8.

Paiva, L. B., Goldbeck, R., Santos, W. D., and Squina, F. M. 2013. Ferulic acid and derivatives: Molecules with potential application in the pharmaceutical field. *Brazilian J. Pharm. Sci.* 49: 395–411.

Pal, D., Mishra, P., Sachan, N., and Ghosh, A. K. 2011. Biological activities and medicinal properties of *Cajanus cajan* L. Millsp. *J. Adv. Pharm. Technol. Res.* 2: 207–224.

Palanisamy, U., Ling, L. T., Manaharan, T., and Appleton, D. 2011. Rapid isolation of geraniin from *Nephelium lappaceum* rind waste and its antihyperglycemic activity. *Food Chem.* 127: 21–27.

Palanisamy, U. D., Manaharan, T., Teng, L. L., and Masilamani, T. 2014. Rambutan rind in the management of hyperglycemia. *Food Res. Int.* 44: 2278–2282.

Pan, L. -H., Li, X. -F., Wang, M. -N., Zha, X. -Q., Yang, X. -F., Liu, Z. -J., et al. 2014. Comparison of hypoglycemic and anti-oxidant effects of polysaccharides from four different *Dendrobium* species. *Int. J. Biol. Macromol.* 64: 420–427.

Pan, M., Hsieh, M., Hsu, P., Ho, S., Lai, C., Wu, H., et al. 2008. 6-Shogaol suppressed lipopolysaccharide-induced up-expression of iNOS and COX-2 in murine macrophages. *Mol. Nutr. Food Res.* 52: 1467–1477.

Pan, S. -Y., Zhou, S. -F., Gao, S. -H., Yu, Z. -L., Zhang, S. F., Tang, M. K., et al. 2013. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. *Evid. Based Complement. Alternat. Med.*, article ID 627375, 25 pages.

Panda, B. H. and Hazra, S. 2010. *In vitro* regeneration of *Semecarpus anacardium* L. from axenic seedling-derived nodal explants. *Trees* 24: 733–742.

Panda, B. H. and Hazra, S. 2012. *In vitro* morphogenic response in cotyledon explants of *Semecarpus anacardium* L. *Plant Biotechnol. Rep.* 6: 141–148.

Panda, B. M. and Hazra, S. 2012a. Micropropagation of *Semecarpus anacardium* L.: A medicinally important tree species. *Plant Biosyst.* 146: 61–68.

Panda, S. and Kar, A. 2006. Evaluation of the antithyroid, antioxidative and antihyperglycemic activity of scopoletin from *Aegle marmelos* leaves in hyperthyroid rats. *Phytother. Res.* 20: 1103–1105.

Panda, S., Jafri, M., Kar, A., and Meheta, B. K. 2009. Thyroid inhibitory, anti-peroxidative and hypoglycemic effects of stigmasterol isolated from *Butea monosperma*. *Fitoterapia* 80: 123–126.

Pande, D., Malik, S., Bora, M., and Srivastava, P. S. 2002. A rapid protocol for *in vitro* micropropagation of *Lepidium sativum* L. and enhancement in the yield of lepidine. *In Vitro Cell. Dev. Biol. Plant* 38: 451–455.

Pandey, A. K., Gupta, P. P., and Lal, V. K. 2013. Preclinical evaluation of hypoglycemic activity of *Ipomoea digitata* tuber in streptozotocin-induced diabetic rats. *Basic Clin. Physiol. Pharmacol.* 24: 35–39.

Pandey, S. and Jaiswal, V. S. 2002. Micropropagation of *Terminalia arjuna* Roxb. from cotyledonary nods. *Indian J. Exp. Biol.* 40: 950–953.

Pandeya, K. B., Tripathi, I. P., Mishra, M. K., Dwivedi, N., Pardhi, Y., Kamal, A., et al. 2013. A critical review on traditional herbal drugs: An emerging alternative drug for diabetes. *Int. J. Organic Chem.* 3: 1–22.

Paneda, C., Villar, A. V., Alonso, A., Goni, F. M., Varela, F. Brodbeck, U., et al. 2001. Purification and characterization of insulin-mimetic inositol phosphoglycan-like molecules from grass pea (*Lathyrus sativus*) seeds. *Mol. Med.* 7: 454–460.

Papandreou, M. J., Barbouche, R., Guieu, R., Kieny, M. P., and Fenouillet, E. 2002. The α-glucosidase inhibitor 1-deoxynojirimycin blocks human immunodeficiency virus envelope glycoprotein-mediated membrane fusion at the CXCR4 binding step. *Mol. Pharmacol.* 61: 186–193.

Paracatu, L. C., de Faria, C. M., Zeraik, M. L., Quinello, C., Renno, C., Palmeira, P., et al. 2015. Hydrophobicity and antioxidant activity acting together for the beneficial health properties of nordihydroguaiaretic acid. *Food Funct.* 6: 1818–1831.

Parasuraman, S., Thing, G. S., and Dhanaraj, S. A. 2014. Polyherbal formulation: Concept of Ayurveda. *Phcog. Rev.* 8: 73–80.

Pardo, F., Perich, F., Villarroel, L., and Torres, R. 1993. Isolation of verbascoside, an antimicrobial constituent of *Buddleja globosa* leaves. *J. Ethnopharmacol.* 39: 221–222.

Pari, L. and Latha, M. 2004. Protective role of *Scoparia dulcis* plant extract on brain antioxidant status and lipid peroxidation in streptozotocin diabetic male Wistar rats. *BMC Complement. Antern. Med.* 4: 16–19.

Pari, L. and Saravanan, G. 2002. Antidiabetic effects of Cogent db, a herbal drug in alloxan-induced diabetes mellitus. *Comp. Biochem. Physiol. C Taxicol. Pharmacol*. 131: 19–25.

Pari, L. and Saravanan, G. 2004. Antidiabetic effect of diasulin, a herbal drug, on blood glucose, plasma insulin and hepatic enzymes of glucose metabolism in hyperglycemic rats. *Diabetes Obes. Metab.* 6: 286–292.

Pari, L. and Satheesh, M. A. 2006. Effect of pterostilbene on hepatic key enzymes of glucose metabolism in streptozotocin-nicotinamide-induced diabetic rats. *Life Sci*.79: 641–645.

Park, C. H., Noh, J. S., Kim, J. H., Tanaka, T., Zhao, Q., Matsumoto, K., et al. 2011. Evaluation of morroniside, iridoid glycoside from Corni Fructus, on diabetes-induced alterations such as oxidative stress, inflammation, and apoptosis in the liver of type 2 diabetic db/db mice. *Biol. Pharm. Bull*. 34: 1559–1565.

Park, C. H., Noh, J. S., Tanaka, T., and Yokozawa, T. 2010. Effects of morroniside isolated from Corni Fructus on renal lipids and inflammation in type 2 diabetic mice. *J. Pharm. Pharmacol.* 62: 374–380.

Park, H. G., Bak, E. J., Woo, G. H., Kim, J. M., Quan, Z., Yoon, H. K., et al. 2012b. Licochalcone E has an antidiabetic effect. *J. Nutr. Biochem*. 23: 759–767.

Park, H. J., Choi, Y. A., Tae, J., Kang, C. S., Kim, D. K. Thuong, P. T., et al. 2006. Suppression of cyclooxygenase-2 expression in colonic epithelial cells by ilekudinol B isolated from *Weigela subsessilis*. *Nat. Prod. Sci*. 12: 38–43.

Park, H. J., Kim, D. H., Choi, J. W., Park, J. H., and Han, Y. N. 1998. A potent antidiabetic agent from *Kalopanax pictus*. *Arch. Pharm. Res*. 21: 24–29.

Park, J. H., Lee, S. H., Chung, I. M., and Park, Y. 2012a. Sorghum extract exerts an anti-diabetic effect by improving insulin sensitivity *via* PPAR-γ in mice fed a high-fat diet. *Nutr. Res. Pract*. 6: 322–327.

Park, K. Y., Jung, G. O., Choi, J., Lee, K. T., and Park, H. U. 2002. Potent antimutagenic and their anti-lipid peroxidative effect of kaikasaponin III and tectorigenin from the flower of *Pueraria thunbergiana*. *Arch. Pharm. Res*. 25: 320–324.

Park, M. W., Ha, J., and Chung, S. H. 2008a. 20(S)-gingenoside Rg3 enhances glucose-stimulated insulin secretion and activates AMPK. *Biol. Pharm. Bull*. 31: 748–751.

Park, S., Ahn, I. S., Kim, J. H., Lee, M. R., Kim, J. S., and Kim, H. J. 2010. Glycollins, one of the phytoalexins derived from soybeans under fungal stress, enhance insulin sensitivity and exert insulinotropic actions. *J. Agric. Food Chem*. 58: 1551–1557.

Park, S., Ahn, I. S., Kwon, D. Y., Ko, B. S., and Jun, W. K. 2008b. Gingenoside Rb1 and Rg1 suppress triglyceride accumulation in 3T3-L1 adipocytes and enhance β-cell insulin secretion and viability in Min6 cells via PKA-dependent pathways. *Biosci. Biotechnol. Biochem*. 72: 2815–2823.

Park, S., Kim, D. S., and Kang, S. 2011. *Gastradia elata* Blume water extract improved insulin resistance by decreasing body fat in diet induced obese rats: Vanillin and 4-hydroxybenzaldehyde are the bio-active candidates. *Eur. J. Nutr.* 50: 107–118.

Park, S. M., Hong, S. M., Sung, S. R., Lee, J. E., and Kwon, D. Y. 2008. Extracts of Rehmanniae radix, Ginseng radix and Scutellariae radix improve glucose-stimulated insulin secretion and beta-cell proliferation through IRS2 induction. *Genes Nutr.* 2: 347–351.

Parveen, S. and Shahzad, A. 2012. *In vitro* propagation of medicinally important *Cassia* species—A review. *J. Funct. Environ. Bot*. 2: 1–11.

Parvin, A., Alam, M. M., Haque, M. A., Bhowmilk, A., Ali, L., and Rokeya, B. 2013. Study of the hypoglycemic effects of *Tamarindus indica* Linn. seeds on non-diabetic and diabetic model rats. *Br. J. Pharm. Res*. 3: 1094–1105.

Patade, G. R. and Marita, A. R. 2014. Metformin: A journey from countryside to the bedside. *J. Obes. Metab. Res*. 1: 127–130.

Patel, K., Gadewar, M., Tahilyani, V., and Patel, D. K. 2012. A review on pharmacological and analytical aspects of diosgenin: A concise report. *Nat. Prod. Bioprospect*. 2: 46–52.

Patel, L. S. and Patel, R. S. 2015. Rapid in vitro micro propagation of *Asparagus racemosa* Willd. from nodal explants. *Int. J. Curr. Microbiol. App. Sci*. 4: 607–717.

Patel, M. B. and Mishra, S. M. 2009. Aldose reductase inhibitory activity and anti cataract potential of some traditionally acclaimed antidiabetic medicinal plants. *Orient. Pharm. Exp. Med*. 9: 245–251.

Patel, M. B. and Mishra, S. 2011. Hypogycemic activity of alkaloidal fraction of *Tinospora cordifolia*. *Phytomedicine* 18: 1045–1052.

Patel, R., Shervington, A., Pariente, J. A., Martinez-Burgos, M. A., Salido, G. M., Adeghate, E., Singh, J., 2006. Mechanism of exocrine pancreatic insufficiency in streptozotocin-induced type 1 diabetes mellitus. *Ann. N. Y. Acad. Sci*. 1084: 71–88.

Patel, S. S. and Goyal, R. K. 2011. Cardioprotective effects of gallic acid in diabetes-induced myocardial dysfunction in rats. *Pharmacognosy Res.* 3: 239–245.

Patel, S. S., Shah, S. S., and Goyal, R. K. 2009. Antihyperglycemic, antihyperlipidemic and antioxidant effects of Dihar, a polyherbal Ayurvedic formulation in streptozotocin-induced diabetic rats. *Indian J. Exp. Biol*. 47: 564–570.

Patel, T. P., Soni, S., Parikh, P., Gosai, J., Chruvattil, R., and Gupta, S. 2013. Swertiamarin: An active lead from *Enicostemma littorale* regulates hepatic and adipose tissue gene expression by targeting PPAR-γ and improves insulin sensitivity in experimental NIDDM rat model. *Evid. Based Complement. Alternat. Med*. 2013(358673): 11.

Patial, V., Devi, K., Sharma, M., Bhattacharya, A., and Ahuja, P. S. 2012. Propagation of *Picrorhiza kurroa* Royle ex Benth: An important medicinal plant of Western Himalaya. *J. Med. Plants Res.* 6: 4848–4860.

Patil, S. and Jain, G. 2014. Holistic approach of *Trigonella foenum-graecum* in phytochemistry and pharmacology—A review. *Curr. Trends Technol. Sci*. 3: 34–49.

Patil, A., Nirmal, S., Pattan, S., Tambe, V., and Tare, M. 2012. Anti-diabetic effect of polyherbal combinations in streptozotocin-induced diabetes involve inhibition of α-amylase and α-glucosidase with amelioration of lipid profile. *Phytopharmacology* 2: 46–57.

Patil, R. N., Patil, R. Y., Ahirwar, B., and Ahirwar, D. 2011a. Isolation and characterization of anti-diabetic component (bioactivity-guided fractionation) from *Ocimum sanctum* L. (Lamiaceae) aerial part. *Asian Pac. J. Trop. Med*. 4: 278–282.

Patil, V. M., Dhande, G. A., Thigale, D. M., and Rajput, J. C. 2011b. Micropropagation of pomegranate (*Punica granatum* L.) Bhagava cultivar from nodal explants. *Afr. J. Biotechnol*. 10: 18130–18136.

Paunescu, A. 2009. Biotechnology for endangered plant conservation. A critical review. *Romanian Biotechnol. Lett*. 14: 4095–4103.

Pavia, L. B., Goldbeck, R., Santos, W. D., and Squina, F. M. 2013. Ferulic acid and derivatives: Molecules with potential application in the pharmaceutical field. *Brazilian J. Pharm. Sci*. 49: 395–411.

Payton-Stewart, F., Schoene, N. W., Kim, Y. S., Burow, M. E., Cleveland, T. E., Boue, S. M., et al. 2009. Molecular effects of soy phytoalexin glyceollins in human prostate cancer cells LNCaP. *Mol. Carcinog.* 48: 862–871.

Pedreschi, R., Campos, D., Noratto, G., Chrinos, R., and Cisneros-Zevallos, L. 2003. Andean Yacon roots (*Smallanthus sonchifolius* Poepp. Endl) frutoligossaccharides as potential novel source of probiotics. *J. Agric. Food Chem.* 15: 213–218.

Peng, R., Xie, H., Wu, L., Zhou, Y., Xiang, X., Peng, S., et al. 2014. Preparation and biological activities of castanospermine and 6-O-butanoyl castanospermine. *J. Chem. Pharm. Res.* 6: 288–293.

Peng, Y., Liu, F., and Ye, J. 2005. Determination of phenolic acids and flavones in *Lonicera japonica* Thumb. by capillary electrophoresis with electrochemical detection. *Electroanalysis* 17: 356–362.

Pengvicha, P., Temsiririrkkul, R., Prassain, J. K., Tezuka, Y., Kadota, S., Thirawarapan, S. S., et al. 1998a. 4-Hydoxybenzoic acid: A hypoglycaemic constituent of aqueous extract of *Pandanus odorus* root. *J. Ethnopharmacol*. 62: 79–84.

Pengvicha, P., Thirawarapan, S. S., and Watanabe, H. 1998b. Possible mechanism of hypoglycaemic effect of 4-hydroxybenzoic acid, a constituent of *Pandanus odorus* root. *Jap. J. Pharmacol*. 78: 395–398.

Pereiraa, D. F., Kappela, V. D., Cazarolli, L. H., Boligonc, A. A., Athaydec, M. L., Guessera, S. M., et al. 2012. Influence of the traditional Brazilian drink *Ilex paraguariensis* tea on glucose homeostasis. *Phytomedicine* 19: 868–877.

Perez, R. M., Perez, C., Zavala, M. A., Perez, S., Hernandez, H., and Lagunes, F. 2000. Hypoglycemiceffects of lactucin-8-O-methylacrylate of *Parmentiera edulis* fruit. *J. Ethnopharmacol.* 71: 391–394.

Perez-Gutierrez, R. M., Vargas, S. R., Garcia, B. E., and Gallardo, N. Y. 2009. Hypoglycemic activity of constituents from *Astianthus viminalis* in normal and streptozotocin-induced diabetic mice. *J. Nat. Med.* 63: 393–401.

Perfumi, M., Arnold, N., and Tacconi, R. 1991. Hypoglycemic activity of *Salvia fruticosa* Mill. from Cyprus. *J. Ethnopharmacol*. 34: 135–140.

Perry, R. J., Samuel, V. T., Peterson, K. F., and Shulman, G. I. 2014. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. *Nature* 510: 84–91.

Persaud, S. J. 1999. Pancreatic β-cell lines: Their roles in β-cell research and diabetes therapy. In: *Advances in Molecular and Cell Biology.* Vol. 29. Hartford, CT: JAI Press Inc.

Persaud, S. J., Al-Majed, H., Raman, A., and Jones, P. M. 1999. *Gymnema sylvestre* stmulates insulin release *in vitro* by increased membrane permeability. *J. Endocrinol*. 163: 207–212.

Perveen, R., Funk, K., Thuma, J., Wulf, R. S., Cao, Y., Akkerman, J. W., et al. 2011. A novel small molecule 1,2,3,4,6-penta-O-galloyl-α-D-glucopyranose mimics the antiplatelet actions of insulin. *PLoS One* 6: e26238.

Perveen, S., Khanam, M. N., Anis, M., and El-Atta, H. A. 2015. *In vitro* mass propagation of *Murraya koenigii* L. *J. Appl. Res. Med. Aromatic Plants* 2: 60–68.

Petchi, R. R., Vijaya, C., and Parasuramon, S. 2014. Antidiabetic activity of polyherbal formulation in streptozotocin–nicotinamide induced diabetic Wistar rats. *J. Tradit. Complement. Med*. 4: 108–117.

Petrova, M., Niklova, M., Dimitrova, L., and Zayova, E. 2015. Micropropagation and evaluation of flavonoid content and anti-oxidant activity of *Salvia officinalis* L. *Genet. Plant Physiol*. 5: 48–60.

Petrus, A. J. A. 2013. Ethanobotanical and pharmacological profile with propagation strategies of *Mukia maderaspatana* (L.) M. Roem.—A consise overview. *Indian J. Nat. Prod. Resour.* 4: 9–26.

Peungvicha, P., Temsiririrkkul, R., Prasain, J. K., Tezuka, Y., Kadota, S., Thirawarapan, S., and Watanabe, H. S. 1998a. 4-Hydroxybenzoic acid: A hypoglycemic constituent of aqueous extract of *Pandanus odorus* root. *J. Ethnopharmacol.* 62: 79–84.

Peungvicha, P., Thirawarapan, S. S., and Watanabe. H. 1998b. Possible mechanism of hypoglycemic effect of 4-Hydroxybenzoic acid, a constituent of *Pandanus odorus* root. *Jap J. Pharmacol.* 78: 395–398.

Phan, M. A. T., Wang, J., Tang, J., Lee, Y. Z., and Ng, K. 2013. Evaluation of α-glucosidase inhibition potential of some flavonoids from *Epimedium brevicornum*. *Food Sci. Technol.* 53: 492–498.

Pietropaolo, M. 2001. Pathogenesis of diabetes: Our current understanding. *Clini. Cornerstone Diabetes* 4: 1–21.

Ping, L. J., Wawrosch, C., and Kopp, B. 2009. Enhanced micropropagation of *Dendrobium houshanense* C. Z. Tang et S. J. Cheng through protocorm-like bodies: The effects of cytokines, carbohydrate sources and cold treatment. *Scientia Horticulturae* 123: 258–262.

Piotrowska, H., Kucinska, M., and Murias, M. 2012. Biological activity of piceatannol: Leaving the shadow of resveratrol. *Mutat. Res.* 750: 60–82.

Pitiphanpong, J., Chitprasert, S., Goto, M. Jiratchariyakul, W., Sasaki, M., and Shotipruk, A. 2007. New approach for extraction of charantin from *Momordica charantia* with pressurized liquid extraction. *Sep. Purif. Technol*. 52: 416–422.

Pniewski, T., Kapusta, J., and Legocki, A. B. 2002. *In vitro* micropropagation of four lupin species. *Acta Physiologiae Plantarum*. 24: 417–424.

