Handbook of Nutraceuticals for Clinical Use

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Springer

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ISBN 978-3-319-73641-9 ISBN 978-3-319-73642-6 (eBook)
https://doi.org/10.1007/978-3-319-73642-6

Library of Congress Control Number: 2018930752

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The current use of nutraceuticals for clinical purposes evolves from the traditional use of botanicals and dietary supplements for preventive or therapeutic purposes. It is based on knowledge of the pharmacological activities of natural compounds and clinical evidence of efficacy and safety. In this context, the use of nutraceuticals by experts in nutrition is rapidly increasing. Despite the availability of a large number of nutraceuticals in the market, the same compound is often offered by different industries at different dosages and concentrations, with different titrations, and often with different suggestions of efficacy.

Many well-written, academic books on nutraceuticals already exist, however for the most part, they summarize scientific literature rather than answer common questions such as: "Who is the appropriate recipient for this nutraceutical?", "What kind of product and what dosage should I prescribe/suggest? How long should the treatment last?", "What kinds of side effects are to be expected?"

This handbook aims to provide healthcare personnel with a practical and quick guide to an evidence-based approach for use of nutraceuticals in clinical practice.

Each product is defined as per therapeutic indication, supposed main mechanism of action, scientific level of clinical evidence (tradition, epidemiological data, case reports, one or more clinical trials, meta-analyses of clinical trials), oral biovailability, range of tested doses (efficacious and safe), relative and absolute contraindications, possible side effects (for suggested dosages) and their management, and possible additive or synergistic nutraceuticals. Each entry concludes with a list of suggested readings.

Bologna, Italy

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Nutraceuticals Active on Central Nervous System

	Bacopa
Main source	*Bacopa monnieri*
Main indication	Mid-to-moderate cognitive decline, depression, anxiety
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not determined: possible a serotonergic, dopaminergic, GABAergic, cholinergic action
Level of support	Randomized clinical trials
Population tested	Adults, Elderly, Children
Dose ranges	>300 mg/day (>35% bacosides) The title and the extract standardization are important requirements for the effectiveness
Treatment duration	Long-term
Main expected effect	Improvement of depressive and stress symptoms [Hamilton Depression Rating Scale (HAM-D), Mini Mental State Examination (MMSE), Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)]
Secundary positive effects	Adaptogenic effect, improvement of irritable bowel syndrome (preliminary data)
Possible side effects (for suggested dosages)	Mild dyspepsia, constipation, diarrhea, xerostomia, fatigue
Relative controindication	Pregnancy and lactation, bradycardia, ulcers, thyroid disorders
Possible pharmacokinetic interactions of clinical interest	Mild inhibition of CYP1A2, CYP3A4, CYP2C9 and CYP2C19
Possible additive or synergistic nutraceuticals	Nutraceuticals with mood improving effects (eg. saffron, rhodiola, L-theanine, vitamins B, selenium, copper, magnesium)
Suggested recent bibliography	Cicero AF et al. Prev Alz Dis. 2017;1:12–15. Chaudhari KS et al. Ann Neurosci. 2017;24(2):111–122.

	Chamomile
Main source	*Matricaria chamomilla, German chamomile*
Main indication	Mild-to-moderate anxiety, sleep disorders
Oral bioavailability	Definitive data not available in humans

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A.F.G. Cicero, A. Colletti, *Handbook of Nutraceuticals for Clinical Use*,
https://doi.org/10.1007/978-3-319-73642-6_1

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	Chamomile
Supposed main mechanism of action	Benzodiazepine-like activity (apigenin)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	220–1100 mg/day of dry extract (apigenin titration 1–1.5%) The title and standardization of flavonoids (as rutin) and terpenoids (as farnesene) could be important to detect the most effective extracts
Treatment duration	Symptomatic/Cyclic
Main expected effect	Improvement of anxiety sypmtoms (latency, quality and duration of sleep)
Secundary positive effects	Improvement of dyspepsia
Possible side effects (for suggested dosages)	Allergy to chamomile
Relative controindication	Pregnancy and lactation (not enough information available as supplement), hormone sensitive cancers conditions (some chemicals in chamomile act like estrogen), allergies to ragweed or related plants
Possible pharmacokinetic interactions of clinical interest	Per high dosages with contraceptive drugs and estrogens (chamomile might have some estrogen-like effects), sedative medications as benzodiazepines, zolpidem or barbiturates (sleepiness and drowsiness), alcohol (sleepiness and drowsiness), tamoxifen (decreased effectiveness), warfarin (increased effectiveness), medications substrates of CYP1A2 and 3A4 (increased effectiveness)
Possible additive or synergistic nutraceuticals	Mood improving nutraceuticals
Suggested recent bibliography	Miraj S, Alesaeidi S. Electron Physician. 2016;8(9):3024–31. Chang SM, Chen CH. J Adv Nurs. 2016;72(2):306–15.

	Cocoa
Main source	*Theobroma cacao L.*
Main indication	Mild-to-moderate depression, cognitive decline, cardiovascular disease prevention
Oral bioavailability	The bioavailability of polyphenols is widely variable: cold roasted cocoa > hot roasted cocoa and cold chocolate cold worked > dark chocolate hot worked Dietary fat intake, form and the dose ingested, gut transit time, fecal degration rate and intestinal eubiosis could influence the bioavailability of cocoa polyphenols
Supposed main mechanism of action	Improvement of nitric oxide (NO) endothelial concentrations, reduction of oxidative stress
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, children

	Cocoa
Dose ranges	250–1000 mg/day of dry extract total polyphenols The title and the standardization of total flavonoids could be important to recognize the most effective extracts
Treatment duration	Long-term
Main expected effect	Improvement of cognitive function and mood
Secundary positive effects	Improvement of blood pressure, insulin-resistance, endothelial function and arterial stiffness
Possible side effects (for suggested dosages)	Mild-gastrointestinal side effects
Relative controindication	Gastroesophageal reflux disease (GERD), migraine
Possible pharmacokinetic interactions of clinical interest	Adenosine (rediced effect), clozapine, phenylpropanolamine, theophylline, MAO inhibitors (increased effects), litium (improved bioavailability)
Possible additive or synergistic nutraceuticals	Nutraceuticals with mood improving effects, Nootropics
Suggested recent bibliography	Socci V et al. Front Nutr. 2017;4:19. Grassi D et al. Curr Pharm Des. 2016;22(2):145–51.