Poitout, V., Olson, L. K., and Robertson, R. P. 1996. Insulin secreating cell lines: Classification, characteristics and potential applications. *Diabetes Metab.* 22: 7–14.

Poongothai, S., Karkuzhali, K., Sharadha, J., Deepa, R., and Mohan, V. 2002. Evaluation of safety and efficacy of Hyponidd, an Ayurvedic compound: A double blind, placebo controlled study in type 2 diabetic patients with secondary failure to oral drugs. *Int. J. Diab. Dev. Countries* 22: 19–24.

Popoola, O. K., Elbagory, A. M., Ameer, F., and Hussein, A. A. 2013. Marrubiin. *Molecules* 18: 9049–9069.

Porchezhian, E. and Dobriyal, R. M. 2003. An overview on the advances of *Gymnema sylvestre*: Chemistry, pharmacology and patents. *Pharmazie* 58: 5–12.

Postic, C., Dentin, R. and Girard, J. 2004. Role of the liver in the control of carbohydrate and lipid homeostasis. *Diabetes Metab.* 30: 398–408.

Potterat, O. 2009. Goji (*Lycium barbarum* and *L. chinense*): Phytochemistry, pharmacology and safety in the perspective of traditional uses and recent popularity. *Planta Med.* 76: 7–19.

Poulsen, M. M., Vestergaard, P. F., Clasen, B. F., Radko, Y., Christensen, L. P., Stodkilde-Jorgensen, H., et al. 2013. High-dose resveratrol supplementation in obese men: An investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. *Diabetes* 62: 1186–1195.

Powers, A. C. 2008. Diabetes mellitus. In: *Principles of Harrison's Internal Medicine*. Fauci, A. S., Braunwald, E., Kasper, D. L., Hauser, S. L., Longo, D. L., Jameson, J. L. and Loscalzo, J. (Eds). Vol. 2, 17th Edition. New York: McGraw Hill, 2275–2304.

Prabhakar, P. K. and Doble, M. 2011. Effect of natural products on commercial oral antidiabetic drugs in enhancing 2-deoxyglucose uptake by 3T3-L1 adipocytes. *Ther. Adv. Endocrinol. Metab.* 2: 103–114.

Prabhakar, P. K., Prasad, R., Ali, S., and Doble, M. 2013. Synergistic interaction of ferulic acid with commercial hypoglycemic drugs in streptozotocin induced diabetic rats. *Phytomedicine* 20: 488–494.

Prachayasittikul, S., Suphapong, S., Worachartcheewan, A., Lawung, R., Ruchirawat, S., and Prachayasittikul, A. 2009. Bioactive metabolites from *Spilanthes acmella* Murr. *Molecules* 14: 850–867.

Pradeep, N. S., Alai, M. H., and Avinash, M. D. 2011. Standardization of Ayurvedic polyherbal formulation: Anti-diabetic churna. *Int. J. Res. Ayurveda Pharm.* 2: 1793–1794.

Pranakhon, R., Pannangpetch, P., and Aromdee, C. 2011. Anti-hyperglycemic activity of agarwood leaf extract in streptozotocin-induced diabetic rats and glucose uptake enhancement activity in rat adipocytes. *Songklanakarin J. Sci. Technol.* 33: 405–410.

Prasad, K. 2001. Secoisolariciresinol diglucoside from flaxseed delays the development of type 2 diabetes in Zucker rat. *J. Lab. Clin. Med.* 138: 32–39.

Prathanturarug, S., Soonthornchareonnon, N., Chuakul, W., Phaidee, Y., and Saralamp, P. 2005. Rapid micropropagation of *Curcuma longa* using bud explants pre-cultured in thidiazuron-supplemented liquid medium. *Plant Cell Tiss. Org. Cult.* 80: 347–351.

Pratley, R. E. and Salsali, A. 2007. Inhibition of DPP-4: A new therapeutic approach for the treatment of type 2 diabetes. *Curr. Med. Res. Opin.* 23: 919–931.

Praveen, N., Thiruvengadam, M., Yang, Y. S., Kim, S. H., Murthy, H. H., and Chang, I. M. 2014. Production of gymnemic acid from hairy root cultures of *Gymnema sylvestre* R.Br. as influenced by polyunsaturated fatty acids and their anti-oxidant activity. *Ind. Crops Products* 54: 54–61.

Prem, D., Singh, S., Gupta, P. P., Singh, J., and Kadyan, S. P. S. 2005. Callus induction and *de novo* regeneration from callus in Guar (*Cyamopsis tetragonoloba*). *Plant Cell Tiss. Org. Cult.* 80: 209–214.

Prince, S. M. and Kamalakkannan, N. 2006. Rutin improves glucose homeostasis in streptozotocin diabetic tissues by altering glycolytic and gluconeogenic enzymes. *J. Biochem. Mol. Toxicol.* 20: 96–102.

Puhan, P. and Rath, S. P. 2012. *In vitro* propagation of *Aegle marmelos* (L.) Correa, a medicinal plant through axillary bud multiplication. *Adv. Biosci. Biotechnol.* 3: 121–125.

Pumarola, S. S., Antolin, M. M. C., Llopis, P. M., and Calvo, T. M. A. 2014. D-fagomine for the control of inflammatory processes related to an overactivation of the humoral immune response. Patent No: WO 2014125013 A1.

Punithavathi, V. R., Prince, P. S., Kumar, R., and Selvakumari, J. 2011. Antihyperglycaemic, antilipid peroxidative and antioxidant effects of gallic acid on streptozotocin induced diabetic Wistar rats. *Eur. J. Pharmacol.* 650: 465–471.

Punyarani, K. and Sharma, J. G. 2010. Micropropagation of *Costus speciosus* (Koen.) Sm. using nodal segment culture. *Not. Sci. Biol.* 2: 58–62.

Punyarani, K. and Sharma, J. G. 2012. Micropropagation and microrhizome induction in *Costus pictus* D. Don using *in vitro* and *ex vitro* nodal segments as explant. *Notulae Scientia Biologicae* 4: 72–78.

Puri, D., Prabhu, K. M., Dev, G., Agarwal. S., and Murthy, P. S. 2011. Mechanism of antidiabetic action of compound GII purified from Fenugreek (*Trigonella foenum graecum*) seeds. *Indian J. Clin. Biochem.* 26: 335–346.

Purohit, A. and Sharma, A. 2006. Antidiabetic efficacy of *Bougainvillea spectabilis* bark extract in streptozotocin induced diabetic rats. *J. Cell Tissue Res.* 6: 537–540.

Purohit, P., Bais, R. T., Sing, P., and Khan, S. 2014. *In vitro* regeneration of *Hemidesmus indicus* (L.) R. Br. an important endangered medicinal plant. *UK J. Pharm. Biosci.* 2: 25–31.

Purup, S., Larsen, E., and Christensen, L. P. 2009. Differential effects of falcarinol and related aliphatic C_{17}-polyacetylenes on intestinal cell proliferation. *J. Agric. Food Chem.* 57: 8290–8296.

Qadan, F., Verspohl, E. J., Nahrstedt, A., Petereit, F., and Matalka, K. Z. 2009. Cinchonain Ib isolated from *Eriobotrya japonica* induces insulin secretion *in vitro* and *in vivo*. *J. Ethnopharmacol.* 124: 224–227.

Qadri, N. M., Rehman, Z., and Shireen, K. 2006. Evaluation of antidiabetic activity of Diabrid, a herbal formulation in type -2 diabetic patients. *J. Chem. Soc. Pak.* 28: 281–283.

Qi, M. Y., Chen, K., Liu, H. R., Su, Y. H., and Yu, S. Q. 2011. Protective effect of icariin on the early stage of experimental diabetic nephropathy induced by streptozotocin *via* modulating transforming growth factor β1 and type IV collagen expression in rats. *J. Ethnopharmacol.* 138: 731–736.

Qi, M. Y., Liu, H. R., Dai, D. Z., Li ,N., and Dai, Y. 2008. Total triterpene acids, active ingredients from *Fructus corni*, attenuate diabetic cardiomyopathy by normalizing ET pathway and expression of FKBP12.6 and SERCA2a in streptozotocin-diabetic rats. *J. Pharm. Pharmacol.* 60: 1687–1694.

Qiao, W., Zhao, C., Qin, N., Zhai, H. Y., and Duan, H. Q. 2011. Identification of trans-tiliroside as active principle with anti-hyperglycemic, anti-hyperlipidemic and antioxidant effects from *Potentilla chinesis*. *J. Ethnopharmacol.* 135: 515–521.

Qujeq, D., Tatar, M., Feizi, F., Parsian, H., Faraji, A. S., and Halalkhor, S. 2013. Effect of *Urtica dioica* leaf alcoholic and aqueous extracts on the number and the diameter of the islets in diabetic rats. *Int. J. Mol. Cell. Med* 2(1): 21–26.

Radha, R. and Amrithaveni, M. 2009. Role of medicinal plant *Salacia reticulata* in the management of type II diabetic subjects. *Anc. Sci. Life* 29: 14–16.

Rady, M. R., Mattr, M. A., Ghareeb, H. A., Hanafy, M. S., Saker, M. M., Edid, S. A., et al. 2014. *In vitro* cultures of *Silybum marianum* and silymarin accumulation. *J. Genetic Eng. Biotechnol.* 12: 75–79.

Raga, D. D., Alimboyoguen, A. B., Fierro, R. S., and Ragasa, C. Y. 2010. Hypoglycemic effects of tea extracts and ent-kaurenoic acid from Smallanthus sonchifolius. *Nat. Prod. Res.* 24: 1771–1782.

Ragavan, B. and Krishnakumari, S. 2006. Antidiabetic effect of *Terminalia arjuna* bark extract in alloxan induced diabetic rats. *Indian J. Clin. Biochem.* 21: 123–128.

Raghu, A. V., Geetha, S. P., Martin, G., Balachandren, I., and Ravindran, P. N. 2006. *In vitro* propagation through mature nodes of *Tinospora cordifolia* (Willd.) Miers ex. Hook. f & Thoms., an important Ayurvedic medicinal plant. *In Vitro Cell. Dev. Biol. Plant* 42: 584–588.

Raghuram Reddy, A., Goverdhan Readdy, P., Venkateshwarlu, E., Srinivas, N., Ramya, C. H., and Nirmala, D. 2012. Anti-diabetic and hypo-lipidemic effect of *Acalypha indica* in streptozotocin-nicotinamide induced type-2 diabetic rats. *Int. J. Pharm. Pharm. Sci*. 4: 205–212.

Ragi, T. P. and Sahaya Shibu, B. 2014. *In vitro* propagation of *Boerhavia diffusa* L. (Nyctaginaceae) *via* nodal and leaf explants. *AsPac J. Mol. Biol. Biotechnol.* 22: 219–223.

Rahman, M. M., Amin, M. N., and Hossain, M. F. 2004. In vitro propagation of banyan tree (*Ficus benghalensis* L.)—A multipurpose and keystone species of Bangladesh. *Plant Tissue Cult.* 14: 135–142.

Rajagopal, K. and Sasikala, K. 2008a. Antihyperglycaemic and antihyperlipidaemic effects of *Nymphaea stellata* in alloxan-induced diabetic rats. *Singapore Med. J.* 49: 137–141.

Rajagopal, K. and Sasikala, K. 2008b. Antidiabetic activity of hydro-ethanolic extracts of *Nymphaea Stellata* flowers in normal and alloxan induced diabetic rats. *Afr. J. Pharm. Pharmacol.* 2: 173–178.

Rajagopal, P. L., Premaletha, K., Kiron, S. S., and Sreejith, K. R. 2013. Phytochemical and pharmacological review on *Cassia fistula* Linn.—The golden shower. *Int. J. Pharm. Chem. Biol. Sci.* 3: 672–679.

Rajendra, K. and D'Souza, L. 1998. Direct organogenesis from intermodal segments of mature *Murraya koenigii*. *Phytomorphology* 48: 427–431.

Rajesh V., Sarthaki, R., Palani, R., and Jayaraman, P. 2014. *In vitro* evaluation of *Memecylon umbellatum* Burm. F for antihyperglycemic activity and phytochemical potential. *Int. J. Pharmacogn. Phytochem. Res.* 6: 785–791.

Rajesham, V. V., Ravindernath, A. D., and Bikshapathi, D. V. R. N. 2012. A review on medicinal plants and herbal drug formulations in diabetes mellitus. *Indo Am. J. Pharm Res.* 2: 1200–1212.

Ramachandran, S., Rajasekaran, A., and Adhirajan, N. 2013. *In vivo* and *in vitro* antidiabetic activity of *Terminalia paniculata* bark: An evaluation of possible phytoconstituents and mechanisms for blood glucose control in diabetes. *ISRN Pharmacol.* 2013(484675): 10.

Ramachandrana, V., Saravanana, R., and Senthilraja, P. 2014. Anti-diabetic and anti-hyperlipidemic activity of asiatic acid in diabetic rats, role of HMG CoA: *In vivo* and *in silico* approaches. *Phytomedicine* 21: 225–232.

Raman, B. V., Krishna, A. N. V., Rao, B. N., Saradhi, M. P., and Rao, M. V. B. 2012. Plants with antidiabetic activities and their medicinal values. *Int. Res. J. Pharm.* 3: 11–15.

Ramirez-Espinosa, J. J., Garcia-Jimenez, S., Rios, M. Y., Medina-Franco, J. L., Lopez-Vallejo, F., Webster, S. P., et al. 2013. Antihyperglycemic and sub-chronic antidiabetic actions of morolic and moronic acids, *in vitro* and *in silico* inhibition of 11β-HSD 1. *Phytomedicine* 20: 571–576.

Ramkumar, K. M., Lee, A. S., Krishnamurthi, K., Devi, S. S., Chakrabarti, T., Kang, K. P., et al. 2009. *Gymnema montanum* Hook protects against alloxan-induced oxidative stress and apoptosis in pancreatic β-cells. *Cell Physiol. Biochem.* 24: 429–440.

Ramsay, M. M., Jacskon, A. D., and Porley, R. D. 2000. A pilot study of ex situ conservation of UK bryophytes. Canary Islands, Spain: *BGCI*, 10–15.

Ranasinghe, P., Jayawardana, R., Galappaththy, P., Constantine, G. R., de Vas Gunawardana, N., and Katulanda, P. 2012. Efficacy and safety of 'true' cinnamon (*Cinnamomum zeylanicum*) as a pharmaceutical agent in diabetes: A systematic review and meta-analysis. *Diab. Med.* 29: 1480–1492.

Rangarajan, T., Nandakumar, N., Rajendran, P., Haribabu, L., Nishigaki, I., and Balasubramoniam, M. P. 2014. D-pinitol promotes apoptosis in MCF-7 cells via induction of p53 and Bax and inhibition of Bcl-2 and NF-κB. *Asian Pac. J. Cancer Prev.* 15: 1757–1762.

Rao, A. R., Veeresham, C., and Asres, K. 2013. *In vitro* and *in vivo* inhibitory activities of four Indian medicinal plant extracts and their major components on rat aldose reductase and generation of advanced glycation end products. *Phytother. Res.* 27: 753–760.

Rashid, M. H., Khalekuzzaman, M., Hasan, M. F., Das, R., Hossain, M. S., and Mahabbat-Ekhoda, S. 2009. Establishment of an efficient method for micropropagation of an important medicinal herb (*Scoparia dulcis* L.) from shoot tips and nodal segments. *Int. J. Sustain. Crop. Prod.* 4: 5–9.

Rashmi, N. G., Gurupadayya, B. M., Sirisha, T., Jinesh, B. N., and Chetan, G. S. 2014. Development and validation of an anti-diabetic polyherbal formulation containing curcumin using RP-UFLC method. *Hygeia J. D. Med.* 6: 36–44.

Rasool, R., Kamili, A. N., Ganai, B. A., and Akbar, S. 2009. Effect of BAP and NAA on shoot regeneration in *Prunella vulgaris*. *J. Nat. Sci. Maths Qassim Univ* 3: 22–26.

Rastogi, S., Kulshreshtha, D. K., and Rawat, A. K. S. 2006. *Streblus asper* Lour. (Shakhotaka): A review of its chemical, pharmacological and ethnomedicinal properties. *Evid. Based Complemen. Alternat. Med.* 3: 217–222.

Rathinamoorthy, R. and Thilagavathi, G. 2014. *Terminalia chebula*—Review on pharmacological and biochemical studies. *Int. J. PharmTech Res.* 6: 97–116.

Rau, O., Wurglics, M., Dingermann, T., Abdel-Tawab, M., and Schubert-Zsilavecz, M. 2006. Screening of herbal extracts for activation of the human peroxisome proliferator-activated receptor. *Pharmazie* 61: 952–956.

Ray, R., Gururaja, K. V. and Ramachandra, T. V. 2011. Predictive distribution modeling for rare Himalayan medicinal plant, *Berberis aristata* DC. *J. Environ. Biol.* 32: 725–730.

Reddy, A. R., Bavaji, M., and Rao, J. V. S. 2006. Micropropagation of *Azadirachta indica* A. Juss *via* cotyledonary nodes. *Indian J. Biotechnol.* 5: 309–311.

Reddy, G. T., Kumar, B. R., and Mohan, G. K. 2005. Anithyperglycemic activity of *Momordica dioica* fruits in alloxan-induced diabetic rats. *Nigerian J. Nat. Prod. Med.* 9: 33–34.

Reddy, K. S., Reddy, Y. P., and Devanna, N. 2014. Standardization of a polyherbal formulation: Dia-Care. *J. Adv. Sci. Res.* 5: 34–35.

Reddy, S. V., Tiwari, A. K., Kumar, U. S., Rao, R. J., and Rao, J. M. 2005. Free radical scavenging, enzyme inhibitory constituents from antidiabetic Ayurvedic medicinal plant *Hydnocarpus wightiana* Blume. *Phytother. Res.* 19: 277–281.

Reed, M. J., Meszaros, K., Entes, L. J., Claypool, M. D., Pinkett, J. G., Gadbois, T. M., et al. 2000. A new rat model of type-2 diabetes: The fat fed, streptozotocin-treated rats. *Metabolism* 49: 1390–1394.

Rees, D. A., Alcolado, J. C., 2005. Animal models of diabetes mellitus. *Diabetic Med.* 22: 359–370.

Remashree, A. B., Thomas, T. V., Raghu, A. V., Nabeesa, E., and Neelakandan, N. 2007. Micropropagation of *Syzigium cumini* (L.) Skeels, a multipurpose tree. *Res. J. Bot.* 2: 208–213.

Ren, S., Zhang, H., Mu, Y., Sun, M., and Liu, P. 2013. Pharmacological effects of Astragaloside IV: A literature review. *J. Tradit. Chin. Med.* 33: 413–416.

Rengarajan, T., Nandakumar, N., Rajendran, P., Haribabu, L., Nishigaki, I., and Balasubramanian, M. P. 2014. D-pinitol promotes apoptosis in MCF-7 cells via induction of p53 and Bax and inhibition of Bcl-2 and NF-κB. *Asian Pac. J. Cancer Prev.* 15: 1757–1762.

Resurreccion-Magno, M., Villasenor, I., Harada, N., and Monde, K. 2005. Antihyperglycaemic flavonoids from *Syzygium samarangense* (Blume) Merr. and Perry. *Phytother. Res.* 19: 246–251.

Reyes-Escogido, M. L., Gonzalez-Mondragon, E. G., and Vazquez-Tzompantzi, E. 2011. Chemical and pharmacological aspects of capsaicin. *Molecules* 16: 1253–1270.

Riaz, A., Khan, R. A., and Ahmed, M. 2013. Glycemic response of *Citrus limon*, pomegranate and their combinations in alloxan-induced diabetic rats. *Aust. J. Basic Appl. Sci.* 7: 215–219.

Riaz, H., Raza, S. A., Hussain, S., Mahmood, S., and Malik, F. 2014. An overview of ethnopharmacological properties of *Boerhaavia diffusa*. *Afr. J. Pharm. Pharm.* 8: 49–58.

Ribnicky, D. M., Kuhn, P., Poulev, A., Logendra, S., Zuberi, A., Cefalu, W. T., and Raskin, I. 2009. Improved absorption and bioactivity of active compounds from an anti-diabetic extract of *Artemisia dracunculus* L. *Int. J. Pharm.* 370: 87–92.

Richter, B., Bandeira-Echtler, E., Bergerhoff, K., et al. 2008. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* 16: CD006739.

Rimando, A. M., Nagmani, R., Feller, D. R., and Yokoyama, W. 2005. Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters. *Agric. Food Chem.* 53: 3403–3407.

Ritthiwigrom, T. and Pyne, S. G. 2012. Isolation, biological properties, and synthesis of natural casurines. *Studies Nat. Prod. Chem*. 36: 1–26.

Robinson, J. P., Britto, S. J., Balakrishnan, V. 2009. Micropropagation of *Costus speciosus* (Koem.ex.retz) Sm., an antidiabetic plant by using explants of pseudostems. *Bot. Res. Int.* 2: 182–185.

Rodriguez-Mateos, A., Cifuents-Gomez, T., Tabatabaee, S., Lecras, C., and Spencer, J. P. 2012. Procyanidin, anthocyanin, and chlorogenic acid contents of highbush and lowbush blueberries. *J. Agric. Food. Chem.* 60: 5772–5778.

Roehrs, M., Figueiredo, C. G., Zanchi, M. M., Bochi, G. V., Moresco, R. N., Quatrin, A., et al. 2014. Bixin and norbixin have opposite effects on glycemia, lipidemia, and oxidative stress in streptozotocin-induced diabetic rats. *Int. J. Endocrinol*. 2014(839095): 10.

Roksana, R., Islam, R., and Hossain, M. 2013. *In Vitro Culture of Allium sativum* L. Germany: LAP Lambert Academic Publishing, GmbH & Co. KG, 128.

Rosen, E. D. and Spiegelman, B. M. 2006. Adipocytes as regulators of energy balance and glucose homeostasis. *Nature* 444: 847–853.

Rosenstock, J. and Zinman, B. 2007. Dipeptidyl peptidase-4 inhibitors and the management of type 2 diabetes mellitus. *Curr. Opin. Endocrinol. Diabetes Obes*. 14: 98–107.

Rosenstock, J., Sankoh, S., and List, J. F. 2008. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. *Diabetes Obes. Metab.* 10: 376–386.

Rosenzweig, T., Abitbol, G., and Taler, D. 2007. Evaluating the anti-diabetic effects of *Sarcopoterium spinosum* extracts *in vitro*. *Israel J. Plant Sci*. 55: 103–109.

Rout, G. R. 2005. In vitro somatic embryogenesis in callus cultures of *Azadirachta indica* A. Juss—A multipurpose tree. *J. Forest Res.* 10: 263–267.

Rout, J. R. and Sahoo, S. L. 2013. *In vitro* propagation and antioxidant enzymes activities of *Elephantopus scaber* L. *AsPac J. Mol. Biol. Biotechnol*. 21: 59–66.

Roy, R., Gururaja, K. V., and Ramachandra, T. V. 2011. Predictive distribution modeling for rare Himalayan medicinal plant *Berberis aristata* DC. *J. Environ. Biol*. 32: 725–730.

Royhan, A. Susilowati, R., and Sunarti. 2009. Effect of white-skinned sweet potato (*Ipomoea batatas* L.) pancreatic beta cells and insulin expression in streptozotocin induced diabetic rats. *Majalah Kesehatan Pharma Medika* 1: 45–49.

Rozza, A. L., Hiruma-Lima, C. A., Tanimoto, A., and Pellizzon, C. H. 2012. Morphologic and pharmacological investigations in the epicatechin gastroprotective effect. *Evid. Based Complement. Altern. Med.* 2012(708156): 8.

Ruan, C. T., Lam, S. H., Chi, T. C., Lee, S. S., and Su, M. J. 2012. Borapetoside C from *Tinospora crispa* improves insulin sensitivity in diabetic mice. *Phytomedicine* 19: 719–724.

Ruan, C. T., Lam, S. H., Lee, S. S., and Su, M. J. 2013. Hypoglycemic action of borapetoside A from the plant *Tinospora crispa* in mice. *Phytomedicine* 20: 667–775.

Rugini, E. and Verma, D. C. 1983. Micropropagation of difficult-to-propagate almond (*Prunus amygdalus* Batsch) cultivar. *Plant Sci. Lett*. 28: 273–281.

Ruitton-Ugilienco, R. L. 1981. Comparison of two methods of insulin determination: Enzymun-test insulin (Boerng) and ^{125}I insulin RIA-Kit (bioMerieux) used as a reference (French). *Ann. Biologie. Clinique.* 39: 295–296.

Rungprom, W., Siripornvisal, S., Keawsawai, S., and Songtrai, M. 2010. α-Glucosidase inhibitors from medicinal plants for diabetes therapy. *Agric. Sci. J.* 41: 30–34.

Ryadin, A. R., Ranamukaarachchi, S. L., Soni, P., and Shrestha, R. P. 2014. Vegetative propagation of five local cultivars of Malay apple (*Syzygium malaccense*) in Ternate Island. *Int. J. Adv. Sci. Eng. Inf. Technol.* 4: 35–39.

Rzodkiewicz, P., Gasinska, E., Maslinski, S., and Bujalska-Zadrozny, M. 2015. Antinociceptive properties of esculetin in non-inflammatory and inflammatory models of pain in rats. *Clin. Exp. Pharmacol. Physiol.* 42: 213–219.

Saboo, S. S., Chavan, R. W., Tapadia, G. G., and Khadabadi, S. S. 2014. An important ethnomedicinal plant *Balanite aegyptiaca* Del. *Int. J. Phytopharmacol*. 4: 75–78.

Sachdeva, A. K., Kuhad, A., and Chopra, K. 2014. Naringin ameliorates memory deficits in experimental paradigm of Alzheimer's disease by attenuating mitochondrial dysfunction. *Pharmacol. Biochem. Behav.* 127: 101–110.

Sadhana, P. H. and Shirly, R. A. 2002. *In vitro* propagation of cashew from young trees. *In Vitro Cell. Dev. Biol. Plant* 38: 152–156.

Sahni, R. and Gupta, S. C. 2002. *In vitro* plantlet regeneration from seedling nodal explants of *Acacia catechu*. *Indian J. Exp. Biol*. 40: 1050–1055.

Sahoo, M. R., Dhanabal, S. P., Jadhav, A. N., Reddy, V., Muguli, G., Babu, U. V., et al. 2014. *Hydnocarpus*: An ethnopharmacological, phytochemical and pharmacological review. *J. Ethnopharmacol.* 154: 17–25.

Sahu, G. and Gupta, P. K. 2012. A review on *Bauhonia veriegata* L. *Int. Res. J. Pharm.* 3: 48–51.

Sahu, P. K., Giri, D. D., Singh, R., Pandey, P., Gupta, S., Shrivastava, A. K., et al. 2013. Therapeutic and medicinal uses of *Aloe vera*: A review. *Pharmocol. Pharm*. 4: 599–610.

Said, O., Fulder, S., Khalil, K., Azaizeh, H., Kassis, E., and Saad, B. 2008. Maintaining a physiological blood glucose level with Glucolevel, a combination of four anti-diabetes plants used in the traditional Arab herbal medicine. *Evid. Based Complement. Alternat. Med*. 5: 421–428.

Saikia, R., Choudhury, M. D., Talukdar, A. D., and Chetia, P. 2012. An *in silico* insight into molecular mechanism of hypoglycemic activity of scoparic acid D, a diterpenoid from *Scoparia dulcis* L. *Asian J. Pharm. Clin. Res*. 5: 153–158.

Saikia, R., Choudhury, M. D., Talukdar, D. A., and Chetia, P. 2011. Antidiabetic activity of ethno medicinal plant *Scoparia dulcis* L. (Family: Scrophulariaceae): A review. *Assam Univ. J. Sci. Technol Biol. Environ. Sci.* 7: 173–180.

Saini, R. and Jaiwal, P. K. 2000. *In vitro* multiplication of *Peganum harmala*, an important medicinal plant. *Indian J. Exp. Biol.* 38: 499–503.

Saini, R., Rishi,A., Saini,S., Saini, G., and Batra, A. 2010. Rapid *in vitro* propagation of *Boerhaavia diffusa* (L.) through nodal segments. *J. Exp. Sci.* 1: 45–48.

Sajeeth, C. I., Manna, P. K., Manavalan, R., and Jolly, C. I. 2010. Phytochemical investigation and antioxidant activity of a polyherbal formulation (ESF/AY/500) on streptozotocin-induced oxidative stress in rats. *Der. Pharma Chemica* 2: 184–189.

Sakai, A. and Engelmann, F. 2007. Vitrification, encapsulation-vitrification and droplet vitrification: A review. *CryoLetters* 28: 151–172.

Sakthi, R. and Mohan, N. 2012. Micropropagation and plant regeneration from leaf and node explants of *Scoparia dulcis*. *J. Acad. Indus. Res.* 1: 144–147.

Sala, A., Recio, M. C., Schinella, G. R., Manez, S., Giner, R. M., Cerda-Nicolas, M., et al. 2003. Assessment of the anti-inflammatory activity and free radical scavenger activity of tiliroside. *Eur. J. Pharmacol.* 461: 53–61.

Saleem, R., Ahmad, M., Hussain, S. A., Qazi, A. M., Ahmad, S. I., Qazi, M. H., et al. 1999. Hypotensive, hypoglycaemic and toxicological studies on the flavonol C-glycoside shamimin from *Bombax ceiba*. *Planta Med*. 65: 331–334.

Salib, J. Y., Michael, H. N., and Eskande, E. F. 2013. Anti-diabetic properties of flavonoid compounds isolated from *Hyphaene thebaica* epicarp on alloxan induced diabetic rats. *Pharmacogn. Res.* 5: 22–29.

Sancheti, S., Sancheti, S., and Seo, S. Y. 2013. Antidiabetic and antiacetylcholinesterase effects of ethyl acetate fraction of *Chaenomeles sinensis* (Thouin) Koehne fruits in streptozotocin-induced diabetic rats. *Exp. Toxicol. Pathol*. 65: 55–60.

Sancho, R. A. S. and Pastore, G. M. 2012. Evaluation of the effects of anthocyanins in type 2 diabetes. *Food Res. Int*. 46: 378–386.

Sangeetha, K. N., Sujatha, S., Muthusamy, V. S., Anand, S., Nithya, N., Velmurugan, D., et al. 2010. 3-Beta-taraxerol of Mangifera indica, a PI3K dependent dual activator of glucose transport and glycogen synthesis in 3T3-L1 adipocytes. *Biochim. Biophys Acta* 1800: 359–366.

Sang-Mi, K., Min, L. Y., Mi-ju, K., Song-Yee, N., Sung-Hee, K., and Hwan-Hee, J. 2013. Effects of *Agrimonia pilosa* Ledeb. water extract on α-glucosidase inhibition and glucose uptake in C2C12 skeletal muscle cells. *Korean J. Food Nutr.* 26: 806–813.

Sankaranarayanan, C. and Pari, L. 2011. Thymoquinone ameliorates chemical-induced oxidative stress and β-cell damage in experimental hyperglycemic rats. *Chem. Biol. Interact.* 190: 148–154.

Sankhala, L. N. Saini, R. K., and Saini, B. S. 2012. A review on chemical and biological properties of *Tinospora cordifolia*. *Int. J. Med. Arom. Plants.* 2: 340–344.

Sano, S., Sugiyama, K., Ito, T., Katano, Y., and Ishihato, A. 2011. Identification of the strong vasorelaxing substance scirpusin B, a dimer of piceatannol, from passion fruit (*Passiflora edulis*) seeds. *J. Agric. Food Chem*. 59: 6209–6213.

Santhakumari, P., Prakasam, A., and Pugalendi, K. V. 2006. Antihyperglycemic activity of *Piper betle* leaf on streptozotocin-induced diabetic rats. *J. Med. Food*. 9: 108–112.

Santos, F. A., Frota, J. T., Arruda, B. R., de Melo, T. S., da Silva, A. A. C. A., Brito, G. A. C., et al. 2012. Antihyperglycemic and hypolipidemic effects of α, β-amyrin, a triterpenoid mixture from *Protium heptaphyllum* in mice. *Lipids Health Dis.* 11: 98–116.

Sarasan, V., Soniya, E. V., and Nair, G. M. 1994. Regeneration of Indian sarsaparilla, *Hemidesmus indicus* R. Br. through organogenesis and somatic embryogenesis. *Indian J. Exp. Biol.* 32: 284–287.

Saravanamuttu, S. and Sudarsanam, D. 2012. Antidiabetic plants and their active ingredients: A review. *Int. J. Pharm. Sci. Res*. 3: 3639–3650.

Saravanan, N., Rajasankar, S., and Nalini, N. 2007. Antioxidant effect of 2-hydroxy-4-methoxy benzoic acid on ethanol-induced hepatotoxicity in rats. *J. Pharm. Pharmacol*. 59: 445–453.

Saravanan, R. and Pari, L. 2005. Antihyperlipidemic and antiperoxidtive effect of Diasulin, a polyherbal formulation in alloxan-induced hyperglycemic rats. *BMC Complement. Altern. Med*. 5: 14–19.

Saravanan, R. and Ramachandran, V. 2013. Modulating efficacy of Rebaudioside A, a diterpenoid on antioxidant and circulatory lipids in experimental diabetic rats. *Environ. Toxicol. Pharmacol*. 36: 472–483.

Saravanan, S., Islam, V. I., Thirugnanasambantham, K., Pazhanivel, N., Raghuraman, N., Paulraj, M. G., et al. 2014. Swertiamarin ameliorates inflammation and osteoclastogenesis intermediates in IL-1β induced rat fibroblast-like synoviocytes. *Inflammation Res.* 63: 451–462.

Sarkar, M. K. I., Jahan, M. A. A., Uddin, M. E., and Khatun, M. M. 2015. *In vitro* micro propagation of medicinal plant *Abroma Augusta* L. (Ulatkambal). *Am. Int. J. Res. Form. Appl. Nat. Sci.* (AIJRFANS) 11: 1–4.

Sasaki, T., Lee, W., Morimura, H., Li, S., Li, Q., and Asada, Y. 2011. Chemical constituents from *Sambucus adnata* and their protein–tyrosine phosphatase 1B inhibitory activities. *Chem. Pharm. Bull.* 59: 1396–1399.

Satapathy, G., Thirunavoukkarasu, M., Behera, P. R., and Panda, P. K. 2014. *In vitro* micropropagation of biofuel feedstock pongam [*Pongamia pinnata* (L.) Pierre] through cotyledonary node culture and assessment of colonel uniformity by RAPD markers. *Int. J. Pure App. Biosci.* 2: 248–257.

Satheesh, M. A. and Pari, L. 2004. Antioxidant effect of *Boerhavia diffusa* L. in tissues of alloxan induced diabetic rats. *Indian J. Exp. Biol*. 42: 989–992.

Satheesh, M. A. and Pari, L. 2006. The antioxidant role of pterostilbene in streptozotocin-nicotinamide-induced type 2 diabetes mellitus in Wistar rats. *J. Pharm. Pharmacol*. 58: 1483–1490.

Satheesh, M. A. and Pari, L. 2008. Effect of pterostilbene on lipids and lipid profiles in streptozotocin-nicotinamide induced type 2 diabetes mellitus. *J. Appl. Biomed*. 6: 31–37.

Satheesh G., Tushar, K. V., Unnikrishnan, K. P., Hashim, K. M., and Balachandran, I. 2008. *Hemidesmus indicus* (L.) R. Br.: A review. *J. Plant Sci.* 3: 146–156.

Sathyagowri, S. and Seran, T. H. 2011. *In vitro* plant regeneration of ginger (*Zingiber officinale* Rosc.) with emphasis on initial culture establishment. *Int. J. Med. Arom. Plants* 1: 195–202.

Sauvaire,Y., Petit, P., Broca, C., Manteghetti, M., Baissac, Y., and Fernandez Alvarez, J. 1998. 4-hydroxyisoleucine: A novel amino acid potentiator of insulin secretion. *Diabetes* 47: 206–210.

Saxena, A. M., Bajpai, M. B., and Mukherjee, S. K. 1991. Swerchirin induced blood suger lowering of streptozotocin-treated hyperglycaemic rats. *Indian J. Exp. Biol.* 29: 674–675.

Saxena, A. M., Bajpai, M. B., Murthy, P. S., and Mukherjee, S. K. 1993. Mechanism of blood glucose lowering by a swerchirin containing hexane fraction of *Swertia chirayita*. *Indian J. Exp. Biol*. 31: 178–181.

Saxena, M., Bajpai, M. B., and Mukherjee, S. K. 1991. Swerchirin induced blood sugar lowering of streptozotocin treated hyperglycemic rats. *Indian J. Exp. Biol*. 29: 674–675.

Schafer, A. and Hogger, P. 2007. Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol®) effectively inhibit α-glucosidae. *Diabetes Res. Clin. Pract.* 77: 41–46.

Seetharam, Y. N., Barad, A., Chalegeri, G., Jyothiswaran, G., Ghanti, K. S., and Bhakri. V. 2002. *In vitro* shoot regeneration from leaf and nodal explants of *Enicostemma hyssopifolium* (Willd.) Ver.—A valuable medicinal plant. *Indian J. Biotechnol*.1: 401–404.

Seiter, M. A., Salcher, S., Rupp, M., Hagenbuchner, J., Kiechl-Kohlendorfer, U., Mortier, L., et al. 2014. Discovery of Sanggenon G as a natural cell-permeable small-molecular weight inhibitor of X-linked inhibitor of apoptosis protein (XIAP). *FEBS Open. Biol*. 54: 659–671.

Sellamuthu, P. S., Arulselvan, P., Fakurazi, S., and Kandasamy, M. 2014. Beneficial effects of mangiferin isolated from *Salacia chinensis* on biochemical and hematological parameters in rats with streptozotocin-induced diabetes. *Pak. J. Pharm. Sci*. 27: 161–167.

Semwal, B. C., Gupta, J., Singh, S., Kumar, Y., and Giri, M. 2009. Antihyperglycemic activity of *Berberis aristata* D.C. in the alloxan induced diabetic rats. *Int. J. Green Pharm*. 3: 259–262.

Sen, A., Sharma, M. M., Grover, D., and Batra, A. 2009. *In vitro* regeneration of *Phyllanthus amarus* Schum. and Thonn.: An important medicinal plant. *Our Nat*. 7: 110–115.

Senarath, W. T. P. S. K. 2010. In vitro propagation of *Coscinium fenestratum* (Gaertn.) Colebr. (Menispermaceae)—An endangered medicinal plant. *J. Natn. Foundation Sri Lanka* 38: 219–223.

Sendogdu, N., Aslan, M., Orhan, D. D., Ergun, F., and Yesilada, E. 2006. Anti-diabetic and antioxidant effects of *Vitis vinifera* L. leaves in streptozotocin-diabetic rats. *Pharm. Sci*. 3: 7–18.

Seo, C. R, Yang, D. K., Song, N. J., Yun, U. J., Gwon, A. R., Jo, D. G., et al. 2014. Cucurbitacin B and cucurbitacin I suppress adipocyte differentiation through inhibition of STAT3 signaling. *Food Chem. Toxicol*. 64: 217–224.

Seo, E., Lee, E. -K., Lee, C. S., Chun, K. H., Lee, M. -Y., and Jun, H. -S. 2014. *Psoralea corylifolia* L. seed extract ameliorates streptozotocin-induced diabetes in mice by inhibition of oxidative stress. *Oxid. Med. Cell. Longiv*. 2014: 9. http://dx.doi.org/10.1155/2014/897296.

Seran, T. H. 2013. *In vitro* propagation of ginger (*Zingiber officinale* Rosc.) through direct organogenesis: A review. *Pakistan J. Biol. Sci*. 16: 1826–1835.

Sezik, E., Aslan, M., Yesilada, E., and Ito, S. 2005. Hypoglycaemic activity of *Gentiana olivieri* and isolation of the active constituent through bioassay-directed fractionation techniques. *Life Sci*. 76: 1223–1238.

Shah, G., Shri, R., Panchal, V., Sharma, N., Singh, B., and Mann, A. S. 2011. Scientific basis for the therapeutic use of *Cymbopogon citratus* stapf (Lemon grass). *J. Adv. Pharm. Technol. Res*. 2: 3–8.

Shah, S. T., Zamir, R., Muhammed, T., and Ali, H. 2006. Mass propagation of *Bougainvillea spectabilis* through shoot tip culture. *Pak. J. Bot*. 38: 953–959.

Shah, T. I., Sharma, E., and Ahmad, G. 2014. *Juglans regia* L.: A phytopharmocological review. *World J. Pharm. Sci*. 2: 364–373.

Shahida, A. N., Choo, C. Y., and Wong, T. W. 2011. Acute/subchronic oral toxicity of *Brucea javanica* seeds with hypoglycemic activity. *J. Nat. Remedies* 11: 60–68.

Shan, J. J. and Tian, G. Y. 2003. Studies on physico-chemical properties and hypoglycemic activity of complex polysaccharide AMP-B from *Atractylodes macrocephala* Koidz. *Yao Xue Xue Bao*. 38: 438–341.