	Curcumin
Main source	*Curcuma longa*
Main indication	Mild-to-moderate depression, neuroprotection
Oral bioavailability	Very low (< 1%) Biopharmaceutical interventions (eg. nanoemulsion, micelles) are important to improve the curcumin intestinal absorption and its clinical efficacy
Supposed main mechanism of action	Modulation of hypothalamic–pituitary–adrenal axis, stimulation of synpasin I, cAMP responsive element-binding protein and brain-derived neurotrophic factor, MAO inhibition and regulation of Nrf2 transcription gene
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	Curcumin in specific pharmaceutical forms (e.g. biopharmaceutical strategies as micelles or nanoemulsions): >400/500 mg/day Natural curcumin: >1 g/day (usually 1.5 g/day)
Treatment duration	Usually long-term for comorbidities
Main expected effect	Improvement of depressive symptoms [Hamilton Depression Rating Scale (HAM-D)] and reduction of serum and salivary stress markers such as cortisol and interleuchins
Secundary positive effects	Improvement of cardiovascular disease risk factors [Reduction of inflammatory markers, plasma glutathione concentrations, insulin-resistance], prevention and/or treatment of any inflammation related disease
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps and/or upset, diarrhea, dizziness

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	Curcumin
Relative controindication	Pregnancy and lactation, Gilbert's disease or gallbladder problems, infertility, iron deficiency, bleeding problems, hormone-sensitive conditions (breast cancer, uterine cancer, ovarian cancer, uterine fibroids or endometriosis)
Possible pharmacokinetic interactions of clinical interest	Inhibition of CYP2C9; possible interactions with anticoagulant, antiplatelet and anticoagulant drugs, NSAIDs.
Possible additive or synergistic nutraceuticals	Mood improving nutraceuticals
Suggested recent bibliography	Al-Karawi D et al. Phytother Res. 2016;30:175–83. Yu JJ et al. J Clin Psychopharmacol. 2015;35:406–10.

	Escholtzia
Main source	*Eschscholtzia californica*
Main indication	Mild-to-moderate anxiety
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined
Level of support	Open label/pilot trials
Population tested	Adults
Dose ranges	100–200 mg/day of dry extract
Treatment duration	Cyclic
Main expected effect	Improvement of anxiety [State-Trait Anxiety Inventory (STAI)]
Secundary positive effects	Improvement of insomnia (inclonclusive data)
Possible side effects (for suggested dosages)	Mild headache, nausea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Sedative medications as benzodiazepines, zolpidem or barbiturates (sleepiness and drowsiness), alcohol (sleepiness and drowsiness)
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Zhou ES et al. Med Clin North Am. 2017;101(5):865–879. Chung MS, Kim GH. Nutr Res Pract. 2010; 4(4):290–4.

	Folic acid (5′-methyltetrahydrofolate)
Main source	Dietary supplements
Main indication	Mid-to-moderate depression, mild-cognitive decline, hyperhomocysteinemia
Oral bioavailability	30–98% (folate from foods > bioavailable of folate supplements > bioavailable of folic acid)

	Folic acid (5′-methyltetrahydrofolate)
Supposed main mechanism of action	Precursor of tetrahydrofolic acid and methyltetrahydrofolate (essential for the maintenance of normal erythropoiesis and cofactors for the synthesis of purine and thymidylate nucleic acids), cofactor in serveral enzymatic reactions (eg. interconversion of amino acids as histidine and glutamic acid or methione and homocysteine)
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	250–2500 mcg/day: for depression, the dosages of folic acid used are 400–1200 mcg/day It is advisable to reduce folate dosage to less than 1 mg/day (and probably even less) addying Vit. B12, in case of reduced Vit. B12 plasma level.
Treatment duration	Long-term (elderly)/Cyclic (in adults usually 30–90 days)
Main expected effect	Improvement of depressive symptoms [Edinburgh Postnatal Depression Scale (EPDS), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)]
Secundary positive effects	Improvement of folate deficiency and hyperhomocysteinemia, prevention of birth defects, anemia, age-related macular degeneration
Possible side effects (for suggested dosages)	Mild diarrhea, abdominal cramps, irritability, stomach upset, nausea, rash, sleep disorders, confusion
Relative controindication	Cancer (preliminary data)
Possible pharmacokinetic interactions of clinical interest	Fosphenytoin, methotrexate, phenoarbital, phenytoin, primidone, pyrimethamine (drecreased effectiveness of drugs)
Possible additive or synergistic nutraceuticals	Vitamin D and group B vitamins (especially B12)
Suggested recent bibliography	Araújo JR et al. Ageing Res Rev. 2015;22:9–19. Almeida OP et al. Int Psychogeriatr 2015; 27:727–737.

	Griffonia
Main source	*Griffonia simplicifolia*
Main indication	Mid-to-moderate depression and mild-anxiety
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Serotonin precursor
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–3000 mg/day The title and the standardization of 5-Hydroxytryptophan (5-HTP) could be important to recognize the most effective extracts
Treatment duration	Cyclic (usually 30–90 days)

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	Griffonia
Main expected effect	Improvement of depressive symptoms [Edinburgh Postnatal Depression Scale (EPDS), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], improvement of anxiety [State-Trait Anxiety Inventory (STAI)]
Secundary positive effects	Improvement of migraine
Possible side effects (for suggested dosages)	Mild diarrhea, abdominal cramps, dyspepsia, irritability, sleep disorders, confusion, rare eosinophilia-myalgia syndrome (EMS)
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	MAOIs, tricyclic antidepressants, SSRIs, carbidopa, pentazocine, meperidine, tramadol and other drugs that interact with serotonin
Possible additive or synergistic nutraceuticals	It is suggested to avoid its use in patients treated with fully dosed natural or chemical antidepressant drugs
Suggested recent bibliography	Rondanelli M et al. Eat Weight Disord. 2012;17(1):e22–8. Emanuele E et al. Neuro Endocrinol Lett. 2010;31(5):663–6.

	Hawthorn
Main source	*Crataegus monogyna, Crataegus oxyacantha*
Main indication	Mild-to-moderate anxiety, mainly in heart failure patients
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Benzodiazepine-like activity, positive inotropic effect
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–900 mg/day of dry extract (oligomeric procyanidins 15–20%) The title and the standardization of oligomeric procyanidins (15–20%) could be important to recognize the most effective extracts
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of anxiety [Hamilton Anxiety Rating Scale (HAM-A)]
Secundary positive effects	Improvement of insomnia, heart failure symptoms (fatigue, swelling, weakness, ability to exercise), and blood pressure
Possible side effects (for suggested dosages)	Mild headache, dizziness, stomach upset, sweating, nausea, vomit, fatigue, palpitations, insomnia, agitation
Relative controindication	Pregnancy and lactation (not enough information available), heart disease (hawthorn could interact with many prescription drugs: its prescription must be limited to healthcare providers)
Possible pharmacokinetic interactions of clinical interest	Digoxin, beta-blockers, calcium channel blockers, 5-phosphodiesterase-5-inhibitors (sildenafil, tadalafil, vardenafil) because of the risk of potentiated effects. With nitrates it increases the risk of dizziness and lightheadedness
Possible additive or synergistic nutraceuticals	Mood improving nutraceuticals
Suggested recent bibliography	Kure C et al. Front Pharmacol. 2017;8:117. Orhan IE. Curr Med Chem. 2016 Sep 18. PMID: 27,655,074.

	Hypericum
Main source	St. John's wort
Main indication	Mild-to-moderate depression
Oral bioavailability	Few data available in humans even if hypericin and hyperforin seem to be well absorbed
Supposed main mechanism of action	MAO inhibition, Serotonin, dopamine, GABA and acetylcolhine reuptake inhibitor
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	100–900 mg/day (0.15–1.2 mg/day of hypericin) Dosages vary by titration of the extracts
Treatment duration	Long-term/Cyclic (>6 weeks)
Main expected effect	Improvement of depressive symptoms [Hamilton Depression Rating Scale (HAM-D) and Self Rating Depression Scale (SRDS)]
Secundary positive effects	Relaxation and anxiolytic effects Improvement of obsessive-compulsive disorder (OCD), seasonal affective disorder (SAD), social phobia, attention deficit-hyperactivity disorder (ADHD)
Possible side effects (for suggested dosages)	Photosensitivity, gastrointestinal symptoms, hepatotoxicity headache, dizziness, tiredness, xerostomia, restlessness, thyroid stimulation (high levels of circulating thyrotropin), mania hepisodes
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Hypericum is a potent inducer of CYP450 (1A2, 2C9, 3A4) and P-glycoprotein, thus reducing the efficacy of large number of drugs. It could be increase the risk of serotoninergic syndrome when associated with tricyclic antidepressants and SSIRs The association with *Griffonia simplicifolia* could also increase the risk of serotoninergic syndrome (for contemporary use of high dosages of both plants)
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Cui YH, Zheng Y. Neuropsychiatr Dis Treat. 2016; 12:1715–23. Apaydin EA et al. Syst Rev. 2016; 5(1):148.

	Hop
Main source	*Humulus lupulus*
Main indication	Mild-to-moderae anxiety, insomnia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not determined: possible a GABA-A agonism effect The 2-methyl-3-buten-2-ol it seems to be the metabolite with major sedative action
Level of support	Randomized clinical trials
Population tested	Adults, elderly

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	Hop
Dose ranges	80–460 mg/day of dry extract (rutin titration 0.3–0.5%) The title and the standardization of flavonoids (as rutin) and terpenoids (as farnesene) could be important to recognize the most effective extracts
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of anxiety sypmtoms and sleep disorders (latency, quality and duration of sleep)
Secundary positive effects	Improvement of menopausal sundrome and depressive symptoms (preliminary data)
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (no information available), hormone sensitive cancers conditions (some chemicals in hops act like estrogen)
Possible pharmacokinetic interactions of clinical interest	Sedative medications as benzodiazepines, zolpidem or barbiturates and alcohol (sleepiness and drowsiness)
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Abdi F et al. BMJ Open. 2016;6(4):e010734. Van Cleemput M et al. J Nat Prod. 2009;72(6):1220–30.

	Lavender
Main source	*Lavandula angustifolia*
Main indication	Mild-to-moderate anxiety
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined: possible a GABA-A agonism effect
Level of support	Randomized clinical trials
Population tested	Adults
Dose ranges	2–4.5 ml/day of alcohol tincture (1:2) or 6–12 ml/day of alcohol tincture (1:5), 20–30 mg of dry extract
Treatment duration	Symptomatic/Cyclic
Main expected effect	Relaxation and anxiolytic effect (State-Trait Anxiety Inventory, STAI)
Secundary positive effects	Improvement of mood and depressive symptoms (Hospital Anxiety and Depression Scale, HADS)
Possible side effects (for suggested dosages)	Gastrointestinal symptoms (>80 mg/day), headache
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Perry R et al. Phytomedicine. 2012; 19(8–9):825–35. Woelk H, Schlafke S. Phytomedicine. 2010; 17(2),94–99.

	L-arginine
Main source	Dietary supplements
Main indication	Mild-to-moderate anxiety
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Nitric oxide donator, modulation of HPA (hypothalamic–pituitary–adrenal) axis, 5-HT4 (5-hydroxytryptamine 4) receptor antagonist
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	5–20 g/day
Treatment duration	Cyclic (usually 30–60 days)
Main expected effect	Improvement of anxiety
Secundary positive effects	Improvement of athletic performance, blood pressure, arterial stiffness, heart failure, erectile dysfunction and male infertility
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects (diarrhea and stomach cramps)
Relative controindication	Pregnancy and lactation (not enough data available in humans) Kidney disease, recent heart attack
Possible pharmacokinetic interactions of clinical interest	Nitrates (mild dizziness and/or headache), antihypertensive drugs (eg. captopril, analapril, losartan, valsartan, diltiazem, amlodipine, furosemide), sildenafil
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Lakhan SE, Vieira KF. Nutr J. 2010;9:42. Smriga M et al. Biomed Res. 2007; 28:85–90.

	L-lysine
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild-to-moderate anxiety
Oral bioavailability	Excellent (>90%)
Supposed main mechanism of action	Modulation of HPA (hypothalamic–pituitary–adrenal) axis, 5-HT4 (5-hydroxytryptamine 4) receptor antagonist
Level of support	Randomized clinical trials
Population tested	Adults
Dose ranges	600–3000 mg/day
Treatment duration	Cyclic (usually 30–60 days)
Main expected effect	Relaxation and anxiolytic effect (State-Trait Anxiety Inventory, STAI)
Secundary positive effects	Improvement of athletic performance, prevention and treatment of cold sores and Herpes simplex
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects (diarrhea and stomach cramps)
Relative controindication	Pregnancy and lactation (not enough data available in humans) Kidney disease

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	L-lysine
Possible pharmacokinetic interactions of clinical interest	Calcium interacts with lysine that may increase the plasma levels of calcium
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Lakhan SE, Vieira KF. Nutr J. 2010;9:42. Smriga M et al. Biomed Res. 2007; 28:85–90.

	L-theanine
Main source	*Camellia sinensis*, *Boletus badius* In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild-to-moderate anxiety and depression
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Possible a serotonergic, dopaminergic, GABAergic, cholinergic action and a reversible inhibition of the NMDA (N-methyl-D-aspartate) receptor
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–250 mg/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Neuroprotective, relaxation and anxiolytic effect
Secundary positive effects	Improvement of mood, depressive symptoms, memory and cognition, sleep quality
Possible side effects (for suggested dosages)	Rare gastrointestinal side effects
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Hidese S et al. Acta Neuropsychiatr. 2016; 1–8. Scheid L et al. J Nutr. 2012;142(12):2091–6.