Shang, N., Guerrero-Analco, J. A., Mussallam, L., Saleem, A., Muhammad, A., Walshe-Roussel, B., et al. 2012. Adipogenic constituents from the bark of *Larix laricina* du Roi (K. Koch; Pinaceae), an important medicinal plant used traditionally by the Cree of Eeyou Istchee (Quebec, Canada) for the treatment of type 2 diabetes symptoms. *J. Ethnopharmacol*. 141: 1051–1057.

Shang, W., Yang, Y., Zhou, L., Jiang, B., Jin, H., and Chen, M. 2008. Gingenoside Rb1 stimulates glucose uptake through insulin-like signaling pathways in 3T3-L1 adipocytes. *J. Endocrinol*. 198: 561–569.

Sharaf, S. A., Shibli, R. A., Kasrawi, M. A., and Baghdadi, S. H. 2012. Conservation of wild shih (*Artemisia herba-alba* Asso) shoot tips by encapsulation-dehydration and encapsulation-vitrification. *Plant Cell Tiss. Org. Cult*. 108: 437–444.

Sharan, M., Castello, M. C., and Sharan, M. 2012. *In vitro* culture studies of *Bixa orellana* L: III Plant regeneration from roots through direct and indirect somatic embryogenesis. *Eur. J. Exp. Biol*. 2: 156–162.

Sharma, A. and Sharma, V. 2013. A brief review of medicinal properties of *Asparagus racemosus* (Shatawari). *Int. J. Pure Appl. Biosci*. 1: 48–52.

Sharma, B. and Bansal, Y. K. 2010. In vitro propagation of *Gymnema sylvestre* (Retz) R. Br. through apical bud culture. *J. Med. Plant Res*. 4: 1473–1476.

Sharma, G. and Nautiyal, A. R. 2009. Influence of explants type and plant growth regulators on *in vitro* multiple shoots generation of Laurel from Himalaya. *Nat. Sci*. 7: 1–7.

Sharma, H. and Vashistha, B. D. 2015. Plant tissue culture: A biological tool for solving the problem of propagation of medicinally important woody plants—A review. *Int. J. Adv. Res*. 3: 402–411.

Sharma, M., Sahni, R., Kansal, R., and Koundal, K. R. 2004. Transformation of oilseed mustard *Brassica juncea* (L.) Czern & Coss cv. Pusajaikisan with snowdrop lectin gene. *Indian J. Biotechnol.* 3: 97–102.

Sharma, M. L., Bani, S., and Singh, G. B. 1989. Anti-arthritic activity of boswellic acids in bovine serum albumin (BSA) induced arthritis. *Int. J. Immunopharmacol.* 11: 647–452.

Sharma, P., Dubey, G., and Kaushik, S. 2011. Chemical and medico-biological profile of *Cyamopsios tetragonoloba* (L.) Taub: An overview. *J. Appl. Pharm. Sci.* 1: 32–37.

Sharma, P., Singh, R., and Bhardwaj, P. 2013. Anti-diabetic activity of *Cassia sophera* in streptozotocin-induced diabetic rats and its effect on insulin secreation from isolated pancreatic islats. *Int. J. Phytomed.* 5: 314–319.

Sharma, S. and Agarwal, N. 2011. Nourishing and healing prowess of garden cress (*Lepidium sativum* Linn.)—A review. *Indian J. Nat. Prod. Resour.* 2: 292–297.

Sharma, S., Katoch, V., Rathour, R., and Sharma, T. R. 2010. *In vitro* propagation of endangered temperate Himalayan medicinal herb *Picrorhiza kurroa* Royle ex Benth. using leaf explants and nodal segments. *J. Plant Biochem. Physiol.* 19: 111–114.

Sharma, S., Mehta, B. K., Mehta, D., Nagar, H., and Mishra, A. 2012. A review of pharmacological activity of *Syzygium cumini* extracts using different solvents and their effective doses. *Int. Res. J. Pharm.* 3: 54–58.

Sharma, S., Rathi, N., Kamal, B., Punder, D., Kaur, B., and Arya, S. 2010. Conservation of biodiversity of highly important medicinal plants of India through tissue culture technology—A review. *Agric. Biol. J. N. America* 1: 827–833.

Sharma, S., Singh, A. K., Singh, R. P., Singh, M. K., Singh, P., and Mohapatra, C. 2014. Effects of plant growth regulator on *in vitro* callogenesis of garden cress (*Lepidium sativum* L.). *The Bioscan* 9: 1–6.

Sharma, V. and Agrawal, R. C. 1986. Glycyrrhiza glabra—A plant for the future. *Mintage J. Pharm. Med. Sci.* 2: 15–20.

Shatnawi, M. A., Shibli, R. A., Migdadi, H., Obeidat, A., Ereifej, K., and Abu-Ein, A. M. 2006. Influences of different carbon sources on wild pear (*Pyrus syriaca*) growth and sugar uptake. *World J. Agric. Sci.* 2: 156–161.

Sheehan, E. W., Zemaitis, M. A., Slatkin, D. J., and Schiff, P. L. Jr. 1983. A constituent of *Pterocarpus marsupium*, epicatechin, as a potential anti-diabetic agent. *J. Nat. Prod.* 46: 232–234.

Shen, J. Z., Ma, L. N., Han, Y., Liu, J. X., Yang, W. Q., Chen, L., et al. 2012. Pentamethylquercetin generates beneficial effects in monosodium glutamate-induced obese mice and C2C12 myotubes by activating AMP-activated protein kinase. *Diabetologia* 55: 1836–1846.

Shen, P., Liu, M. H., Ng, T. Y., Chan, Y. H., and Yong, E. L. 2006a. Differential effects of isoflavones from *Astragalus membranaceus* and *Pueraria thomsonii* on the activation of PPARalpha, PPARgamma, and adipocyte differentiation *in vitro*. *J. Nutr.* 136: 899–905.

Shen, S. C. and Chang, W. C. 2013. Hypotriglyceridemic and hypoglycemic effects of vescalagin from Pink wax apple [*Syzygium samarangense* (Blume) Merrill and Perry cv. Pink] in high-fructose diet-induced diabetic rats. *Food Chem.* 136: 858–863.

Shen, S. -C., Chang, W. -C., and Chang, C. -L. 2012. Fraction from wax apple [*Syzygium samarangense* (Blume) Merrill and Perry] fruit extract ameliorates insulin resistance *via* modulating insulin signaling and inflammation pathway in tumor necrosis factor α-treated FL83B mouse hepatocytes. *Int. J. Mol. Sci.* 13: 8562–8577.

Shen, Z. F., Chen, Q. M., Liu, H. F., and Xie, M. Z. 1989. The hypoglycemic effect of clausenacoumarine. *Yao. Xue. Xue. Bao.* 24: 391–392.

Shen, Z. F., Xie, M. Z. 1985. The anti-hyperglycemic effect of kakonein and aspirin. *Acta Pharmaceutica Sinica* 20: 863–865.

Sheng, Q., Yao, H., Xu, H., Ling, X., and He, T. 2004. Isolation of plant insulin from *Momordica charantia* seeds by gel filtration and RP-HPLC. *Zhong Yao Cai.* 27: 414–416.

Shibano, M., Tsukamoto, D., Masuda, A., Tanaka, Y., and Kusano, G. 2001. Two new pyrrolidine alkaloids, radicamines A and B as inhibitors of alpha-glucosidase from *Lobelia chinensis* Lour. *Chem. Pharm. Bull.* 49: 1362–1365.

Shibli, R. A., Shatnawi, M. A.,Subaih, W., and Ajlouni, M. 2006. *In vitro* conservation and cryopreservation of plant genetic resources: A review. *World J. Agric. Sci.* 2: 372–382.

Shimura, M., Hasumi, A., Minato, T., et al. 2005. Isohumulones modulate blood lipid status through the activation of PPAR-α. *Biochem. Biophys. Acta* 1736: 51–60.

Shin, D. M., Choi, K. M., Lee, Y. S., Kim, W., Shin, K. O., Oh, S., et al. 2014. *Echinacea purpurea* root extract enhances the adipocyte differentiation of 3T3-L1 cells. *Arch. Pharm. Res.* 37: 803–812.

Shin, K. H. and Woo, W. S. 1986. Inhibition of hepatic microsomal drug-metabolizing enzymes by imperatorin. *Arch. Pharm. Res.* 9: 81–86.

Shirazi, Z., Piri, K., Asl, A. M., and Hasanloo, T. 2013. Establishment of *Inula helenium* hairy root culture with the use of *Agrobacterium rhizogenes*. *Int. Res. J. Appl. Basic Sci.* 4: 1034–1038.

Shirwaikar, A., Rajendran, K., and Barik, R. 2006. Effect of aqueous bark extract of *Garuga pinnata* Roxb. in streptozotocin-nicotinamide induced type-II diabetes mellitus. *J. Ethnopharmacol.* 107: 285–290.

Shirwaikar, A., Rajendran, K., and Punitha, I. S. R. 2005. Antidiabetic activity of alcoholic stem extract of *Coscinium fenestratum* in streptozotocin-nicotinamide induced type 2 diabetic rats. *J. Ethnopharmacol.* 97: 369–374.

Shirwaikar, A., Rajendran, K., and Punitha, I. S. R. 2008. Antihyperglycemic activity of the aqueous stem extract of *Coscinium fenestratum*. in non-insulin dependent diabetic rats. *Pharm. Biol.* 43: 707–712.

Shou, S. -Y., Miao, L. -X., Zai, W. -S., Huang, X. -Z., and Guo, D. -P. 2008. Factors influencing shoot multiplication of lotus (*Nelumbo nucifera*). *Biologia Plantarum* 52: 529–532.

Shriram, V., Kumar, V., and Shitole, M. G. 2008. Indirect organogenesis and plant regeneration in *Helicteres isora* L., an important medicinal plant. *In Vitro Cell. Dev. Biol. Plant* 44: 186–193.

Shukla, A., Bigoniya, P., and Srivastava, B. 2012. Hypoglycemic activity of *Lepidium sativum* L. seed total alkaloid in alloxan-induced diabetic rats. *Res. J. Med. Plant* 6: 587–596.

Siddiqui, B. S., Hasan, M., Mairai, F., Mehmood, I., Hafizur, R. M., Hameed, A., et al. 2014. Two new compounds from the aerial parts of *Bergenia himalaica* Boriss and their anti-hyperglycemic effect in streptozotocin-nicotinamide induced diabetic rats. *J. Ethnopharmacol.* 152: 561–567.

Sidhu, Y. 2010. *In vitro* micro-propagation of medicinal plants by tissue culture. *Plymouth Stud. Sci.* 4: 432–449.

Silva, G. C., Pereira, A. C., Rezende, B. A., da Silva, J. P., Cruz, J. S., de Souza, M., et al. 2013. Mechanism of the antihypertensive and vasorelaxant effects of the flavonoid tiliroside in resistance arteries. *Planta Med.* 79: 1003–1008.

Silva, M., Valencia, A., Grossi-de-Sa, M. F., Rocha, T. L., Freire, É., de Paula, J. E., and Espindola, L. S. 2009. Inhibitory action of Cerrado plants against mammalian and insect α-amylases. *Pesticide Biochem. Physiol.* 95: 141–146.

Silva, R. M., Oliveira, F. A., Cunha, K. M., Maia, J. L., Maciel, M. A., Pinto, A. C., et al. 2005. Cardiovascular effects of trans-dehydrocrotonin, a diterpene from *Croton cajucara* in rats. *Vascul. Pharmacol.* 43: 11–18.

Silva, R. M., Santos, F. A., Rao, V. S. N., Maciel, M. A., and Pinto, A. C. 2001. Blood glucose- and triglyceride-lowering effect of *trans*-dehydrocrotonin, a diterpene from *Croton cajucara* Benth., in rats. *Diabetes Obes. Metab.* 3: 452–456.

Simmonds, M. S. J. and Howes, M. J. R. 2005. Plants used in the treatment of diabetes. In: *Traditional Medicines for Modern Times: Antidiabetic Plants*. Soumyanath, A. (Ed). Boca Raton, FL: CRC Press, Taylor & Francis.

Singh, A. 2008. Phytochemicals of Gentianaceae: A review of pharmacological properties. *Int. J. Pham. Sci. Nanotechnol.* 1: 33–36.

Singh, A., Duggal, S., Singh, H., Singh, J., and Katekhaye, S. 2010. Withanolides: Phytoconstituents with significant pharmacological activities. *Int. J. Green Pharm.* 4: 229–237.

Singh, A., Nagori, B. P., and Mathu, K. 2013. *Tecoma stan*: An important medicinal plant. *Int. J. Pharm Erud.* 3: 13–21.

Singh, B. M., Wawrosch, C., Joshi, S. D., and Kopp, B. 2012. Micropropagation of *Bauhinia variegata* L. from tissue culture. *Nepal J. Sci. Technol.* 13: 39–41.

Singh, D. and Kakkar, P. 2009. Antihyperglycemic and anti-oxidant effect of *Berberis aristata* root extract and its role in regulating carbohydrate metabolism in diabetic rats. *J. Ethnopharmacol.* 123: 22–26.

Singh, D., Yadav, K., Maurya, R., and Srivastava, A. K. 2009. Antihyperglycaemic activity of alpha-amyrin acetate in rats and db/db mice. *Nat. Prod. Res.* 23: 876–882.

Singh, M. P. and Pathak, K. 2015. Animal models for biological screening of anti-diabetic drugs: An overview. *Eur. J. Exp. Biol.* 5: 37–48.

Singh, N. K. and Sehgal, C. B. 1999. Micropropagation of Holy Basil (*Ocimum sanctum* Linn.) from young inflorescences of mature plants. *Plant Growth Regulation* 29: 161–166.

Singh, R., Kaur, N., Kishore, L., and Gupta, G. K. 2013. Management of diabetic complications: A chemical constituents based approach. *J. Ethnopharmacol*. 150: 51–70.

Singh, R., Kharb, P., and Rani, K. 2011. Rapid micropropagation and callus induction of *Catharanthus roseus in vitro* using different explants. *World J. Agric. Sci*. 7: 699–704.

Singh, S. D. A., Krishna, V., Mankani, K. L., Manjunatha, B. K., Vidya, S. M., and Manohara, Y. N. 2005. Wound healing activity of the leaf extracts and deoxyelephantopin isolated from *Elephantopus scaber* Linn. *Indian J. Phrmacol*. 37: 238–242.

Singh, S. K., Joshi, T., Kanojiya, S., Tripathi, V., and Mishra, D. K. 2015. Callus culture and *in vitro* biosynthesis of echitamine from *Alstonia scholaris* (L.) R. Br. *Plant Cell Tiss. Org. Cult*. 120: 367–372.

Singh, V. and Radhav, P. K. 2012. Review on pharmacological properties of *Caesalpinia bonduc* L. *Int. J. Med. Arom. Plants* 2: 514–530.

Singhal, S., Rathore, A. S., Lohar, V., Dave, R., and Dave, J. 2014. Pharmacological evaluation of Sugar Remedy, a polyherbal formulation, on streptozotocin-induced diabetic mellitus in rats. *J. Tradit. Complement. Med*. 4: 189–195.

Sinha, D., Dwivedi, C., Dewangan, M. K., Yadav, R., Rao, S. P., Chandrakar, K., et al. 2014. Anti-diabetic potential of herbal plants and polyherbal formulation. *Int. J. Phytother. Res*. 4: 28–49.

Siril, E. A. and Joseph, N. 2013. Micropropagation of annatto (*Bixa orellana* L.) from mature tree and assessment of genetic fidelity of micropropagated plants with RAPD markers. *Physiol. Mol. Biol. Plants* 19: 147–155.

Siriwan, D., Miyawaki, C., Miyamoto, T., Naruse, T., Okazaki, K., and Tamura, H. 2011. Chemopreventive activity of sesquiterpene lactones from yacon against TPA-induced Raji cells deformation. *Pak. J. Biol. Sci*. 14: 605–609.

Sitasawad, S. L., Shewade, Y., and Bhonde, R. 2000. Role of bitter gourd fruit juice in streptozotocin-induced diabetic state *in vivo* and *in vitro*. *J. Ethnopharmacol*. 73: 71–79.

Sivakumar, V., Rajan, M. S. D., Sadiq, A. M., and Jayanthi, M. 2014. *In vitro* micropropagation of *Tinospora cordifolia* (Willd.) Miers ex Hook. F and Thoms, an important medicinal plant. *J. Pharmacog. Phytochem*. 3: 5–10.

Sivashanmugan, A. T. and Chatterjee, T. K. 2013. *In vitro* and *in vivo* anti-diabetic activity of *Polyalthia longifolia* (Sonner.) Thw. leaves. *Orient Pharm. Exp. Med*. 13: 289–300.

Skalova, I., Viehmannova, I., and Vitamvas, J. 2012 . *In vitro* conservation of *Smallanthus sonchifolius* under slow-growth conditions. *Agricultura Tropica et Subtropica* 45: 147–150.

Smirin, P., Taler, D., Abitbol, G., Brutman-Barazani, T., Kerem, Z., Sampson, S. R., et al. 2010. *Sarcopoterium spinosum* extract as an antidiabetic agent: *In vitro* and *in vivo* study. *J. Ethanopharmacol*. 129: 10–17.

Smith Y. R. A., Adanlawo, I. G. and Oni, O. S. 2012. Hypoglycemic effect of saponin from the root of *Garcinia kola* (bitter kola) on alloxan-induced diabetic rats. *J. Drug Deliv. Ther.* 2: 9–12.

Smulders, M. J. M. and Klerk, G. J. 2011. Epigenetics in plant tissue culture. *Plant Growth Regul*. 63: 137–146.

Soares de Moura, R., da Costa, G. F., Moreira, A. S., Queiroz, E. F., Garcia-Souza, E. P., Resende, A. C., et al. 2012. *Vitis vinifera* L. grape skin extract activates the insulin-signalling cascade and reduces hyperglycaemia in alloxan-induced diabetic mice. *J. Pharm. Pharmacol*. 64: 268–276.

Soetikno, V., Sari, F. R., Sukumaran,V., Lakshmanan, A. P., Mito, S., and Harima, M. 2012. Curcumin prevents diabetic cardiomyopathy in streptozotocin-induced diabetic rats: Possible involvement of PKC–MAPK signaling pathway. *Eur. J. Pharmaceut. Sci*. 47: 604–614.

Sohn, E. J., Kim, C. S., Kim, Y. S., Jung, D. H., Jang, D. S., Lee, Y. M., and Kim, J. S. 2007. Effects of magnolol (5,5′-diallyl-2,2′-dihydroxybiphenyl) on diabetic nephropathy in type 2 diabetic Goto–Kakizaki rats. *Life Sci*. 80: 468–475.

Sokeng, S. D., Rokeya, B., Hannan, J. M., Junaida, K., Zitech, P., Ali, L., et al. 2007. Inhibitory effect of *Ipomoea aquatica* extracts on glucose absorption using a perfused rat intestinal preparation. *Fitoterapia* 78: 526–529.

Soliman, H. I. and Hegazi, G. A. E. 2013. In vitro clonal propagation and molecular characterization of jujube (*Ziziphus jujube* Mill.). *Life Sci. J.* 10: 573–583.

Song, C., Huang, L., Rong, L., Zhou, Z., Peng, X., Yu, S. et al. 2012c. Anti-hyperglycemic effect of *Potentilla discolor* decoction on obese-diabetic (Ob-db) mice and its chemical composition. *Fitoterapia* 83: 1474–1483.

Song, M. K., Roufogalis, B. D., and Huang, T. H. 2012b. Reversal of the caspase-dependent apoptotic cytotoxicity pathway by taurine from *Lycium barbarum* (Goji Berry) in human retinal pigment epithelial cells: Potential benefit in diabetic retinopathy. *Evid. Based Complement. Altern. Med.* 2012: 323784.

Song, Y., Zhang, Y., Zhou, T., Zhang, H., Hu, X., and Li, Q. 2012a. A preliminary study of monosaccharide composition and α-glucosidase inhibitory effect of polysaccharides from pumpkin (*Cucurbita moschata*) fruit. *Int. J. Food Sci. Tech.* 47: 357–361.

Soniya, E. V. and Das, M. R. 2002. In vitro propagation of *Piper longum*—An important medicinal plant. *Plant Cell Tiss. Org. Cult.* 70: 325–327.

Sotaniemi, E. A., Haapakoski, E., and Rautio, A. 1995. Ginseng therapy in non-insulin dependent diabetic patients. *Diabetes Care* 18: 1373–1375.

Soulange, J. G., Ranghoo-Sanmukhiya, V. M., and Seeburrun, S. D. 2007. Tissue culture and RAPD analysis of *Cinnamomum camphora* and *Cinnamomum verum*. *Biotechnology* 6: 239–244.