	L-tryptophan
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild-to-moderate depression and premenstrual dysphoric disorder (PMDD)

	L-tryptophan
Oral bioavailability	About 70%
Supposed main mechanism of action	Precursor of serotonin
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	3 g/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of depressive symptoms and premenstrual dysphoric disorder (PMDD)
Secundary positive effects	Improvement of athletic performance (inconclusive), adjuvant in smoking cessation
Possible side effects (for suggested dosages)	Mild dose-related heartburn, dyspepsia, belching, nausea, diarrhea, loss of appetite, headache, xerostomia, sexual problems, visual blurring, lightheadedness, muscle weakness
Relative controindication	Pregnancy and lactation, liver and kidney disease, eosinophilia, patients with reversal circadian rhythm (the tryptophan/large neutral aminoacids ratio is unbalanced)
Possible pharmacokinetic interactions of clinical interest	Antidepressant drugs (increased risk of anxiety), heart problems, shivering Sedative medications (increased risk of somnolence)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Ogawa S, Fujii T. J Clin Psychiatry. 2014; 75(9):e906–15. Emanuele E et al. Neuro Endocrinol Lett. 2010;31(5):663–6.

	Magnesium
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild anxiety, psychophysical stress
Oral bioavailability	20–50%. Calcium, iron, copper, manganese, phosphorous and alcohol might decrease its bioavailability. Magnesium aspartate, citrate, chloride and lactate are more bioavailable than magnesium hydroxide, oxide, and sulfate.
Supposed main mechanism of action	Antagonist of NMDA (N-methyl-D-aspartate) receptor and modulation of hypothalamic–pituitary–adrenal axis Cofactor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis, responsible of several processes including hormone receptor binding, gating of calcium channels, muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability, neurotransmitter release
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	200–400 mg/day
Treatment duration	Cyclic (usually 30–90 days)

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	Magnesium
Main expected effect	Improvement of anxiety and perceived stress
Secundary positive effects	Improvement of depressive symptoms, attention deficit-hyperactivity disorder, chronic fatigue syndrome, premenstrual syndrome, myalgia, cramps, headache, fibromyalgia, osteoporosis, high blood pressure
Possible side effects (for suggested dosages)	Mild diarrhea, stomach upset, nausea, heartbeat
Relative controindication	Pregnancy (>350 mg/day: few data available), kidney failure, heart block, bleeding disorders (preliminary data)
Possible pharmacokinetic interactions of clinical interest	Per large doses with quinolone and antibiotics and bisphosphonates (decreased effectiveness of drugs), calcium channel blockers (increased effect of drugs), muscle relaxants (increased risk of side effects], potassium sparing diuretics (risk of hypermagnesemia)
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Martínez-González MÁ, Sánchez-Villegas A. Magnes Res. 2016;29(3):102–111. Cheungpasitporn W et al. Intern Med J. 2015; 45(4):436–40.

	Magnolia
Main source	*Magnolia officinalis*
Main indication	Mild-to-moderate anxiety
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Modulation of HPA (hypothalamic–pituitary–adrenal) axis, GABA-A and cannabinoid (CB1, 2) receptors agonist
Level of support	Randomized clinical trials
Population tested	Adults
Dose ranges	250–600 mg/day of dry extract The title and the standardization of magnolol and honokiol could be important to recognize the most effective extracts
Treatment duration	Symptomatic/Cyclic (usually 30–60 days)
Main expected effect	Improvement of anxiety symptoms and stress [Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)]
Secundary positive effects	Improvement of mood memory, cognition and depression symptoms [Hamilton Depression Rating Scale (HAM-D)] Reduction of physical and mental fatigue, weight, inflammation, nasal congestion, headache
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation Surgery (magnolia might cause bleeding during and after surgery and slow down the nervous system if combined with anesthesia)
Possible pharmacokinetic interactions of clinical interest	Alcohol and sedative medications (benzodiazepines, barbiturates and CNS depressants) might cause sleepiness and drowsiness

	Magnolia
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Talbott SM et al. J Int Soc Sports Nutr. 2013; 10(1):37. Rempel V, et al. ACS Med Chem Lett. 2012; 4(1):41–5.

	Melatonin (5-Methoxy-N-Acetyltryptamine)
Main source	Dietary supplements
Main indication	Insomnia, alterations of the circadian rhythm
Oral bioavailability	30–50%
Supposed main mechanism of action	Melatonin receptors (MT1, MT2) agonist
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	1–10 mg/day
Treatment duration	Cyclic (usually 30–60 days)
Main expected effect	Adjustment of body's internal clock with improvement of sleeping disorders and insomnia
Secundary positive effects	Night blood pressure decrease and immune-system modulation
Possible side effects (for suggested dosages)	Mild stomach cramps, headache, depression, sleepiness, dizziness, irritability
Relative controindication	Pregnancy and lactation (melatonin might interfere with ovulation), bleeding disorders, depression, diabetes, seizure disorders
Possible pharmacokinetic interactions of clinical interest	Sedative medications (increased risk of sleepiness and drowsiness), caffeine (it may decrease the effectiveness of melatonin), fluvoxamine and birth control pills as ethinyl estradiol or norethindrone (they may increase the effectiveness of melatonin), nifedipine (melatonin may decrease the effectiveness of nifedipine), anticoagulant/antiplatelet drugs (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Zhang W et al. Neurol Sci. 2016; 37(1):57–65. Ferracioli-Oda E et al. PLoS One. 2013; 8(5):e63773.

	Melissa
Main source	*Melissa officinalis, M. graveolens, M. calamintha, M. romana, M. glandulosa, M. glomerata, M. montana*
Main indication	Mild-to-moderate anxiety and related insomnia
Oral bioavailability	Not determined
Supposed main mechanism of action	Benzodiazepine-like activity, inhibition of monoamine oxidase (MAO-A)
Level of support	Randomized clinical trials
Population tested	Adults, elderly

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	Melissa
Dose ranges	300–600 mg/day of dry extract (rosmarinic acid 35–40 mg/g of dry extract) The title and the standardization of rosmarinic acid (35–40 mg/g of dry extract) could be important to identify the most effective extracts
Treatment duration	Symptomatic/Cyclic (usually 30–90 days)
Main expected effect	Improvement of anxiety [Hamilton Anxiety Rating Scale (HAM-A)] and stress
Secundary positive effects	Improvement of cold sores, dyspepsia and insomnia
Possible side effects (for suggested dosages)	Mild headache, dizziness, stomach upset, nausea, wheezing
Relative controindication	Pregnancy and lactation (not enough information available)
Possible pharmacokinetic interactions of clinical interest	Sedative medications as benzodiazepines, zolpidem or barbiturates (sleepiness and drowsiness), alcohol (sleepiness and drowsiness)
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Shakeri A et al. J Ethnopharmacol. 2016; 188:204–28. Sarris J et al. Am J Psychiatry. 2016; 173(6):575–87.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*) In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild-to moderate depression, neurocognitive decline, cerebrovascular disease prevention, hypertriglyceridemia
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Improvement of functionality and dynamism of neuronal cells Reduction of the release and synthesis of inflammatory cytokines
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	2–4 g/day of eicosapentanoic and/or docosahexaenoic acid The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Treatment duration	Long-term
Main expected effect	Mood stabilization
Secundary positive effects	Cardiovascular disease prevention, triglyceride lowering effect, anti-proarrhytmic and antinflammatory effects, macula protection, brain protection
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time
Relative controindication	Allergy to fish derived products