Soumyanath, A. and Srijayanta, S. 2005. *In vitro* models for assessing anti-diabetic activity. In: *Traditional Medicines for Modern Times: Antidiabetic Plants.* Soumyanath, A. (Ed). Boca Raton, FL: CRC Press, Taylor & Francis.

Souza, A., Mbatchi, B., and Herchuelz, A. 2011. Induction of insulin secreation by an aqueous extract of *Tabernanhte jboga* Bail. (Apocynaceae) in rat pancreatic islets of Langerhans. *J. Ethnopharmacol.* 133: 1015–1020.

Sreedevi, R. and Damodharam, T. 2015. *In vitro* propagation and phytochemical studies of Indian teak (*Tectona grandis* L.). *Arch. Appl. Sci. Res.* 7: 22–27.

Sreenathkumar, S. and Arcot, S. 2010. Anti-diabetic activity of *Nymphaea pubescens* Willd—A plant drug of aquatic flora. *J. Pharm. Res.* 3: 3067–3069.

Sridevi, P., Bhagavan, R. M., Harikumar, V. V., and Rangarao, P. 2014. Synthesis of derivatives of 4-hydroxy isoleucine from fenugreek and evaluation of their anti-diabetic activity. *Int. J. Phytopharm.* 4: 6–10.

Srilatha, B. R. and Ananda, S. 2014. Antidiabetic effects of *Mukia maderaspatana* and its phenolics: An *in vitro* study on gluconeogenesis and glucose uptake in rat tissues. *Pharm. Biol.* 52: 597–602.

Srinivasan, K. 2007. Black pepper and its pungent principle-piperine: A review of diverse physiological effects. *Crit. Rev. Food Sci. Nutr.* 47: 735–748.

Srinivasan, K. and Ramarao, P. 2007. Animal models in type 2 diabetes research: An overview. *Indian J. Med. Res.* 125: 451–472.

Srinivasan, K., Viswanad, B., Asrat, L., Kaul, C. L., and Ramarao, P. 2005. Combination of high-fat-diet and low dose of streptozotocin treated rat: A model for type 2 diabetes and pharmacological screening. *Pharmacol. Res.* 52: 313–320.

Srinivasan, R., Selvam, G. G., Karthikeyan, K., Chandran, C., Kulothungan, S., and Govindasamy, C. 2012. *In vitro* propagation of shoot and callus culture of *Tectona grandis* (L.). *Global J. Biotechnol. Biochem.* 7: 26–29.

Srivastava, A., Longia, G. S., Singh, S. P., and Joshi, L. D. 1987. Hypoglycemic and hypolipidemic effects of *Cyamopsis tetragonoloba* (guar) in normal and diabetic guinea pigs. *Indian J. Physiol. Pharmacol.* 31: 77–83.

Srivastava, S., Lal, V. K., and Pant, K. K. 2012. Polyherbal formulations based on Indian medicinal plants as anti-diabetic phytotherapeutics. *Phytopharmacology* 2: 1–15.

Srivastava, S. and Srivastava, A. K. 2007. Hairy root culture for mass-production of high-value secondary metabolites. *Cri. Rev. Biotechnol.* 27: 29–43.

Stefkov, G., Kulevanova, S., Miova, B., Dinevska-Kjovkarovska, S., Molgaard, P., Jager, A. K., et al. 2011. Effects of *Teucrium polium* spp. capitatum flavonoids on the lipid and carbohydrate metabolism in rats. *Pharm. Biol.* 49: 885–892.

Stephan Ambrose, S., Solairaj, P., and Subramoniam, A. 2013. Hepatoprotective activity of ellagic acid against anti-tuberculosis drugs. *J. Pharmacol. Pharmacother.* 4: 60–62.

Stephan, R. and Jayabalan, N. 2001. Propagation of *Coriandrum sativum* L. through somatic embryogenesis. *Indian J. Exp. Biol.* 39: 387–389.

Sterne, J. 1957. Du nouveau dans les antidiabetiques. La NN dimethylamine guanyl guanide (N.N.D.G.). *Maroc. Med.* 36: 1295–1296.

Stockhausen, K. 2000. The declaration of Helsinki: Revising ethical research guidelines for the 21st century. *Med. J. Austral.* 172: 252–253.

Stoha, S. J., Miller, H., and Kaata, G. R. 2012. A review on the efficacy and safety of banaba (*Lagerstroemia speciosa* L.) and corosolic acid. *Phytother. Res.* 26: 317–324.

Street, R. A., Sidana, J., and Prinsloo, G. 2013. *Cichorium intybus*: Traditional uses, phytochemistry, pharmacology, and toxicology. *Evid. Based Complement. Altern. Med.* 2013(579319): 13.

Su, C. F., Cheng, J. T., and Li, I. M. 2007. Increase of acetylcholine release by *Panax ginseng* root enhances insulin secretion in Wistar rats. *Neurosci. Lett.* 412: 101–104.

Subash-babu, P., Alshatwi, A. A., and Ignacimuthu, S. 2014. Beneficial antioxidative and antiperoxidative effect of cinnamaldehyde protect streptozotocin-induced pancreatic β-cells damage in Wistar rats. *Biomol. Ther.* 22: 47–54.

Subash-Babu, P., Ignacimuthu, S., and Alshatwi, A. A. 2015. Nymphayal increases glucose stimulated insulin secreation by RIN-5F cells and GLUT4 mediated insulin sensitization in type 2 diabetic rat liver. *Chem. Biol. Interact.* 226: 72–81.

Subash-Babu, P., Paul, A. S., Icnacimuthu, S., Alshatwi, A. A. 2013. Antinociceptive, immunomodulatory and antipyretic activity of nymphayol isolated from *Nymphaea stellata* (Willd.) flowers. *Biomol. Ther. (Seol)* 21: 391–397.

Subash-Babu, P., Ignacimuthu, S., Agastian, P. and Varghese, B. 2009. Partial regeneration of β-cells in the islets of langerhans by nymphayol, a sterol isolated from *Nymphaea stellata* (Willd.) flowers. *Bioorgan. Med. Chem.* 17: 2864–2870.

Subash-Babu, P., Prabuseenivasan, S., and Ignacimuthu, S. 2007. Cinnamaldehyde—A potential antidiabetic agent. *Phytomedicine* 14: 15–22.

Subatra, D. C. and Srinivasan, V. M. 2008. *In vitro* propagation of *Gymnema sylvestre*. *Asian J. Plant Sci.* 7: 660–665.

Subramoniam, A. 2003. Pharmacological evaluation in herbal drug development. In: *GMP for Botanicals*. Verpoorte, R. and Mukherjee, P.K. (Eds). Business Horizons, New Delhi, pp 321–330.

Subramoniam, A. 2014. An overview of present scenario, challenges and future perspectives in plant based medicine development. *Ann. Phytomed.* 3: 31–36.

Subramoniam, A. 2016. *Plants with Anti-Diabetes Mellitus Properties*. Boca Raton, FL: CRC Press, Taylor & Francis.

Sudhersan, C. and Hussain, J. 2003. *In vitro* clonal propagation of multipurpose tree, *Ziziphus spina-christi* (L.) Desf. *Turk. J. Bot.* 27: 167–171.

Sugihara, Y., Nojima, H., Matsuda, H., Murakami, T., Yoshikawa, M., and Kimura, I. 2000. Antihyperglycemic effects of gymnemic acid IV, a compound derived from *Gymnema sylvestre* leaves in streptozotocin diabetic mice. *J. Asian Nat. Prod. Res.* 2: 321–327.

Sugla, T., Purkayastha, J., Singh, S. K., Solleti, S. K., and Sahoo, L. 2007. Micropropagation of *Pongamia pinnata* through enhanced axillary branching. *In Vitro Cell. Dev. Biol. Plant* 43: 409–414.

Suh, J. M., Jonker, J. W., Ahmadian, M., Goetz, R., Lackey, D., Osborn, O., et al. 2014. Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer. *Nature* 513: 436–439.

Sujatha, K. and Hazra, S. 2007. Micropropagation of *Pongamia pinnata* Pierre. *In Vitro Cell. Dev. Biol. Plant* 43: 608–613.

Suk., S., Seo, S. G., Yu, J. G., Yang, H., Jeong, E., Jang, Y., et al. 2015. A bioactive constituent of ginger, 6-shogaol, prevents adipogenesis and stimulates lipolysis in 3T3-L1 adipocytes. *J. Food. Biochem.* doi:10.1111/jfbc.12191.

Sultana, N., Choudhary, M. I., and Khan, A. 2009. Protein glycation inhibitory activities of *Lawsonia inermis* and its active principles. *J. Enzyme Inhib. Med. Chem.* 24: 257–261.

Sultana, Z., Jami, S., Ali, E., Begum, M., and Haque, M. 2014. Investigation of antidiabetic effect of ethanolic extract of *Phyllanthus emblica* Linn. fruits in experimental animal models. *Pharmacol. Pharm.* 5: 11–18.

Sumbul, S., Ahmad, M. A., Asif, M., and Akhtar, M. 2011. *Myrtus communis* Linn. A review. *Indian J. Nat. Prod. Resour.* 2: 395–402.

Sun, M., Tang, Y., Ding, T., Liu, M., and Wang, X. 2015. Investigation of cytochrome P450 inhibitory properties of maslinic acid, a bioactive compound from *Olea europaea* L., and its structure-activity relationship. *Phytomedicine* 22: 56–65.

Sun, Q. and Li, Y. 2014. The Inhibitory effect of pseudolaric acid B on gastric cancer and multidrug resistance *via* Cox-2/PKC-α/P-gp pathway. *PLoS ONE* 9: e107830.

Sundaram, R., Naresh, R., Shanthi, P., and Sachdanandam, P. 2012. Antihyperglycemic effect of iridoid glucoside, isolated from the leaves of *Vitex negundo* in streptozotocin-induced diabetic rats with special reference to glycoprotein components. *Phytomedicine* 19: 211–216.

Sundarraj, S., Thangam, R. Sreevani, V., Kaveri, K., Gunasekaran, P., Achiraman, S., and Kannan, S. 2012. γ-Sitosterol from *Acacia nilotica* L. induces G2/M cell cycle arrest and apoptocis through c-Myc suppression in MCF-7 and A549 cells. *J. Ethnopharmacol.* 141: 803–809.

Suntres, Z. E., Coccimiglio, J., and Alipour, M. 2015. The bioactivity and toxicological actions of carvacrol. *Crit. Rev. Food Sci. Nutr.* 55: 304–318.

Sureshbabu, K. Tiwari, A. K., Srinivas, P. V., Ali, A. Z., Chinaraju, B., and Rao, J. M. 2004. Yeast and mammalian alpha-glucosidase inhibitory constituents from Himalayan rhubarb *Rheum emodi* Wall.ex Meisson. *Bioorg. Med. Chem. Lett.* 14: 3841–3845.

Suryanarayana, P., Kumar, P. A., Saraswat, M., Petrash, J. M., and Reddy, G. B. 2004. Inhibition of aldose reductase by tannoid principles of *Emblica officinalis*: Implications for the prevention of sugar cataract. *Mol. Vis.* 10: 148–154.

Suther, A. C., Banabalikar, M. M., and Biyani, M. K. 2001. Pharmacological properties of genistein, an isoflavone from soy (Glycine max): Part II—Anti-cholesterol activity, effects on osteopoporosis and menopausal symptoms. *Indian J. Exp. Biol.* 39: 520–525.

Suzuki, A., Matsunaga, K., Sashida, Y., and Ohizumi, Y. 1999. Properties of amentoflavone, a potent caffeine-like Ca2+ releaser in skeletal muscle sarcoplasmic reticulum. *Eur. J. Pharmacol.* 372: 97–102.

Syed, G. H. and Siddiqui, A. 2011. Effects of hypolipidemic agent nordihydroguaiaretic acid on lipid droplets and hepatitis C virus. *Hepatology* 54: 1636–1646.

Syed, M. A., Vrushabendraswamy, B. M., Gopakumar, P., Dhanapal, R., and Chandrashekara, V. M. 2005. Anti-diabetic activity of *Terminalia catappa* Linn. leaf extracts in alloxan-induced diabetic rats. *Iranian J. Pharmacol. Ther.* 4: 36–39.

Syiem, D. and Majaw, S. 2011. Effect of different solvent extracts of *Potentilla fulgens* L. on aldose reductase and sorbitol dehydrogenase in normoglycemic and diabetic mice. *Pharmacologyonline* 3: 63–72.

Szkudelski, T. and Szkudelska, K. 2015. Resveratrol and diabetes: From animal to human studies. *Biochim. Biophys. Acta* 1852: 1145–1154.

Tabassum, A. and Nag, K. K. 2008. *In vitro* regeneration of *Tinospora cordifolia* Miers, a medicinal climbing shrub. *Vegetos An Int. J. Plant Res.* 28: 125–128.

Tabassum, N., Tai, H., Jung, D. -W., and Williams, R. 2015. Fishing for nature's hit: Establishment of zebrafish as a model for screening antidiabetic natural products. *Evid. Based Complement. Alternat. Med.* 2015: 287847.

Taha, R. A., Mustafa, N. S., and Hassan, S. A. 2013. Protocol for micropropagation of *Ficus carica* cultivars. *World J. Agric. Sci.* 9: 383–388.

Taher, M. 2005. Isolation and In Vitro Antidiabetic Properties of a Proanthocyanidin from *Cinnamomum zeylanicum*. Ph. D. Thesis, Universiti Teknologi, Malaysia.

Tahtamouni, R. W., Shibli, R. A., Al-Abdallat, A. M., Al-Qudah, T. S., Younis, L., Al-Baba, H., et al. 2015. *In vitro* conservation and cryopreservation of medicinal and aromatic plants: A review. *Jordan L. Agric. Sci.* 11: 147–167.

Takagi, S., Miura, T., Ishihara, E., Ishida, T., and Chinzei, Y. 2010. Effect of corosolic acid on dietary hypercholesterolemia and hepatic steatosis in KK-Ay diabetic mice. *Biomed. Res.* 31: 213–218.

Takahashi, M., Konno, C., and Hikino, H. 1986. Isolation and hypoglycemic activity of coixans A, B, and C, glycans of *Coix lachrymal-jobi* var. mayuen seeds. *Planta Med.* 1: 64–65.

Takii, H., Kometani, T., Nishimura, T., Nakae, T., Okada S., Fushiki, T. 2000. Anti-diabetic effect of glycyrrhizin in genetically diabetic KK-Ay mice. *Biol. Pharm. Bull.* 24: 484–487.

Tamrakar, A. K., Jaiswal, N., Yadav, P. P., Maurya, R., and Srivastava, A. K. 2011. Pongamol from *Pongamia pinnata* stimulates glucose uptake by increasing surface GLUT4 level in skeletal muscle cells. *Mol. Cell. Endocrinol.* 339: 98–104.

Tamrakar, A. K., Yadav, P. P., Tiwari, P., Maurya, R., and Srivastava, A. K. 2008. Identification of pongamol and karanjin as lead compounds with antihyperglycemic activity from *Pongamia pinnata* fruits. *J. Ethnopharmacol.* 118: 435–439.

Tanabe, K., Nakamura, S., Omagari, K., and Oku, T. 2011. Repeated ingestion of the leaf extract from *Morus alba* reduces insulin resistance in KK-Ay mice. *Nutr. Res.* 31: 848–854.

Tanaka, M., Misawa, E., Ito, Y., Habara, N., Nomaguchi, K., Yamada, M., et al. 2006. Identification of five phytosterols from *Aloe vera* gel as anti-diabetic compounds. *Biol. Pharm. Bull.* 29: 1418–1422.

Tang, J. J., Li, J. G., Qi, W., Qiu, W. W., Li, P. S., Li, B. L., and Song, B. L. 2011. Inhibition of SREBP by a small molecule, betulin, improves hyperlipidemia and insulin resistance and reduces atherosclerotic plaques. *Cell Metab.* 13: 44–56.

Tang, Q., and Desai, T. A. 2016. Approaching a cure for type 1 diabetes. *Nat. Med.* 22: 236–237.

Taniguchi, S., Asano, N., Tomino, F., and Miwa, I. 1998. Potentiation of glucose-induced insulin secretion by fagomine, a pseudo-sugar isolated from mulberry leaves. *Horm. Metab. Res.* 30: 679–683.

Tanko, Y., Abdulaziz, M. M., Adelaiye, A. B., Faithu, M. Y., and Musa, K. Y. 2009a. Effects of hydromethanolic leaves extract of *Indigofera pulchra* on blood glucose levels of narmoglycemic and alloxan-induced diabetic Wister rats. *Int. J. Appl. Res. Nat. Prod.* 1: 13–18.

Tanko, Y., Abdulaziz, M. M., Adelaiye, A. B., Faithu, M. Y., and Musa, K. Y. 2009b. Effects of ethyl acetate portion of *Indigofera pulchra* leaves extract on blood glucose levels of alloxan-induced diabetic and narmoglycemic Wister rats. *Asian J. Med. Sci.* 1: 10–14.

Tanwar, R. S., Sharma, S. B., Singh, U. R., and Prabhu, K. M. 2010. Attenuation of renal dysfunction by antihyperglycemic compound isolated from fruit pulp of *Eugenia jambolana* in streptozotocin-induced diabetic rats. *Indian J. Biochem. Biophys.* 47: 83–89.

Tayyab, F., Lal, S. S., Mishra, M., and Kumar, U. 2012. A review: Medicinal plants and its impact on diabetes. *World J. Pharm. Res.* 1: 1019–1046.

Tedong, L., Madiraju, P., Martineau, L. C., Vallerand, D., Arnason, J. T., Desire, D. D., Lavoie, L., Kamtchouing, P., and Haddad, P. S. 2010. Hydroethanolic extract of cashew tree (*Anacardium occidentale*) nut and its principal compound, anacardic acid stimulate glucose uptake in C2C12 muscle cells. *Mol. Nutr. Food Res.* 54: 1753–1762.

Teixeira da Silva, J. A. 2013. A review of the *in vitro* propagation of *Bauhinia* spp. *J. Horticultural Res.* 21: 39–47.

Telang, M., Dhulap, S., Mandhare, A., and Hirwani, R. 2013. Therapeutic and cosmetic applications of mangiferin: A patent review. *Expert. Opin. Ther. Pat.* 23: 1561–1580.

Terashima, S., Shimizu, M., Horie, S., and Morita, N. 1991. Studies on aldose reductase inhibitors from natural products. IV. Constituents and aldose reductase inhibitory effect of *Chrysanthemum morifolium*, *Bixa orellana* and *Ipomoea batatas*. *Chem. Pharm. Bull.* (Tokyo) 39: 3346–3347.

Termentzi, A., Alexiou, P., Demopoulos, V. J., and Kokkalou, E. 2008. The aldose reductase inhibitory capacity of *Sorbus domestica* fruit extracts depends on their phenolic content and may be useful for the control of diabetic complications. *Pharmazie* 63: 693–696.

Terruzzi, I., Senesi, P., Magni, C., Montesano, A., Scarafoni, A., Luzi, L., and Durant, M. 2011. Insulin mimetic action of conglutin-γ, a lupin seed protein in mouse myoblasts. *Nutr. Metab. Cardiovasc. Dis.* 21: 197–205.

Thakkar, N. V. and Patel, J. A. 2010. Pharmacological evaluation of Glyoherb: A polyherbal formulation on streptozotocin-induced diabetic rats. *Int. J. Diabetes Dev. Ctries.* 30: 1–7.

Thakur, M., Sharma, D. R., Kanwar, K., and Kant, A. 2002. *In vitro* regeneration of *Acacia catechu* Willd. from callus and mature nodal explants—An improved method. *Indian J. Exp. Biol.* 40: 850–853.

Thayamini, H. S. 2013. *In vitro* propagation of ginger (*Zingiber officinale* Rosc.) through direct organogenesis: A review. *Pakistan J. Biol. Sci.* 16: 1826–1835.

The Wealth of India. 1992. A dictionary of Indian raw materials and industrial products. 1948–1992. Vol 1–11 (including revised editions). Publication and Information Directorate, CSIR, New Delhi.

Thembela, Y. 2010. Isolation and identification of poisonous triterpenoids from *Elaeodendron croceum*. Doctoral Thesis, University of Pretoria. URL: http://upetd.up.ac.za/thesis/available/etd-09142010-200331/.

Thilaga, S., Largia, M. J. V., Parameswari, A., Nair, R. R., and Ganesh, D. 2013. High frequency somatic embryogenesis from leaf tissues of *Emblica officinalis* Gaertn., a high value tree for non-timber forest products. *Aust. J. Crop Sci.* 7: 1480–1487.