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Possible pharmacokinetic interactions of clinical interest	Warfarin (possible increasing effect for use of high dosages)
Possible additive or synergistic nutraceuticals	Mood improving nutraceuticals
Suggested recent bibliography	Sarris J, et al. Am J Psychiatry. 2016; 173(6):575–87. Lin PY, et al. Mol Psychiatry. 2012; 17:1161–1163.

	Passionflower
Main source	*Passiflora incarnata, P. edulis*
Main indication	Mild-to-moderate anxiety and related insomnia
Oral bioavailability	Not determined
Supposed main mechanism of action	Benzodiazepine-like activity
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	300–600 mg/day of dry extract (20/25% of total flavonoids as vitexin and hyperoside) The title and the standardization of total flavonoids (20–25% of dry extract) could be important to identify the most effective extracts
Treatment duration	Symptomatic/Cyclic
Main expected effect	Improvement of anxiety [Hamilton Anxiety Rating Scale (HAM-A)] and stress
Secundary positive effects	Improvement of insomnia
Possible side effects (for suggested dosages)	Mild headache, dizziness, stomach upset, nausea, confusion, drowsiness
Relative controindication	Pregnancy and lactation (some chemicals in passionflower might cause the uterus to contract)
Possible pharmacokinetic interactions of clinical interest	Sedative medications as benzodiazepines, zolpidem or barbiturates (sleepiness and drowsiness), alcohol (sleepiness and drowsiness), clonidine (association of clonidine + passionflower is effective to relieving symptoms related to narcotic drug)
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Miroddi M et al. J Ethnopharmacol. 2013;150(3):791–804. Modabbernia A, Akhondzadeh S. Psychiatr Clin North Am. 2013;36(1):85–91.

	Phellodendron
Main source	*Phellodendron amurense, P. chinense, P. japonicum, P. lavallei, sachalinense, P. sinii, P. wilsonii*
Main indication	Mild-to-moderate anxiety
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Modulation of HPA (hypothalamic–pituitary–adrenal) axis, GABA-A agonist
Level of support	Randomized clinical trials

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	Phellodendron
Population tested	Adults
Dose ranges	250–600 mg/day of dry extract The title and the standardization of berberine could be important to recognize the most effective extracts
Treatment duration	Cyclic
Main expected effect	Improvement of anxiety symptoms and stress [Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)]
Secundary positive effects	Improvement of mood memory, cognition and depression symptoms [Hamilton Depression Rating Scale (HAM-D)] Reduction of weight, inflammation, psoriasis, diarrhea, eye infections, gastric and/or duodonel ulcers
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation (berberine can cross the placenta) Children (newborn infants): Magnolia might cause brain damage
Possible pharmacokinetic interactions of clinical interest	Phellodendron is substrate of CYP450 (3A4): cyclosporine, lovastatin, clarithromycin, indinavir, sildenafil and triazolam are some example of drugs that could interact with this nutraceutical.
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Zhou ES et al. Med Clin North Am. 2017;101(5):865–879. Talbott SM et al. J Int Soc Sports Nutr. 2013; 10(1):37.

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Main source	Dietary supplements Dairy products and derivatives
Main indication	Mild mood disorders, intestinal dysbiosis
Oral bioavailability	*Lactobacilli* and *Bifidobacteria* colonize the intestinal lumen *Saccharomyces* it's a fermenter yeast, but doesn't colonize the intestinal lumen
Supposed main mechanism of action	Modulation of Gut-Brain-Axis and hypothalamic–pituitary–adrenal axis, restore intestinal eubiosis
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>3.5 UFC (live)/day The administration of probiotic strains, to obtain the maximum effectiveness, should be take before the main meal with a lipid vehicle (eg. yogurt or milk)
Treatment duration	Long-term
Main expected effect	Regulation of mood, depressive symptoms and anxiety [Improvement of Leiden Index of Depression Sensitivity (LEIDS-r), Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D)]
Secundary positive effects	Improvement of bowel health, mild improvement of some cardiovascular risk factors (cholesterolemia, blood pressure, inflammatory marker), regulation of the immune system, prevention of urinary infections and improvement of its symptoms.

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Possible side effects (for suggested dosages)	Minors (mostly of gastrointestinal nature)
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	It is possible that probiotics interfere with the molecules subject to intestinal enzymatic metabolism (eg. polyphenols, berberine)
Possible additive or synergistic nutraceuticals	Mood improving nutraceuticals
Suggested recent bibliography	Marx W et al. Proc Nutr Soc. 2017 Sep 25:1–10. Pirbaglou M et al. Nutr Res. 2016; 36(9):889–98.

	Rhodiola
Main source	*Rhodiola rosea*
Main indication	Psyhcophysical stress
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Adaptogen (restoring "cerebral homeostasis"): the exact Supposed main mechanism of action is not yet determined
Level of support	Randomized clinical trials
Population tested	Adults
Dose ranges	340–680 mg/day of dry extract The title and the standardization of salidroside, rhodioloside, rosavin and tyrosol could be important to recognize the most effective extracts
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of mood memory, cognition and depressive symptoms [Hamilton Depression Rating Scale (HAM-D), Mini Mental State Examination (MMSE), Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)]
Secundary positive effects	Reduction of physical and mental fatigue, anxiety and modulation of immune system
Possible side effects (for suggested dosages)	Gastrointestinal symptoms, insomnia, nervousness
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Rhodiola is an inhibitor of CYP3A4 and CYP2C19 (*in vitro*) even if it doesn't interfere with the warfarin metabolism (CYP2C9)
Possible additive or synergistic nutraceuticals	Mood improving nutraceuticals
Suggested recent bibliography	Amsterdam JD, Panossian AG. Phytomedicine. 2016; 23(7):770–83. Chiang HM et al. J Food Drug Anal. 2015;23(3):359–369.

	S-adenosyl-methionine (SAMe)
Main source	Dietary supplements
Main indication	Mild mood disorders
Oral bioavailability	Low

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	S-adenosyl-methionine (SAMe)
Supposed main mechanism of action	Cofactor in methylation, transsulfuration and amino-propylation of over 40 substrates including proteins, lipids, nucleic acids and neurotransmitters also responsible for the regulation humor, increased methylation of catecholamines, plasma serotonin levels, inhibition of re-uptake of norepinephrine, improvement of dopaminergic activity and conversion of phosphatidylcholine into acetylcholine
Level of support	Randomized clinical trials
Population tested	Adults
Dose ranges	800–1600 mg/day
Treatment duration	Cyclic (usually 45–120 days)/Long-term
Main expected effect	Improvement of mood memory, cognition and depressive symptoms [Hamilton Depression Rating Scale (HAM-D), Mini Mental State Examination (MMSE), Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)]
Secundary positive effects	Improvement of osteoarthritis, fibromyalgia, intrahepatic cholestasis and sexual dysfunction
Possible side effects (for suggested dosages)	Mild insomnia, nervousness, bloating, diarrhea, constipation, xerostomia, headache, anorexia, sweating and dizziness
Relative controindication	Pregnancy and lactation (at high dosages not enough data available) Bipolar disorder, Lesch-Nyhan syndrome and Parkinson's disease
Possible pharmacokinetic interactions of clinical interest	Antidepressant drugs, dextromethorphan, tramadol and meperidine (SAMe increases the serotonin levels), levodopa (SAMe could decrease the effects)
Possible additive or synergistic nutraceuticals	Mood improving nutraceuticals
Suggested recent bibliography	Sharma A et al. J Clin Psychiatry. 2017;78(6):e656-e667. Sarris J et al. Pharmacopsychiatry. 2015; 48(4–5):141–4.

	Saffron
Main source	*Crocus sativa*
Main indication	Mild-to-moderate depression
Oral bioavailability	Low
Supposed main mechanism of action	Not determined: possible a serotonergic, dopaminergic, GABAergic, cholinergic action
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>30 mg/day The title and the extract standardization of crocetins, safranals, crocins and pirocrocins are important requirements for the effectiveness
Treatment duration	Cyclic (usually 30–90 days)

	Saffron
Main expected effect	Improvement of depressive and stress symptoms [Depression Rating Scale (HAM-D), Mini Mental State Examination (MMSE), Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)]
Secundary positive effects	Antioxidant
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps
Relative controindication	Pregnancy (possible uterine stimulant and abortifacient effects), bipolar disorder, hypotension
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Mood improving nutraceuticals
Suggested recent bibliography	Cicero AF, et al. Prev Alz Dis 2017;1:12–15 Mashmoul M, et al. Antioxidants 2013;2:293–308.

	Valerian
Main source	*Valeriana officinalis*
Main indication	Mild-to-Moderate Anxiety, sleep disorders
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Benzodiazepine-like activity (valerenic acid), inhibition of GABA-T (GABA transaminase), increase of GAD (GABA decarboxylase), inhibition of GABA reuptake
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	250–1000 mg/day of dry extract (iridoids titration 0.5–2%) The title and the standardization of iridoids (0.5–2%) could be important to recognize the most effective extracts
Treatment duration	Symptomatic/Cyclic (usually 30–90 days)
Main expected effect	Improvement of anxiety sypmtoms (latency, quality and duration of sleep) and insomnia
Secundary positive effects	Possible improvement of depressive symptoms, menstrual disorders, restlessness
Possible side effects (for suggested dosages)	Mild headache, excitability (paradoxical effect), nausea, fatigue
Relative controindication	Pregnancy and lactation (valerian irinoids might be mutagens and cytotoxic in pregnancy and lactation)
Possible pharmacokinetic interactions of clinical interest	Sedative medications as benzodiazepines, zolpidem or barbiturates (sleepiness and drowsiness), alcohol (sleepiness and drowsiness), medications substrates of 3A4 (could increase the effectiveness)
Possible additive or synergistic nutraceuticals	Anxiolytic nutraceuticals
Suggested recent bibliography	Leach MJ, Page AT. Sleep Med Rev. 2015; 24:1–12. Becker A et al. BMC Complement Altern Med. 2014; 14:267.

	Vitamin B1 (thiamine)
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Brain function, Wernicke Korsakoff syndrome, heart failure NYHA I-IV, thiamine deficiency
Oral bioavailability	Low (3–7%)
Supposed main mechanism of action	Cofactor in several enzymatic reactions (eg. in the pentose phosphate cycle and in the Krebs cycle) involved in the energy metabolism and in that of carbohydrates and aminoacids
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	20–30 mg/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of brain and heart function
Secundary positive effects	Improvement of cognitve function and dysmenorrhea
Possible side effects (for suggested dosages)	Mild skin irritations
Relative controindication	Pregnancy and lactation (>25 mg/day)
Possible pharmacokinetic interactions of clinical interest	Alcohol (reduction of thiamine bioavailability)
Possible additive or synergistic nutraceuticals	Cognitive function improvers
Suggested recent bibliography	Gibson GE et al. Ann N Y Acad Sci. 2016;1367(1):21–30. Lu J et al. Neurosci Bull. 2015;31(6):676–84.

	Vitamin C (Ascorbic acid)
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild-to-Moderate depression
Oral bioavailability	50–90% (above 1 g may be less than 50%)
Supposed main mechanism of action	Interaction with the monoaminergic system
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	250–1000 mg/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)]

	Vitamin C (Ascorbic acid)
Secundary positive effects	Improvement of vitamin C deficiency, age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption, tyrosinemia
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day), Hemochromatosis, previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, iron, estrogens (vitamin C could increase the effects), fluphenazine, warfarin, protease inhibitors (vitamin C could drecrease the effects)
Possible additive or synergistic nutraceuticals	Multivitamins, Mood improver nutraceuticals
Suggested recent bibliography	Moretti M et al. CNS Drugs. 2017;31(7):571–583. Amr M et al. Nutr J. 2013;12:31.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild-to-Moderate depression, osteopenia
Oral bioavailability	Ergocalciferol (vit. D2) is apparently absorbed with similar efficiency to cholecalciferol (vit. D3), however 25-OH-vitamin D is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol. The amount of fat with which vit. D is ingested does not seem to significantly modify the bioavailability of vit. D3. Hypochlorhydria and achlorhydria decrease vitamin D bioavailability
Supposed main mechanism of action	Interaction with the monoaminergic system
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	400–3000 IU of cholecalciferol /day (400 IU = 10 mcg)
Treatment duration	Long-term
Main expected effect	Improvement of depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)]
Secundary positive effects	Posible improvement of vit. C deficiency, age-related vision loss, common infections, osteoarthritis, physical performance, iron absorption, heart failure symptoms, cognitive decline
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Previous kidney stones

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	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (increased effects), diltiazem, verapamil (decreased efficacy), thiazide diuretics (elevated serum calcium), proton pump inhibitors, sucrose polyesters and tetrahydrolipstatin (diminish vit. D absorption)
Possible additive or synergistic nutraceuticals	Multivitamins, Mood improver nutraceuticals
Suggested recent bibliography	Grimm MO et al. Int J Mol Sci. 2016;17(11). pii: E1785. Annweiler C. Ann N Y Acad Sci. 2016;1367(1):57–63.