Thimmappaiah, P. G. T. and Anil, S. R. 2002. *In vitro* grafting of cashew (*Anacardium occidentale* L.). *Scientia Horticulturae* 92: 177–182.

Thiripurasundari, U. and Rao, M. V. 2012. Indirect organogenesis from nodal explants of *Coccinia grandis* (L.) Voigt. *Indian J. Biotechnol.* 11: 352–354.

Thorat, K., Patil, L., Limaye, D., and Kadam, V. 2012. *In vitro* models for antidiabetic activity assessment. *Int. J. Res. Pharmaceut. Bio Med. Sci.* 3: 730–733.

Thorens, B. 1996. Glucose transporters in the regulation of intestinal, renal, and liver glucose fluxes. *Am. J. Physiol. Gastrointest. Liver. Physiol.* 270: G541–G553.

Thors, L., Burston, J. J., Alter, B. J., McKinney, M. K., Cravatt, B. F., Ross, R. A., et al. 2010. Biochanin A, a naturally occurring inhibitor of fatty acid amide hydrolase. *Br. J. Pharmacol.* 160: 549–560.

Tian, L. Y., Bai, X., Chen, X. H., Fang, J. B., Liu, S. H., and Chen, J. C. 2010. Antidiabetic effect of methylswertianin and bellidifolin from *Swertia punicea* Hemsl. and its potential mechanism. *Phytomedicine* 17: 533–539.

Tian, Z., Liu, S. B., Wang, Y. C., Li, X. Q., Zheng, L. H., and Zhao, M. G. 2013. Neuroprotective effects of formononetin against NMDA-induced apoptosis in cortical neurons. *Phytother. Res.* 27: 1770–1775.

Ting, G. T., Na, S., Na, X., and Yang, J. C. 2012. Establishment of the clone of *Anemarrhena asphodeloides* rhizomes. *Medicinal Plant* 3: 34–36.

Tiwari,P., Mishra, B. N., and Sangwan, N. S. 2014. Phytochemical and pharmacological properties of *Gymnema sylvestre*: An important medicinal plant. *BioMed. Res. Int.* 214(830285): 18.

Tofighi, Z., Alipouri, F., Hadavinia, H. Abdollahi, M., Hadjiakhoondi, A., and Yassa, N. 2014. Effective antidiabetic and antioxidant fractions of *Otostegia persica* extract and their constituents. *Pharm. Biol.* 52: 961–966.

Toma, A., Makonnen, E., Mekonnen, Y., Debella, A., and Addisakwattana, S. 2014. Intestinal *α-glucosidase* and some pancreatic enzymes inhibitory effect of hydroalcholic extract of *Moringa stenopetala* leaves. *BMC Complement. Altern. Med.* 14: 180–184.

Tomczyk, M. and Latte, K. P. 2009. *Potentilla*—A review of its phytochemical and pharmacological profile. *J. Ethnopharmacol.* 122: 184–204.

Tommasi, T. and Scaramuzzi, F. 2004. *In vitro* propagation of *Ginkgo biloba* by using various bud cultures. *Biologia Plantarum* 48: 297–300.

Tripathi, N., Kumar, S., Singh, R., Singh, C. J., Singh, P., and Varshney, V. K. 2013. Isolation and identification of γ-sitosterol by GC-MS from the leaves of *Girardinia heterophylla* Decne. *Open Bioact Compounds J.* 4: 25–27.

Tripathi, V. and Verma, J. 2014. Current updates of Indian anti-diabetic medicinal plants. *Int. J. Res. Pharm. Chem.* 4: 114–118.

Tripathi, Y. G. and Chaturvedi, P. 1995. Assessment of endocrine response of *Inula racemosa* in relation to glucose homeostasis in rats. *Indian J. Exp. Biol.* 33: 686–689.

Tsai, S. J., Huang, C. S., Mong, M. C., Kam, W. Y., Huang, H. Y., and Yin, M. C. 2012. Anti-inflammatory and antifibrotic effects of naringenin in diabetic mice. *J. Agric. Food Chem.* 60: 514–521.

Tsao, C. C., Shen, Y. C., Su, C. R., Li. C. Y., Liou, M. J., Dung, N. X., et al. 2008. New diterpenoids and the bioactivity of *Erythrophleum fordii*. *Bioorg. Med. Chem.* 16: 9869–9870.

Tsuji, N., Ninov, N., Delawary, M., Osman, S., Roh, A. S., Gut, P., et al. 2014. Whole organism high content screening identifies stimulators of pancreatic beta-cell proliferation. *PLoS ONE* 9: e104112.

Tsutsumi, T., Kobayashi, S., Liu, Y. Y., and Kontani, H. 2003. Anti-hyperglycemic effect of fangchinoline isolated from *Stephania tetrandra* Radix in streptozotocin-diabetic mice. *Biol. Pharm. Bull.* 26: 313–317.

Tupe, M. and Pandhure, N. 2015. *In vitro* propagation of *Tinospora cordifolia* (Willd) Miers. *Int. J. Recent Trends Sci. Technol.* 15: 62–64.

Turker, A., Yucesan, B., and Ekrem, G. 2009. Effect of phytohormones on micropropagation of Self-heal (*Prunella vulgaris* L.), a medicinal plant. *J. Herbs Spices Med. Plants* 15: 293–302.

Tushar, K. V., George, S., Remashree, A. B., and Indira, B. 2008. *Coscinium fenestratum* (Gaertn.) Colebr.—A review of this rare, critically endangered and highly-traded medicinal species. *J. Plant Sci.* 3: 133–145.

Tzeng, T. F., Liou, S. S., Chang, C. J., and Liu, I. M. 2014. The ethanol extract of *Lonicera japonica* (Japanese honeysuckle) attenuates diabetic nephropathy by inhibiting p-38 MAPK activity in streptozotocin-induced diabetic rats. *Planta Med.* 80: 121–129.

Tzeng, Y. M., Chen, K., Rao, Y. K., and Lee, M. J. 2009. Kaempferitrin activates the insulin signaling pathway and stimulates secretion of adiponectin in 3T3-L1 adipocytes. *Eur. J. Pharmacol.* 607: 27–43.

Ubillas, R. P., Mendez, C. D., Jolad, S. D., et al. 2000. Antihyperglycemic acetylenic glucosides from *Bidens pilosa*. *Planta Med.* 66: 82–83.

Uchendu, E., Paliyath, G., Brown, D., and Saxena, P. 2011. *In vitro* propagation of North American ginseng (*Panax quinquefolius* L.). *In Vitro Cell. Dev. Biol. Plant* 47: 710–716.

Udell, R. G. and Hari, S. P. 2001. Corosolic acid formulation and its application for weight-loss management and blood sugar balance. US Patent No: US 7713546 B1.

Ueda, H., Kuroiwa, E., Tachibana, Y., Kawanishi, K., Ayala, F., and Moriyasu, M. 2004. Aldose reductase inhibitors from the leaves of *Myrciaria dubia* (H. B. & K.) McVaugh. *Phytomedicine* 11: 652–656.

Uemura, T., Hirai, S., Mizoguchi, N., et al.2010. Diosgenin present in fenugreek improves glucose metabolism by promoting adipocyte differentiation and inhibiting inflammation in adipocyte tissue. *Mol. Nutr. Food. Res*. 54: 1596–1608.

Umar, A., Ahmed, Q. U., Muhammad, B. Y., Dogaraj, B. B., and Soad, S. Z. 2010. Anti-hyperglycemic activity of the leaves of *Tetracera scandens* Linn. Merr. (Dilleniaceae) in alloxan induced diabetic rats. *J. Ethnopharmacol*. 131: 140–145.

Urias-Silvas, J. E., Cani, P. D., Delmee, E., Neyrinck, A., Lopez, M. G., and Delzenne, M. 2007. Physiological effects of dietary fructans extracted from *Agave tequilana* Gto and *Dasylirion* spp. *Br. J. Nutr.* 13: 1–8.

Usui, S., Suzuki, T., Hattori, Y., Etoh, K., Fujieda, H., Nishizuka, M., et al. 2005. Design, synthesis, and biological activity of novel PPARγ ligands based on rosiglitazone and 15d-PGJ_2. *Bioorg. Med. Chem. Lett*. 15: 1547–1551.

Utsunomiya, H., Yamakawa, T., Kamei, J., Kadonosono, K., and Tanaka, S. 2005. Anti hyperglycemic effects of plum in a rat model of obesity and type 2 diabetes, Wistar fatty rat. *Biomed Res.* 26: 193–200.

Vaidya, H., Goyal, R., and Cheema, S. 2013. Anti-diabetic activity of swertiamarin is due to an active metabolite, gentianine that upregulates PPAR-γ gene expression in 3T3-L1 cells. *Phytother. Res.* 27: 624–627.

Valentina, P., Ilango, K., Kiruthiga, B., and Parimala, M. J. 2013. Preliminary phytochemical analysis and biological screening of extracts of leaves of *Melia dubia* Cav. *Int. J. Res. Ayurveda Pharm*. 4: 417–419.

Valentovic, M. A., Alejandro, N., Betts Carpenter, A., Brown, P. I., Ramos, K. 2006. Streptozotocin (STZ) diabetes enhances benzo(alpha)pyrene induced renal injury in Sprague Dawley rats. *Toxicol. Lett.* 164: 214–220.

Valizadeh, M., Kazemi Tabar, S. K., and Nematzadeh, G. A. 2007. Effect of plant growth regulators on callus induction and regeneration on cumin (*Cuminum cyminum*). *Asian J. Agric. Res*. 1: 17–22.

Van deVenter, M., Roux, S., Bungu, L. C., Louw, J., Crouch, N. R., Grace, O. M., et al. 2008. Anti-diabetic screening and scoring of 11 plants traditionally used in South Africa. *J. Ethnopharmacol*. 119: 81–86.

VanWyk, B. E. and Albrecht, C. 2008. A review of the taxonomy, ethnobotany, chemistry and pharmacology of *Sutherlandia frutescens* (Fabaceae). *J. Ethnopharmacol*. 119: 620–629.

Vareda, P. M. P., Saldanha, L. L., Camaforte, N. A. D., Violata, N. M., Dokkedal, A. L., and Bosqueiro, J. R. 2014. *Myrcia bella* leaf extract presents hypoglycemic activity via PI3K/Akt insulin signaling pathway. *Evid. Based Complement. Altern. Med.* 2014: 10.

Varghese, G. K., Bose, L. V., and Habtemariam, S. 2013. Antidiabetic components of *Cassia alata* leaves: Identification through α-glucosidase inhibition studies. *Pharm. Biol*. 51: 345–349.

Varma, S. D., Mikuni, I., and Kinoshita, J. H. 1975. Flavonoids as inhibitors of lens aldose reductase. *Science* 188: 1215–1216.

Vas, A. and Gulyas, B. 2005. Eburnamine derivatives and the brain. *Med. Res. Rev.* 25: 737–757.

Vasovic, V., Rascovic, A., Mikov, M., Mikov, I., Milijasevic, B., Bukmirovic, S., et al. 2014. Effect of aqueous solution of stevioside on pharmacological properties of some cardioactive drugs. *Vojnosanit. Pregl*. 71: 667–672.

Vasugi, S., Subhashini, S., Balasubramoniam, S., and Chamundeeswari, D. 2011. Detection of anti-oxidants in the development of an effective polyherbal combination in the management of diabetes. *South Asian J. Biol. Sci.* 1: 30–39.

Vasugi, S., Subhashini, S., Balasubramoniam, S., and Chamundeeswari, D. 2011. Role of α-glucosidase inhibitor in the development of polyherbal combination in the management of diabetes. *Drugline* 13: 6–12.

Vasugi, S., Subhashini, S., Balasubramoniam, S., and Chamundeeswari, D. 2012. Detection of an effective polyherbal combination for anti-diabetic potential—An *in vitro* study. *Biomedicine* 32: 12–19.

Vats, V., Grover, J. K., and Rathi, S. S. 2002. Evaluation of anti-hyperglycemic and hypoglycemic effect of *Trigonella foenum-graecum* Linn., *Ocimum sanctum* Linn. and *Pterocarpus marsupium* Linn. in normal and alloxan induced diabetic rats. *J. Ethnopharmacol.* 79: 95–100.

Vazquez, L. H., Palazon, J., and Navarro-Ocana, A. 2012. The pentacyclic triterpenes α, β-amyrins: A review of sources and biological activities. In: *Phytochemicals: A Global Perspective of Their Role in Nutrition and Health*. Rao, V. (Ed). Rijeka, Croatia: InTech, 487–502.

Ved, D. K., Oommen, S., and Singh, A. 2002. *Propagation and Agrotechnology Status of Commercially Important Medicinal Plants Species. Andhra Pradesh Forest Department Sponsored Project on "Community Forest Management."* Report submitted by Foundation for Revitalization of Local Health Traditions, India.

Veerapur, V. P., Prabhakar, K. R., Kandadi, M. R., Srinivasan, K. K., and Unnikrishnan, M. 2010b. Antidiabetic effect of Dodonaea viscosa aerial parts in high fat diet and low dose streptozotocin-induced type 2 diabetic rats: A mechanistic approach. *Pharm. Biol.* 48: 1137–1148.

Veerapur, V. P., Prabhakar, K. R, Thippeswamy, B. S., Bansal, P., Srinivasan, K. K., and Unnikrishnan, M. 2010a. Anti-diabetic effect of *Dodonaea viscosa* (L.) Lacq aerial parts in high fructose fed insulin resistant rats: A mechanism based study. *Indian J. Exp. Biol.* 48: 800–810.

Venkatesan, T. and Pillai, S. S. 2012. Antidiabetic activity of gossypin, a pentahydroxyflavone glucoside, in streptozotocin-induced experimental diabetes in rats. *J. Diabetes* 4: 41–46.

Verma, S., Gill, K. S.,Pruthi, V., Dhygga, K. S., and Randhawa, G. S. 2013. A novel combination of plant growth regulators for *in vitro* regeneration of complete plantlets of guar [*Cyamopsis tetragonoloba* (L.) Taub.]. *Indian J. Exp. Biol.* 51: 1120–1124.

Verma, S., Sharma, H., and Garg, M. 2014. *Phyllanthus amarus*: A review. *J. Pharmacognosy Phytochem.* 3: 18–22.

Vessal, G., Akmali, M., Najafi, P., Moein, M. R., and Sagheb, M. M. 2010. Silymarin and milk thistle extract may prevent the progression of diabetic nephropathy in streptozotocin-induced diabetic rats. *Ren. Fail.* 32: 733–739.

Vessal, M., Hemmati, M., and Vasei, M. 2003. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* 135C: 357–364.

Vijaya Chitra, D. S. and Padmaja, G. 1999. Clonal propagation of mulberry (*Morus indica* L. cultivar M-5) through *in vitro* culture of nodal explants. *Scientia Horticulturae* 80: 289–298.

Vijayan, A., Padmesh, P. P., Hemanthakumar, A. S., and Krishnan, P. N. 2015. Improved *in vitro* propagation, genetic stability and analysis of corosolic acid synthesis in regenerants of *Lagerstroemia speciosa* (L.) Pers. by HPLC and gene expression profiles. *Plant Cell Tiss. Org. Cult.* 120: 1209–1214.

Vilchez, J. and Albany, N. 2014. *In vitro* multiplication of *Psidium guajava* L. in temporary immersion systems. *Rev. Colomb. Biotechnol.* 16: 96–103.

Vipranarayana, S., Prasad, T. N. V. K. V., and Damodharam, T. 2012. *In vitro* seed germination and induction of enhanced shoot multiplication in *Pterocarpus santalinus* Linn. F.: An endemic medicinal plant of Seshachalam Hills, Tirumala. *Int. J. Pure Appl. Sci. Technol.* 9: 118–126.

Vishnuprasad, C. N., Suma Mohan, S., Banerji, A., and Gopalakrishnapillai, A. 2009. Kaempferitrin inhibits GLUT4 translocation and glucose uptake in 3T3-L1 adipocytes. *Biochem. Biophys Res. Commun.* 380: 39–43.

Vishwakarma, S. L., Sonawane, R. D., Rajani M., and Goyal, R. K.2010. Evaluation of effect of aqueous extract of *Enicostemma littorale* Blume in streptozotocin-induced type 1 diabetic rats. *Indian J. Exp. Biol.* 48: 26–30.

Vismaya, Belagihally, S. M., Rajashekhar, S., Jayaram, V. B., Dharmesh, S. M., and Thirumakudalu, S. K. C. 2011. Gastroprotective properties of karanjin from karanja (*Pongamia pinnata*) seeds: Role as antioxidant and H^+, K^+-ATPase inhibitor. *Evid. Based Complement. Alternat. Med.* 2011: 747246.

Viswanathan, V., Kesavan, R., Kavitha, K. V., and Kumpatla, S. 2011. A pilot study on the effects of a polyherbal formulation cream on diabetic foot ulcers. *Indian J. Med. Res.* 134: 168–173.

Viswanathaswamy, A. H. M, Koti, B. C., Gore, A., Thippeswamy, A. H., and Kulkarni, R. V. 2011a. Antihyperglycemic and antihyperlipidemic activity of *Plectranthus amboinicus* on normal and alloxan-induced diabetic rats. *Indian J. Pharm. Sci.* 73: 1391–1345.

Viswanathaswamy, A. H. M., Koti, B. C., Singh, A. K., and Thippeswam, A. H. M. 2011b. Antihyperglycemic and antihyperlipidemic effect of *Rubia cordifolia* leaf extract on alloxan-induced diabetes. *RGUHS J. Pharm. Sci.* 1: 49–54.

Vogl, S., Atanasov, A. G., Binder, M., Bulusu, M., Zehl, M., Fakhrudin, N., et al. 2013. The herbal drug *Melampyrum pratense* L. (Koch): Isolation and identification of its bioactive compounds targeting mediators of inflammation. *Evid. Based Complement. Altern. Med.* 2013(395316): 10.

Vu, L., Pralong, W. F., Cerini, F., Gjinovci, A., Stocklin, R., Rose, K., et al. 1998. Short-term insulin-induced glycogen formation in primary hepatocytes as a screening bio-assay for insulin action. *Anal. Biochem.* 262: 17–22.

Wada, J. and Makino, H. 2009. Historical chronology of basic and clinical research in diabetic nephropathy and contributions of Japanese scientists. *Clin. Exp. Nephrol.* 13: 405–414.

Wahyuni, T. S., Widyawaruyanti, A, Lusida, M. I., Fuad, A., Soetjipto, B. W., Fuchino, H., et al. 2014. Inhibition of hepatic C virus replication by chalepin and pseudane IX isolated from *Ruta angustifolia* leaves. *Fitoterapia* 99: 276–283.

Waki, H., Park, K. W., Mitro, N., Pei, L., Damoiseaux, R., Wilpitz, D. C., et al. 2007. The small molecule harmine is an antidiabetic cell-type-specific regulator of PPARγ expression. *Cell Metab.* 5: 357–370.

Wall, M. E., Wani, M. C., Brown, D. M., Fullas, F., Olwald, J. B., Josephson, F. F., et al. 1996. Effect of tannins on screening of plant extracts for their enzyme inhibitory activities and techniques for their removal. *Phytomedicine* 3: 281–285.

Waltner-Law, M. E., Wang, X. L., Law, B. K., Hall, R. K., Nawano, M., and Granner, D. K. 2002. Epigallocatechin gallate, a constituent of green tea, represseshepatic glucose production. *J. Biol. Chem.* 277: 34933–34940.

Wang, A., Liu, D., Luo, J., Suh, K., Moore, W., and Alkhalidy, H. 2014. Phytochemical genistein promotes pancreatic beta-cell survival and exerts anti-diabetic effect via GPR30-mediated mechanism. *FASEB J.* 29(1): Supplement 1045.44.

Wang, B. L., Zhang, W. J., Zhao, J., Wang, F. J., Fan, L. Q., Wu, Y. X., et al. 2011. Gene cloning and expression of a novel hypoglycaemic peptide from *Momordica charantia*. *J. Sci. Food Agric.* 91: 2443–2448.

Wang, C. P., Zhang, L. Z., Li, G. C., Shi, Y. W., Li, J. L., Xang, X. C., et al. 2014. Mulberroside A protects against ischemic impairment in primary culture of rat cortical neurons after oxygen-glucose deprivation followed by reperfusion. *J. Neurosci. Res.* 92: 944–954.

Wang, G. G., Lu, X. H., Li, W., Zhao, X., and Zhang, C. 2011. Protective effects of luteolin on diabetic nephropathy in streptozotocin-induced diabetic rats. *Evid. Based Complement. Alternat. Med.* 2011(323171): 7.

Wang, H., Zhang, D., Ge, M., Li, Z., Jiang, J., and Li, Y. 2015. Formononetin inhibits enterovirus 71 replication by regulating COX- 2/PGE_2 expression. *Virol. J.* 12: 35–39.

Wang, H. -C., Chen, J. -T., Wu, S. -P., Lin, M. C., and Chang, W. C. 2003. Plant regeneration through shoot formation from callus of *Areca catechu* L. *Plant Cell Tiss. Org. Cult.* 75: 95–98.

Wang, J., Yuan, L. Xiao, H., Xiao, C., Wang, Y., and Liu, X. 2013. Momordin Ic induces HepG2 cell apoptosis through MAPK and PI3K/Akt-mediated mitochondrial pathways. *Apoptosis* 18: 751–765.

Wang, K., Cao, P., Shui, W., Yang, Q., Tang, Z., and Zhang, Y. 2015. *Angelia sinensis* polysaccharide regulates glucose and lipid metabolism disorder in prediabetic and streptozotocin-induced diabetic mice through the elevation of glycogen levels and reduction of inflammatory factors. *Food Funct.* 6: 902–909.

Wang, L., Waltenberger, B., Pferschy-Wenzing, E. -M., Blunder, M., Liu, X., Malainer, C., et al. 2014. Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARγ): A review. *Biochem. Pharmacol.* 92: 73–89.

Wang, M., Zhang, W. B., Zhu, J. H., Fu, G. S., and Zhou, B. Q. 2009. Breviscapine ameliorates hypertrophy of cardiomyocytes induced by high glucose in diabetic rats *via* the PKC signaling pathway. *Acta Pharmacologica Sinica* 30: 1081–1091.

Wang, M., Zhang, W. B., Zhu, J. H., Fu, G. S., and Zhou, B. Q. 2010. Breviscapine ameliorates cardiac dysfunction and regulates the myocardial $Ca(2^{+})$-cycling proteins in streptozotocin-induced diabetic rats. *Acta Diabetologica* 47: 209–218.

Wang, N., Pan, W., Zhu, Zhang, M., Hao, X., Liang, G., et al. 2011. Fangchinoline induces autophagic cell death *via* p53/sestrin2/AMPK signalling in human hepatocellular carcinoma cells. *Br. J. Pharmacol.* 164: 731–742.

Wang, P. H., Tsai, M. J., Hsu, C. Y., Wang, C. Y., Hsu, H. K., and Weng, C. F. 2008b. *Toona sinensis* Roem (Meliaceae) leaf extract alleviates hyperglycemia *via* altering adipose glucose transporter 4. *Food Chem. Toxicol.* 46: 2554–2560.

Wang, Q., Cheng, X. -L., Zhang, D. -Y., Gao, X. -J., Zhou, L., Qin, X. -Y., et al. 2013. Tectorigenin attenuates palmitate-induced endothelial insulin resistance *via* targeting ROS-associated inflammation and IRS-1 pathway. *PLoS ONE* 8: e66417.

Wang, R., He, L. -S., Xia, B., Tong, J. -F., Li, N., and Peng, F. 2009b. A micropropagation system for cloning of hemp (*Cannabis sativa* L.) by shoot tip culture. *Pak. J. Bot.* 41: 603–608.

Wang, T., Fu, F., Zhang, L., Han, B., Zhu, M., and Zhang, X. 2009. Effects of escin on acute inflammation and the immune system in mice. *Pharmacol. Rep.* 61: 697–704.

Wang, W., Xu, J., Li, L., Wang, P., Ji, X., Ai, H., et al. 2010. Neuroprotective effect of morroniside on focal cerebral ischemia in rats. *Brain Res. Bull*. 83: 196–201.

Wang, X., Li, Y. L., Wu, H., Liu, J. Z., Hu, J. X., Liao, N., et al. 2011. Anti-diabetic effect of oleanolic acid: A promising use of a traditional pharmacological agent. *Phytother. Res*. 25: 1031–1040.

Wang, Y., Xin, X., Jin, Z., Hu, Y., Li, X., Wu, J., et al. 2011. Anti-diabetes effects of pentamethylquercetin in neonatally streptozotocin-induced diabetic rats. *Eur. J. Pharmacol*. 668: 347–353.

Wang, Y. N., Wang, H. X., Shen, Z. J., Zhao, L. L., Clarke, S. R., Sun, J. H., et al. 2009. Methyl palmitate, an acaricidal compound occurring in green walnut husks. *J. Econ. Entomol*. 102: 196–202.

Wang, Z., Chen, Z, Yang, S., Wang, Y., Huang, Z., Gao, J., et al. 2014. Berberine ameliorates collagen-induced arthritis in rats associated with anti-inflammatory and anti-angiogenic effects. *Inflammation* 37: 1789–1798.

Wang, Z. Q., Zhang, X., Ribnicky, D. M., Raskin, I., and Cefalu, W. T. 2008a. Bioactives of *Artemisia dracunculus* L. enhance cellular insulin signaling in primary human skeletal muscle culture. *Metabolism* 57(Suppl 1): S58–S64.

Wani, S. J., Kagdi, I. A., Tamboli, P. S., Nirmalkar, V. S., Patil, S. N., and Sidhu, A. K. 2014. Optimization of MS media for callus and suspension culture of *Costus pictus*. *Int. J. Sci. Eng. Res*. 5: 390–397.

Wargent, E. T., Zaibi, M. S., Silvestri, C., Hislop, D. C., Stocker, C. J., Stott, C. G., et al. 2013. The cannabinoid Δ(9)-tetrahydrocannabivarin (THCV) ameliorates insulin sensitivity in two mouse models of obesity. *Nutr. Diabetes* 3: e68. doi:10.1038/nutd.2013.9.

Wei, H., Yan, L. H., Feng, W. H., Ma, G. X., Peng, Y., Wang, Z. M., and Xiao, P. G. 2014. Research progress on active ingredients and pharmacologic properties of *Saussurea lappa*. *Curr. Opin. Complement. Alternat. Med*. 1: e00005.

Wei, S., Chi, H., Kodama, H., and Chen, G. 2013. Anti-inflammatory effect of three iridoids in human neutrophils. *Nat. Prod. Res*. 27: 911–915.

Wei, X., Chen, D., Yi, Y., Qi, H., Gao, X., Fang, H., et al. 2012. Syringic acid extracted from Herba Dendrobii prevents diabetic cataract pathogenesis by inhibiting aldose reductase activity. *Evid. Based Complement. Altern. Med*. 2012(426537): 13.

Weidner, C., deGroot, J. C., Prasad, A., Freiwald, A., Quedenau, C., Kliem, M., et al. 2012. Amorfrutins are potent antidiabetic dietary natural products. *Proc. Natl. Acad. Sci. USA* 109: 7257–7262.

Weiss, L., Zeira, M., Reich, S., Har-Noy, M., Mechoulam, R., Slavin, S., and Gallily, R. 2006. Cannabidiol lowers incidence of diabetes in non-obese mice. *Autoimmunity* 39: 143–151.

Wen, X., Zhang, H. -D., Zhao, L., Yao, Y. -F., Zhao, J. H., and Tang, J. H. 2015. Ginsenoside Rh2 differentially mediates microRNA expression to prevent chemoresistance of breast cancer. *Asian Pac. J. Cancer Prev*. 16: 1105–1109.

WHO. 1993. Research guidelines for evaluating the safety and efficacy of herbal medicines, World Health Organization, Regional Office for the Western Pacific, Manila.

WHO. 1999. *WHO Monographs on Selected Medicinal Plants*. Vol. 1. Geneva, Switzerland: WHO Press.

WHO. 2009. *WHO Monographs on Selected Medicinal Plants*. Vol. 4. Geneva, Switzerland: WHO Press.

Wiedenkeller, D. E. and Sharp, G. W. G. 1983. Effects of forskolin on insulin release and cyclic AMP content in rat pancreatic islets. *Endocrinology* 113: 2311–2313.

Wijayabandara, M. D. J., Khan, S. N. and Choudhary, M. I. 2008. Novel α-glucosidase inhibitors from *Tabernaemontana dichrotoma*. US Patent, Pub. No. US, 2008/0103201. (Appl. No. 11/553, 465).

Wolf, H., Lang, W., and Zander, R. 1984. Alkaline haematin D-575, a new tool for the determination of haemoglobin as an alternative to the cyanhaemoglobin method. II. Standardization of the method using pure chlorohaemin. *Clin. Chem. Acta* 123: 95–104.

Wong, S. M., Wong, M. M., Seligmann, O., and Wagner, H. 1989. New antihepatotoxic naphtho-pyrone glycosides from the seeds of *Cassia tora*. *Planta Med*. 55: 276–280.

Wu, C., Li, Y., Chen, Y., Lao, X., Sheng, L., Dai, R., et al. 2011. Hypoglycemic effect of *Belamcanda chinensis* leaf extract in normal and streptozotocin-induced diabetic rats and its potential active fraction. *Phytomedicine* 18: 292–297.

Wu, J. B., Kuo, Y. H., Lin, C. H., Ho, H. Y., and Shih, C. C. 2014. Tormentic acid, a major component of suspension cells of *Eriobotrya japonica*, suppresses high-fat diet-induced diabetes and hyperlipidemia by glucose transporter 4 and AMP-activated protein kinase phosphorylation. *J. Agric. Food. Chem*. 62: 10717–10726.

Wu, J. B., Lin, W. L., Hsieh, C. C., Ho, H. Y., Tsay, H. S., and Lin, W. C. 2007. The hepatoprotective activity of kinsenoside from *Anoectochilus formosanus*. *Phytother. Res*. 21: 58–61.

Wu, K., Liang, T., Duan, X., Xu, L., Zhang, K., and Li, R. 2013. Anti-diabetic effects of puerarin, isolated from *Pueraria lobata* (Willd.), on streptozotocin-diabatogenic mice through promoting insulin expression and ameliorating metabolic function. *Food Chem Toxicol.* 60: 341–347.

Wu, K. K., Huan, Y., 2007. Diabetic atherosclerosis mouse models. *Atherosclerosis* 191: 241–249.

Wu, Y., Fan, Q., Lu, N., Tao, L., Gao, Y., Qi, Q., et al. 2010. Breviscapine-induced apoptosis of human hepatocellular carcinoma cell line HepG2 was involved in its antitumor activity. *Phytother. Res.* 24: 1188–1194.

Wu, T., Zhou, X., Deng, Y., Jing, Q., Li, M., and Yuang, L. 2011. *In vitro* studies of *Gynura divaricata* (L.) DC extracts as inhibitors of key enzymes relevant for type 2 diabetes and hypertension. *J. Ethnopharmacol.* 136: 305–308.

Xavier, R. X., Gnanam, R., Murugan, M. P., and Pappachan, A. 2012. Clonal propagation of *Phyllanthus amarus*: A hepatoprotector. *Pharmacogn. Mag.* 8: 78–82.

Xi, S., Zhou, G., Zhang, X., Zhang, W., Cai, L., and Zhao, C. 2009. Protective effect of total aralosides of *Aralia elata* (Miq) Seem (TASAES) against diabetic cardiomyopathy in rats during the early stage, and possible mechanisms. *Exp. Mol. Med.* 41: 538–547.

Xia, T. and Wang, Q. 2006a. Antihyperglycemic effect of *Cucurbita ficifolia* fruit extract in streptozotocin-induced diabetic rats. *Fitoterapia* 77: 530–533.

Xia, T. and Wang, Q. 2006b. D-chiro-inositol found in *Cucurbita ficifolia* (Cucurbitaceae) fruit extracts plays the hypoglycaemic role in streptozocin-diabetic rats. *J. Pharm. Pharmacol.* 58: 1527–1532.

Xia, X., Yan, J., Shen, Y., Tang, K., Yin, J., Zhang, Y., et al. 2011. Berberine improves glucose metabolism in diabetic rats by inhibition of hepatic gluconeogenesis. *PLoS One* 6: e16556.

Xia, Y., Sheng, J., Zhao, L., Diao, Y., Zheng, X., Xie, K., et al. 2015. *In vitro* plant regeneration of lotus (*Nelumbo nucifera*). *Open Life Sci.* 10: 142–146.

Xiangyang, Q., Weijun, C., Liegang, L., Ping, Y., and Bijun, X. 2006. Effect of a *Siraitia grosvenori* extract containing mogrosides on the cellular immune system of type 1 diabetes mellitus mice. *Mol. Nutr. Food Res.* 50: 732–738.

Xiang-Yang, Q., Wei-Jun, C., Li-Qin, Z., and Bi-Jun, X. 2008. Mogrosides extract from *Siraitia grosvenori* scavenges free radicals *in vitro* and lowers oxidative stress, serum glucose, and lipid levels in alloxan-induced diabetic mice. *Nutr. Res.* 28: 278–284.

Xiao, K., Song, Q. H., Zhang, S. W., and Xuan, L. J. 2008. Water-soluble constituents of the root barks of *Fraxinus rhynchophylla* (Chinese drug Qinpi). *J. Asian Nat. Prod. Res.* 10: 205–210.

Xie, J. T., Wang, A., Mehendale, S., Wu, J., Aung, H. H., Dey, L., et al. 2003. Anti-diabetic effects of *Gymnema yunnanense* extract. *Pharmacol. Res.* 47: 323–329.

Xie, W., Zhao, Y., and Zhang, Y. 2011. Traditional Chinese medicines in treatment of patients with type 2 diabetes mellitus. *Evid. Based Complement. Altern. Med.* 2011: 726723.

Xie, Y., Huang, X., Hu, S. Y., Qie, X. J., Zhang, Y. J., Ren, P., et al. 2013. Meranzin hydrate exhibits anti-depressive and prokinetic-like effects through regulation of the shared α2-adrenoceptor in the brain-gut axis of rats in the forced swimming test. *Neuropharmacology* 67: 318–325.

Xin, H., Zhou, F., Liu,T., Li, G. -Y., Liu, J., Gao, Z. -Z., et al. 2012. Icariin ameliorates streptozotocin-induced diabetic retinopathy *in vitro* and *in vivo*. *Int. J. Mol. Sci.* 13: 866–878.

Xing, X. H., Zhang, Z. M., Hu, X. Z. Wu, R. Q., and Xu, C. 2009. Antidiabetic effects of *Artemisia sphaerocephala* Krasch. gum, a novel food additive in China, on streptozotocin-induced type 2 diabetic rats. *J. Ethnopharmacol.* 125: 410–416.

Xiu, L. M., Miura, A. B., Yamamoto, K., Kobayashi, T., Song, Q. H., Kitamura, H., et al. 2001. Pancreatic islet regeneration by ephedrine in mice with streptozotocin-induced diabetes. *Am. J. Chin. Med.* 29: 493–500.

Xu, J. -Y., Li, Z. P., Zhang, L., and Ji, G. 2014. Recent insights into farnesoid X receptor in non-alcoholic fatty liver disease. *World J. Gastroenterol.* 20: 13493–13500.

Xu, X. X., Zhang, W., Zhang, P., Qi, X. M., Wu, Y. G., and Shen, J. J. 2013. Superior renoprotective effects of the combination of breviscapine with enalapril and its mechanism in diabetic rats. *Phytomedicine* 20: 820–827.

Xue, J., Ding, W., and Liu, Y. 2010. Anti-diabetic effects of emodin involved in the activation of PPARgamma on high-fat diet-fed and low dose of streptozotocin-induced diabetic mice. *Fitoterapia* 81: 173–177.

Yadav, D., Chaudhary, A. A., Garg, V., Anwar, M. F., Rahman, M. M., Jamil, S. S., et al. 2013. *In vitro* toxicity and antidiabetic activity of a newly developed polyherbal formulation (MAC ST/001) in streptozotocin-induced diabetic Wistar rats. *Protoplasma* 250: 741–749.

Yadav, H., Jain, S., Prasad, G. B., and Yadav, M. 2007. Preventive effect of diabegon, a polyherbal preparation, during progression of diabetes induced by high-fructose feeding in rats. *J. Pharmacol. Sci.* 105: 12–21.

Yadav, U., Bisht, S., Siddique, S. S., and Babu, R. 2014. Micropropagation of *Syzygium cumini* L. using *in vitro* techniques. *Int. J. Sci. Eng. Res.* 5: 1517–1528.

Yadav, U., Lal, M., and Jaiswal, V. S. 1990. *In vitro* micropropagation of the tropical fruit tree *Syzygium cuminii* L. *Plant Cell Tiss. Org. Cult.* 21: 87–92.

Yajima, A., Oono, Y., Nakagawa, R., Nukada, T., and Yabuta, G. 2009. A simple synthesis of four stereoisomers of roseoside and their inhibitory activity on leukotriene release from mice bone marrow-derived cultured mast cells. *Bioorg. Med. Chem.* 17: 189–194.

Yajima, H., Ikeshima, E., Shiraki, M., et al. 2004. Isohumulones, bitter acids derived from hops, activate both peroxisome proliferator-activated receptor alpha and gamma and reduce insulin resistance. *J. Biol. Chem.* 279: 33456–33462.

Yajima, H., Noguchi, T., Ikeshima, E., Shiraki, M., Nawano, M., and Granner, D. K. 2005. Prevention of diet-induced obesity by dietary isomerized hop extract containing isohumulones, in rodents. *Int. J. Obesity* 29: 991–997.

Yamada, K., Hogokowa, M., and Fujimoto, S. 2008a. Effect of corosolic acid on gluconeogenesis in rat liver. *Diabetes Res. Clin. Pract.* 80: 48–55.

Yamada, K., Hosokawa, M.,Yamada, C., et al. 2008. Dietary corosolic acid ameliorates obesity and hepatic steatosis in KK-Ay mice. *Biol. Pharmaceut. Bull.* 31: 651–655.

Yan, F., Benrong, H., Qiang, T., Qin, F., and Jizhou, X. 2005. Hypoglycemic activity of jatrorrhizine. *J. Huazhong Uni. Sci. Technol.* 25: 491–493.

Yang, C. Y., Wang, J., Zhao, Y., Shen, L., Jiang, X., Xie, Z. G., et al. 2010a. Anti-diabetic effects of *Panax notoginseng* saponins and its major anti-hyperglycemic components. *J. Ethnopharmacol.* 130: 231–236.

Yang, H., Ding, C., Duan, Y., and Liu, J. 2005. Variation of active constituents of an important Tibet folk medicine *Swertia mussotii* Franch. (Gentianaceae) between artificially cultivated and naturally distributed. *J. Ethnopharmacol.* 98: 31–35.

Yang, J., Chen, H., Zhang, L., Wang, Q., and Lai, M. -X. 2010b. Antidiabetic effect of standardized extract of *Potentilla discolor* Bunge and identification of its active components. *Drug Dev. Res.* 71: 127–132.

Yang, M. H., Vasquez, Y., Ali, Z., Khan, I. A., and Khan, S. I. 2013. Constituents from *Terminalia* species increase PPARalpha and PPARgamma levels and stimulate glucose uptake without enhancing adipocyte differentiation. *J. Ethnopharmacol.* 149: 490–498.

Yang, Q. -H., Liang, Y., Xu, Q., Zhang, Y., Xiao, L., and Si, L. -Y. 2011. Protective effect of tetramethylpyrazine isolated from *Ligusticum chuanxiong* on nephropathy in rats with streptozotocin-induced diabetes. *Phytomedicine* 18: 1148–1152.

Yang, W., Lu, J., Weng, J., et al. 2010c. Prevalence of diabetes among men and women in China. *N. Engl. J. Med.* 362: 1090–1101.

Yang, W. -C. 2014. Botanical, pharmacological, phytochemical, and toxicological aspects of the antidiabetic plant *Bidens pilosa* L. *Evid. Based Complement. Altern. Med.* 2014(698617): 14.

Yazaki, K. and Okuda, T. 1990. Condensed tannin production in callus and suspension cultures of *Cinnamomum cassia*. *Phytochemistry* 29: 1559–1562.

Ye, Q. F., Qi, S. Y., and Lin, L. D. 1997. Tissue culture and rapid propagation of *Aquilaria sinensis*. *Chin. Bull. Bot.* 14: 60–63.

Yeo, J., Kang, Y. -J., Jeon, S. -M., Jung, U. N., Lee, M. K., Song, H., et al. 2008. Potential hypoglycemic effect of an ethanol extract of *Gynostemma pentaphyllum* in C57BL/KsJ-db/db mice. *J. Med. Food* 11: 709–716.

Yildirim, A. N., San, B., Yildirim, F. Ecevit, F. M., and Ercisli, S. 2015. Micropropagation of promising jujube (*Ziziphus jujuba* Mill.) genotypes. *Erwerbs Obstbau* 57: 135–140.

Yiming, L., Wei, H., Aihua, L., and Fandian, Z. 2008. Neuroprotective effects of breviscapine against apoptosis induced by transient focal cerebral ischaemia in rats. *Pharm. Pharmacol.* 60: 349–355.

Ying, H. -Z., Zang, J. -N., Deng, L. -L., Wang, Z. -Y., and Yu, C. 2013. Pentamethylquercetin reduces fat deposition *via* Sirt1-mediated pathways in male obese mice induced by a high fat diet. *Food Chem. Toxicol.* 62: 463–469.

Yoganandam, G. P. and Jha, B. K. 2010. Effect of EFPTT/09, a herbal formulation, on blood sugar of normal and alloxan induced diabetic rats. *Res. J. Pharm. Biol. Chem. Sci.* 1: 987–997.

Yogisha, S and Raveesha, K. A. 2010. Dipeptidyl peptidase IV inhibitary activity of *Mangifera indica*. *J. Nat. Prod.* 3: 76–79.

Yokozawa, T., Yamabe, N., Kim, H. Y. Kang, K. S., Hur, J. M., Park, C. H., et al. 2008. Protective effects of morroniside isolated from Corni Fructus against renal damage in streptozotocin-induced diabetic rats. *Biol. Pharm. Bull.* 31: 1422–1428.

Yoo, N. H., Jang, D. S., Yoo, J. L., Lee, Y. M, Kim, Y. S., Cho, J. H., and Kim, J. S. 2008. Erigeroflavanone, a flavanone derivative from the flowers of *Erigeron annuus* with protein glycation and aldose reductase inhibitory activity. *J. Nat. Prod.* 71: 713–715.

Yoshikawa, M., Harada, E., Matsuda, H., Murakami, T., Yamahara, J., and Murakami, N. 1993. Elatosides A and B, potent inhibitors of ethanol absorption in rats from the bark of *Aralia elata* Seem: The structure-activity relationships of oleanolic acid oligoglycosides. *Chem. Pharm. Bull. (Tokyo)* 41: 2069–2071.

Yoshikawa, M., Harada, E., Murakami, T., Matsuda, H., Wariishi, N., Yamahara, J., et al.1994b. Escins-Ia, Ib, IIa, IIb, and IIIa, bioactive triterpene oligoglycosides from the seeds of *Aesculus hippocastanum* L.: Their inhibitory effects on ethanol absorption and hypoglycemic activity on glucose tolerance test. *Chem. Pharm. Bull.* 42: 1357–1359.

Yoshikawa, M., Matsuda, H., Harada, E., Murakami, T., Wariishi, N., Jamahara, J., et al. 1994a. Elatoside E, a new hypoglycemic principle from the root cortex of *Aralia elata* Seem: Structure-related hypoglycemic activity of oleanolic acid glycosides. *Chem. Pharm. Bull.* 42: 1354–1356.

Yoshikawa, M., Morikawa, T., Matsuda, H., Tanabe, G., and Muraoka, O. 2002. Absolute stereostructure of potent alpha-glucosidase inhibitor, Salacinol, with unique thiosugar sulfonium sulfate inner salt structure from *Salacia reticulata*. *Bioorg. Med. Chem.* 10: 1547–1554.

Yoshikawa, M., Murakami, T., and Matsuda, H. 1997a. Medicinal foodstuffs. IX. The inhibitors of glucose absorption from the leaves of *Gymnema sylvestre* R.Br. (Asclepiadaceae): Structures of gymnemosides A and B. *Chem. Pharm. Bull.* 45: 1671–1676.

Yoshikawa, M., Murakami, T., Kadoya, M., Matsuda, H., Yamahara, J., Muraoka, O., and Murakami, N. 1996a. Medicinal foodstuff. III. Sugar beet. Hypoglycemic oleanolic acid oligoglycosides, betavulgarosides I, II, III, and IV, from the root of *Beta vulgaris* L. (Chenopodiaceae). *Chem. Pharmaceut. Bull. (Tokyo)* 44: 1212–1217.

Yoshikawa, M., Murakami, T., Matsuda, H., Ueno, T., Kadoya, M., Yamahara, J., et al. 1996c. Bioactive saponins and glycosides. II. Senegae radix. (2): Chemical structures, hypoglycemic activity, and ethanol absorption-inhibitory effect of *E*-senegasaponin C, *Z*-senegasaponin C, and *Z*-senegins II, III and IV. *Chem. Pharm. Bull. (Tokyo)* 44: 1305–1313.

Yoshikawa, M., Murakami, T., Matsuda, H., Yamahara, J., Murakami, N., and Kitagawa, I. 1996b. Bioactive saponins and glycosides. III. Horse chestnut. (1): The structures, inhibitory effects on ethanol absorption, and hypoglycemic activity of escins Ia, Ib, IIa, IIb, and IIIa from the seeds of *Aesculus hippocastanum* L. *Chem. Pharmaceut. Bull.* 44: 1454–1464.

Yoshikawa, M., Murakami, T., Yashiro, K., and Matsuda, H. 1998. Kotalanol, a potent alpha-glucosidase inhibitor with thiosugar sulfonium sulfate structure, from antidiabetic Ayurvedic medicine *Salacia reticulata*. *Chem. Pharm. Bull. (Tokyo).* 46: 1339–1340.

Yoshikawa, M., Nishida, N., Takada, M., and Matsuda, H.. 2002. *Salacia reticulata* and its polyphenolic constituents with lipase inhibitory and lipolytic activity have mild anti-obesity effects in rats. *J. Nutr.* 132: 1819–1824.

Yoshikawa, M., Pongpiriyadacha, Y., Kishi, A., Kageura, T., Wang, T., Morikawa, T., et al. 2003. Biological activities of *Salacia chinensis* originating in Thailand: The quality evaluation guided by alpha-glucosidase inhibitory activity. *Yakugaku Zasshi*. 123: 871–880.

Yoshikawa, M., Shimada, H., Morikawa, T., Yoshizumi, S., Matsumura, N., Murakami, T., Matsuda, H., Hori, K., and Yamahara, J. 1997b. Medicinal foodstuffs. VII. On the saponin constituents with glucose and alcohol absorption-inhibitory activity from a food garnish "Tonburi," the fruit of Japanese *Kochia scoparia* (L.) Schrad.: Structures of scoparianosides A, B, and C. *Chem. Pharmaceut. Bull.* 45: 1300–1305.

Yoshikawa, M., Shimada, H., Nishida, N., Li, Y., Toguchida, I., Yamahara, J., et al. 1998. Antidiabetic principles of natural medicines. II. Aldose reductase and alpha-glucosidase inhibitors from Brazilian natural medicine, the leaves of *Myrcia multiflora* DC (Myrtaceae): Structures of myrciacitrins I and II and myrciaphenones A and B. *Chem. Pharmaceut. Bull.* 46: 113–119.

Yoshikawa, M., Yoshizumi, S., Ueno, T., Matsuda, H., Murakami, T., Yamahara, J., and Murakami, N. 1995. Medicinal foodstuffs. I. Hypoglycemic constituents from a garnish foodstuff "taranome," the young shoot of *Aralia elata* Seem.: Elatosides G, H, I, J and K. *Chem. Pharmaceut. Bull.* 43: 1878–1882.

Youn, J. Y., Park, H. Y., and Cho, K. H. 2004. Anti-hyperglycemic activity of *Commelina communis* L.: Inhibition of alpha-glucosidase. *Diabetes Res. Clin. Pract.* 66: S149–S155.

Yovo, K., Huguet, F., Pothier, J., Durand, M., Breteau, M., and Narcisse, G. 1984. Comparative pharmacological study of sparteine and its ketonic derivative lupanine from seeds of *Lupinus albus*. *Planta Med.* 50: 420–424.

Yu, B. C., Chang, C. K., Su, C. F., and Cheng, J. T. 2008. Mediation of β-endorphin in andrographolide-induced plasma glucose-lowering action in type I diabetes-like animals. *Naunyn Schmiedebergs Arch. Pharmacol.* 377: 529–540.

Yu, B. C., Hung, C. R., Chen, W. C., and Cheng, J. T. 2003. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. *Planta Med.* 69: 1075–1079.

Yu, P. -L., Pu, H. -F., Chen, S. -Y., Wang, S. W., and Wang, P. S. 2010a. Effects of catechin, epicatechin and epigallocatechin gallate on testosterone production in rat leydig cells. *J. Cell. Biochem.* 10: 333–342.

Yu, Y., Liu, L., Wang, X., Liu, X., Xie, L., and Wang, G. 2010b. Modulation of glucagon-like peptide-1 release by berberine: *In vivo* and *in vitro* studies. *Biochem. Pharmacol.* 79: 1000–1006.

Yuan, J. Y., Zhou, J. Y., Hu, Z. B., and Wu, D. Z. 2011. The effects of jatrorrhizine on contractile responses of rat ileum. *Eur. J. Pharmacol.* 663: 74–79.

Yuan, T., Ding, Y., Wan, C., Li, L., Xu, J., Liu, K., et al. 2012. Antidiabetic ellagitannins from pomegranate flowers: Inhibition of α-glucosidase and lipogenic gene expression. *Org. Lett.* 14: 5358–5361.

Yue, W. T. 2012. Regeneration System of *Aguilaria sinensis* (Lihour.) Gilg by Tissue Culture Techniques. Master's Thesis, Forest Cultivation Course, Chinese Academy of Forestry.

Yuuya, S., Hagiwara, H., Suzuki, T., Ando, M., Yamada, A., Suda, K., et al. 1999. Guaianolides as immunomodulators. Synthesis and biological activities of dehydrocostus lactone, mokko lactone, eremanthin, and their derivatives. *J. Nat. Prod.* 62: 22–30.

Zaher, N., Nicolaou, I., and Demopoulos, V. J. 2002. Pyrrolylbenzothiazole derivatives as aldose reductase inhibitors. *J. Enzym. Inhib. Med. Chem.* 17: 131–135.

Zalabani, S. M. F., Hetta, M. H., Ross, S. A., Youssef, A. M. B., Zaki, M. A., and Ismail, A. S. 2012. Youssef, antihyperglycemic and antioxidant activities and chemical composition of *Conyza dioscoridis* (L.) Desf. DC. growing in Egypt. *Aust. J. Basic Appl. Sci.* 6: 257–265.

Zang, Y., Sato, H., and Igarashi, K. 2011. Anti-diabetic effects of a kaempferol glycoside-rich fraction from unripe soybean (Edamame, *Glycine max* L. Merrill. 'Jindai') leaves on KK-A(y) mice. *Biosci. Biotechnol. Biochem.* 75: 1677–1684.

Zang, Y., Zhang, L., Igarashi, K., and Yu, Y. 2015. The anti-obesity and anti-diabetic effects of kaempferol glycosides from unripe soybean leaves in high-fat-diet mice. *Food Funct.* 6: 834–841.

Zapata-Bustos, R., Alonsa-Castro, A. J., Gomez-Sanchez, M., and Salazar-Pliva, L. A. 2014. *Ibervillea sonorae* (Cucurbitaceae) induces the glucose uptake in human adipocytes by activating a PI3K-independent pathway. *J. Ethnopharmacol.* 152: 546–552.

Zapata-Bustos, R., Alonso-Castro, A. J., Romo-Yañez, J., and Salazar-Olivo, L. A. 2009. *Teucrium cubense* induces glucose-uptake in insulin-sensitive and insulin-resistant murine and human adipocytes. *Planta Med.* 75. doi:10.1055/s-0029-1234942.

Zaruwa, M. Z., Manosroi, A., Akihisa, T., Manosroi, W., Rangdaeng, S., and Manosroi, J. 2013. Hypoglycemic activity of the *Anisopus mannii* N. E. Br. methanolic leaf extract in normal and alloxan-induced diabetic mice. *J. Complement. Integr. Med.* 10: 37–46.

Zarzuelo, A., Risco, S., Gamez, M. J., Jimenez, J. J., Camara, M., and Martinez, M. A. 1990. Hypoglycemic action of Salvia lavandulifolia Vahl. spp. oxyodon: A contribution to studies on the mechanism of action. *Life Sci.* 47: 909–915.

Zhang, F., Ye, C., Li, G., Ding, W., Zhou, W., Zhu, H., et al. 2003. The rat model of type 2 diabetic mellitus and its glycometabolism characters. *Exp. Anim.* 52: 4001–4007.

Zhang, H., Matsuda, H., Yamashita, C., Nakamura, S., and Yoshikawa, M. 2009b. Hydrangeic acid from the processed leaves of *Hydrangea macrophylla* var. thunbergii as a new type of anti-diabetic compound. *Eur. J. Pharmacol.* 606: 255–261.

Zhang, J., Li, L., Kim, S. H., Hagerman, A. E., and Lu, J. 2009c. Anti-cancer, anti-diabetic and other pharmacologic and biological activities of penta-galloyl-glucose. *Pharm. Res.* 26: 2066–2080.

Zhang, J. -Y., Sun, H. -J., Song, I. -J., Bae, T. -W., Kang, H. -G., Ko, S. -M., et al. 2014b. Plant regeneration of Korean wild ginseng (*Panax ginseng* Meyer) mutant lines induced by γ-irradiation (^{60}Co) of adventitious roots. *J. Ginseng Res.* 38: 220–225.

Zhang, L., Cui, L., Zhou, G., Jing, H., Guo, Y., and Sun, W. 2013. Pterostilbene, a natural small-molecular compound, promotes cytoprotective macroautophagy in vascular endothelial cells. *J. Nutr. Biochem.* 24: 903–911.

Zhang, L., He, H., and Balschi, J. A. 2007. Metformin and phenformin activate AMP-activated protein kinase in the heart by increasing cytosolic AMP concentration. *Am. J. Physiol. Heart Circ. Physiol.* 293: 457–466.

Zhang, L., Hogan, S., Li, J. R., Sun, S., Canning, C., Jian Zheng, S., et al. 2011. Grape skin extract inhibits mammalian intestinal α-glucosidase activity and suppresses postprandial glycemic response in streptozocin-treated mice. *Food Chem.* 126: 466–471.

Zhang, L., Mao, W., Guo, X., Wu, Y., Li, C., Lu, Z., et al. 2013. *Ginkgo biloba* extract for patients with early diabetic nephropathy: A systematic review. *Evid. Based Complement. Altern. Med.* 2013: 689142.

Zhang, L., Yang, J., Chen, X. Q., Zan, K., Wen, X. D., Chen, H., et al. 2010. Antidiabetic and antioxidant effects of extracts from *Potentilla discolor* Bunge on diabetic rats induced by high fat diet and streptozotocin. *J. Ethnopharmacol.* 132: 518–524.

Zhang, M., Chen, M., Zhang, H. Q., Sun, S., Xia, B., and Wu, F. H. 2009a. *In vivo* hypoglycemic effects of phenolics from the root bark of *Morus alba*. *Fitoterapia* 80: 475–477.

Zhang, M. H., Feng, L., Zhu, M. M., Gu, J. F., Wu, C., and Jia, X. B. 2013. Antioxidative and anti-inflammatory activities of paeoniflorin and oxypaeoniflora on AGEs-induced mesangial cell damage. *Planta Med.* 79: 1319–1323.

Zhang, X., Luo, W., Zhao, W., Lu, J., and Chen, X. 2015. Isocryptotanshinone induced apoptosis and activated MAPK signaling in human breast cancer MCF-7 cells. *J. Breast Cancer* 18: 112–118.

Zhang, Y., Cai, J., Ruan, H., Pi, H., and Wu, Y. 2007. Antihyperglycemic activity of kinsenoside, a high yielding constituent from *Anoectochilus roxburghii* in streptozotocin-diabetic rats. *J. Ethnopharmacol.* 141–145.

Zhang, Y., Ning, Z. -X., and Dong, H. -Q. 2011. Inhibitory potential of trilobatin from *Lithocarpus polystachyus* Rehd against key enzymes linked to type 2 diabetes and its antioxidant activity. *Food Sci.* 32: 32–35.

Zhang, Z., Chen, J., Jiang, X., Wang, J., Yan, X., Zheng, Y., et al. 2014. The *Magnolia* bioactive constituent, 4-O-methylhonokiol protects against high-fat diet-induced obesity and systemic insulin resistance in mice. *Oxi. Med. Cell Longev.* 2014(965954): 10.

Zhang, Z., Chen, J., Zhou, S., Wang, S., Cai, X., Conklin, D. J., et al. 2015. *Magnolia* bioactive constituent 4-O-methylhonokiol prevents the impairment of cardiac insulin signaling and the cardiac pathogenesis in high-fat diet-induced obese mice. *Int. J. Biol. Sci.* 11: 879–891.

Zhao, G., Li, X., Chen, W., Xi, Z., and Sun, L. 2012. Three new sesquiterpenes from *Tithonia diversifolia* and their anti-hyperglycemic activity. *Fitoterapia* 83: 1590–1597.

Zhao, L. Y., Lan, Q. J., Huang, Z. C., Ouyang, L. J., and Zeng, F. H. 2011. Anti-diabetic effect of a newly identified component of *Opuntia dillenii* polysaccharides. *Phytomedicine* 18: 661–668.

Zhao, R., Li, Q., Long, L., Li, J., Yang, R., and Gao, D. 2007. Antidiabetic activity of flavone from *Ipomoea batatas* leaf in non-insulin dependent diabetic rats. *Int. J. Food Sci. Technol.* 42: 80–85.

Zhao, R., Li, Q. W., Li, J., and Zhang, T. 2009. Protective effect of *Lycium barbarum* polysaccharide 4 on kidneys in streptozotocin-induced diabetic rats. *Can. J. Physiol. Pharmacol.* 87: 711–719.

Zheng, X. K., Xhang, L., Wang, W. W., Wu, Y. Y., Zhang, Q. B., and Feng, W. S., et al. 2011. Anti-diabetic activity and potential mechanism of total flavonoids of *Selaginella tamariscina* (Beauv.) Spring in rats induced by high fat diet and low dose streptozotocin. *J. Ethnopharmacol.* 137: 662–668.

Zheng, Y. Q., Wei, W., Zhu, L., and Liu, J. X. 2007. Effects and mechanisms of paeoniflorin, a bioactive glucoside from paeony root, on adjuvant arthritis in rats. *Inflamm. Res.* 56: 182–188.

Zhou, C. X., Qiao, D., Yan, Y. Y., Wu, H. S., Mo, J. X., and Gan, L. S. 2012. A new anti-diabetic sesquiterpenoid from *Acorus calamus*. *Chin. Chem. Lett.* 23: 1165–1168.

Zhou, J., Chan, L., and Zhou, S. 2012. Trigonelline: A plant alkaloid with therapeutic potential for diabetes and central nervous system disease. *Curr. Med. Chem.* 19: 3523–3531.

Zhou, S. and Brown, D. C. W. 2007. A highly efficient protocol for micropropagation of North American Ginseng. In: *Biotechnology and Sustainable Agriculture 2006 and Beyond.* Xu, Z., Li, J., Xue, Y. and Yang, W. (Eds). In: *Proceedings of the 11th IAPTC & B Congress.* 2006 425–428, Beijing, China.

Zhou, T., Deng, X., and Qiu, J. 2012. Antimicrobial activity of licochalcone E against *Staphylococcus aureus* and its impact on the production of staphylococcal alpha-toxin. *J. Microbiol. Technol.* 22: 800–805.

Zhou, Y. X., Zhang, H., and Peng, C. 2014. Puerarin: A review of pharmacological effects. *Phytother. Res.* 28: 961–975.

Zhuang, X. -M., Zhong, Y. -H., Xiao, W. -B., Li, H., and Lu, C. 2013. Identification and characterization of psoralen and isopsoralen as potent CYP1A2 reversible and time-dependent inhibitors in human and rat preclinical studies. *Drug Metab. Dispos.* 41: 1914–1922.

Zia-ul-haq, M., Riaz, M., Feo, V. D., Jaafar, H. Z. E., and Moga, M. 2014. *Rubus fruticosus* L.: Constituents, biological activities and health related uses. *Molecules* 19: 10998–11029.

Zobayed, S. M. A. 2000. *In vitro* propagation of *Lagerstroemia* spp. from nodal explants and gaseous composition in the culture headspace. *Environ. Control Biol.* 38: 1–11.

Zottich, U., Da Cunha, M., Carvalho, A. O., Dias, G. B., Silva, N. C. M., Santos, I. S., et al. 2011. Purification, biochemical characterization and antifungal activity of a new lipid transfer protein (LTP) from *Coffea canephora* seeds with α-amylase inhibitor properties. *Biochim. Biophys. Acta* 1810: 375–383.

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