	Zinc
Main source	Dietary supplements Main dietary Main sources: fish, red meat, grains, legumes, nuts and seeds, oysters, yeast, milk, mushrooms, cocoa and egg yolk In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild-to-moderate depression
Oral bioavailability	20/40% as single component. Some substances (phytate, iron and cadmium), drugs (diuretics, corticosteroids, MAO inhibitors), alcoholic beverages or pathologies (rheumatoid arthritis, malabsorption syndromes) could reduce its bioavailability
Supposed main mechanism of action	Reversible inhibition of the NMDA (N-methyl-D-aspartate) receptor
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	25 mg/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of depressive symptoms [Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)]
Secundary positive effects	Possible prevention or improvement of eczema, psoriasis, acne vulgaris, degenerative retinal lesions, common respiratory infections, male infertility, attention deficit-hyperactivity disorder (ADHD), Wilson's disease, diarrhea, muscle cramps, prostate swelling, anorexia, diabetes, cognitive decline, inflammatory bowel disease, dental plaque formation and gingivitis
Possible side effects (for suggested dosages)	Mild dose-related nausea, mouth irritation, dysgeusia, mouth sores, diarrhea. An increase in prostate cancer risk has been related to high dosages of long-term zinc supplementation (data to be confirmed)
Relative controindication	None identified for standard dosages Pregnancy (preliminary data)
Possible pharmacokinetic interactions of clinical interest	Zinc may decrease the plasma concentrations of certain drugs (eg. ciprofloxacin, cisplatin, penicillamine, amiloride or tetracycline) and micronutrients (calcium, iron, copper and vitamin A)

	Zinc
Possible additive or synergistic nutraceuticals	Multivitamins, mood improver nutraceuticals
Suggested recent bibliography	Sarris J et al. Am J Psychiatry. 2016; 173(6):575–87. Petrilli MA et al. Front Pharmacol. 2017;8:414.

Nutraceuticals Active on Peripheral Nervous System

	Alpha-lipoic acid
Main source	Dietary supplements
Main indication	Peripheral neuropathies, in particular diabetic neuropathies
Oral bioavailability	Approximately 30%
Supposed main mechanism of action	Antioxidant, improvement of vascularization of the nerve and promoter of axonal sprouting
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–1800 mg/day
Duration of treatment	Subacute/Long-term (depending on the disease)
Main expected effect	Improvement of neuropathic symptoms [visual analogue scale (VAS), Total Symptom Score (TSS) and present pain intensity], paresthesia, strength, paresthesia, tendon reflexes
Secundary positive effects	Improvement of Fasting Plasma Glucose (FPG) Post-prandial glycemia (PPG), HbA1c and insulinemia, cholesterolemia, oxidative stress, reactive oxygen species (ROS), nerve conduction velocity and positive neuropathic symptoms, glucose and ascorbate handling, levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) and endothelial nitric oxide synthase (eNOS) activity, activation of Phase II detoxification via the transcription factor Nrf2, and lower expression of matrix metallopeptidase 9 (MMP-9) and vascular cell adhesion protein 1 (VCAM-1) through repression of NF-kappa-B, reduction of malondialdehyde (MDA), hsCRP (high sensible C reactive protein) and body weight
Possible side effects (for suggested dosages)	Mild to moderate rash, stomach burn
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Chemotherapy (the antioxidant properties of alpha-lipoic acid may reduce chemotherapeutic efficacy), thyroid disease (alpha-lipoic acid might interfere with treatments for under-active or over-active thyroid), excessive consumption of alcohol/thiamine deficiency

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A.F.G. Cicero, A. Colletti, *Handbook of Nutraceuticals for Clinical Use*,
https://doi.org/10.1007/978-3-319-73642-6_2

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	Alpha-lipoic acid
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Cakici N et al. Diabet Med. 2016;33(11):1466–1476. Gerritje SM et al. Int J Endocrinol. 2012; 2012: 456–279.

	Coenzyme Q10
Main source	Dietary supplements
Main indication	Heart failure NYHA-I/IV, diabetic and peripheral neuropathies
Oral bioavailability	Highly variable and not completely determined, but in general: Bioavailability ubiquinol > ubiquinone Bioavailability of powder < suspension < emulsion Bioavailability of particles (mm) < particles (μm) < particles (nm) Bioavailability in fasted state < fed state
Supposed main mechanism of action	Improvement of functionality and dynamism of cardiac-muscle cells, antioxidant activity, sensitizing of Ca^{++} channels, inductor of the synthesis of ATP, reduction of oxidative stress and lipid peroxidation
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	200–400 mg/day
Duration of treatment	Cyclic (at least 3 months)/Long-term (depending on the disease)
Main expected effect	Improvement of neuropathic signs and symptoms
Secundary positive effects	Improvement of migraine, myalgia, fibromyalgia, post-training recovery, left ventricular ejection fraction (LVEF) and left atrial diameter; reduction of Major Adverse Cardiovascular Events (MACE) and mortality in heart failure patients
Possible side effects (for suggested dosages)	Mild stomach upset, loss of appetite, nausea and diarrhea
Relative controindication	Pregnancy and lactation (not enough information available)
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data)
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Akbari FM et al. Int J Vitam Nutr Res. 2014; 84(5–6):252–60. Zhang YP et al. Proc Natl Acad Sci USA. 2013;110(2):690–5.

	Curcumin
Main source	*Curcuma longa*
Main indication	Inflammatory or diabetic neuropathies
Oral bioavailability	Very low (< 1%)

	Curcumin
Supposed main mechanism of action	Reduction of tumor necrosis factor-α (TNF-α) levels, inhibition of nuclear factor-kappa B (NF-κB) activation and protein carbonyl, lipid peroxidation and lysosomal enzyme activities (N-acetyl-β-d-glucosaminidase, β-d-glucuronidase, β-d-galactosidase), induction of peroxisome proliferator-activated receptor-gamma (PPAR-γ) and nuclear factor erythroid-2-related factor-2 (Nrf2) activations.
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	Curcumin: >1 g/day (usually 1.5 g/day) Curcumin in specific pharmaceutical forms (for instance: micelles or nanoemulsions): >400/500 mg/day
Duration of treatment	Cyclic (usually 30–90 days)/Long-term (depending on the disease)
Main expected effect	Improvement of symptoms related to inflammatory or diabetic neuropathies
Secundary positive effects	Improvement of plasma vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-alpha), interleukins (IL-23,-17,-1β,-4), glutathione and NrF-2 concentrations, improvement of arthritis, gastritis, irritable bowel syndrome, inflammatory bowel diseases, fibromyalgia, cognitive function, improvement of depressive symptoms [Hamilton Depression Rating Scale (HAM-D)] and reduction of serum and salivary stress markers such as cortisol and interleukins
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps and/or upset, diarrhea, dizziness
Relative controindication	Pregnancy and lactation (only as dietary supplement), Gilbert's disease or gallbladder problems, infertility, iron deficiency, bleeding problems, hormone-sensitive conditions (breast cancer, uterine cancer, ovarian cancer, uterine fibroids or endometriosis)
Possible pharmacokinetic interactions of clinical interest	Inhibition of CYP450 (in particular CYP2C9) Possible interactions with anticoagulant and antiplatelet drugs (aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin), diclofenac, ibuprofen, naproxen and other NSAIDs.

Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Shehzad A et al. J Food Sci. 2017;82(9):2006–2015. Jeenger MK et al. Nutrition. 2015; 31(2):276–82.

	L-acetylcarnitine
Main source	Dietary supplements
Main indication	Diabetic and peripheral neuropathies
Oral bioavailability	14–20%

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	L-acetylcarnitine
Supposed main mechanism of action	Synthesis induction of the nerve growth factor (NGF), regeneration and prevention of peripheral nervous system P loss, modulation of cholinergic and glutamatergic system.
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	> 500 mg/day
Duration of treatment	Cyclic (at least 3 months)/Long-term (depending on the disease)
Main expected effect	Improvement of neuropathic symptoms [visual analogue scale (VAS), Total Symptom Score (TSS) and present pain intensity], paresthesia, strength, paresthesia, tendon reflexes
Secundary positive effects	Improvement of Peyronie's disease, male infertility, age-related testosterone deficiency, cognitive functions
Possible side effects (for suggested dosages)	Stomach upset, nausea, and restlessness, "fishy" odor of the urine, breath, and sweat
Relative controindication	Pregnancy and lactation (not enough data available in humans), hypothyroidism (preliminary data)
Possible pharmacokinetic interactions of clinical interest	Warfarin, Acenocoumarol (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Youle M et al. HIV Med. 2007; 8(4):241–50. Sima AA et al. Diabetes Care. 2005; 28(1):89–94.

	Omega-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Dietary supplements derived from Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*) In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Degenerative and toxic neuropathies, especially in subjects with increased cardiovascular disease risk or hypetriglyceridemia
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Inhibiting the activation of NF-kB and the release of IL-1β and TNF-α
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	2–6 g/day of eicosapentanoic and/or docosahexaenoic acid
Duration of treatment	Cyclic (1–4 months)/Long-term (depending on the disease)
Main expected effect	Prevention against drug-induced peripheral neuropathy
Secundary positive effects	Reduction of articular pain, morning stiffness and of the number of joint pain, cardiovascular prevention and anti-proarrhytmic effects, macula protection, brain protection, mood stabilization

	Omega-3 Polyunsaturated Fatty Acids (EPA/DHA)
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Warfarin (Dose-related increase in bleeding time)
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Yorek MA. Curr Diabetes Rev. 2017; doi: https://doi.org/10.2174/1573399813666170522155327. Ghoreishi Z et al. BMC Cancer. 2012; 12:355.

	Palmitoylethanolamide (PEA)
Main source	Dietary supplements
Main indication	Peripheral, diabetic or chemioterapic neuropathies, carpal tunnel syndrome
Oral bioavailability	Low PEA is a poorly water-soluble substance and the dissolution rate is often the rate-limiting step for oral absorption and bioavailability. Micronized PEA is one of the most bioavailable forms on the market.
Supposed main mechanism of action	Affinity for cannabinoid-like G-coupled receptors GPR55 and GPR119, agonist of peroxisome proliferator-activated receptor alpha (PPAR-α), Cox-2 inhibition
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>600 mg/day
Duration of treatment	Cyclic (usually 30–90 days)/Long-term (depending on the disease)
Main expected effect	Improvement of neuropathic symptoms [visual analogue scale (VAS) and present pain intensity], paresthesia, strength and neurological objectivity
Secundary positive effects	Improvement of joint movements and reduction of pain and inflammation
Possible side effects (for suggested dosages)	Mild gastrointestinal discomfort and diarrhea
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Conigliaro R et al. CNS Neurol Disord Drug Targets. 2011;10(8):916–20. Gabrielsson L et al. Br J Clin Pharmacol. 2016;82(4):932–42.

	Vitamin B1 (thiamine)
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Brain function, Wernicke Korsakoff syndrome, heart failure NYHA I-IV, thiamine deficiency, diabetic, alcoholic and peripheral neuropathies
Oral bioavailability	Low (3–7%)
Supposed main mechanism of action	Cofactor in several enzymatic reactions (eg. in the pentose phosphate cycle and in the Krebs cycle) involved in the energy metabolism and in that of carbohydrates and aminoacids
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	50–300 mg/day
Duration of treatment	Cyclic (usually 30–90 days)/Long-term (depending on the disease)
Main expected effect	Improvement of neuropathic symptoms [visual analogue scale (VAS) and present pain intensity], paresthesia, strength, paresthesia, tendon reflexes
Secundary positive effects	Improvement of brain and heart function [Left Ventricular Ejection Fraction (LVEF)], cognitive function and dysmenorrhea
Possible side effects (for suggested dosages)	Mild skin irritations
Relative controindication	Pregnancy and lactation (>25 mg/day)
Possible pharmacokinetic interactions of clinical interest	Alcohol (reduction of thiamine bioavailability)
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Várkonyi T et al. Minerva Med. 2017;108(5):419–437. Ang CD et al. Cochrane Database Syst Rev. 2008;3:CD004573.

	Vitamin B1, B2, B6, B9, B12 (in combination)
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Deficiency neuropathies, diabetic and alcoholic neuropathies
Oral bioavailability	B1: 3–7% B2: 95% B6: 75% B9: 30–98% B12: highly variable depending on the presence of intrinsic factor of stomach, dosage administered and Main source of extraction
Supposed main mechanism of action	Resolving shortage

	Vitamin B1, B2, B6, B9, B12 (in combination)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	250–750 mg B1, 10–30 mg B2, 90–750 mg B6, 0,4–3 mg B9, 30–75 mcg/die
Treatment duration	Cyclic (at least 1 month)/Long-term (depending on the disease)
Main expected effect	Improvement of neuropathic symptoms [visual analogue scale (VAS) and present pain intensity], paresthesia, strength, paresthesia, tendon reflexes
Secundary positive effects	The pleiotropic activities of group B vitamins are described individually in the various chapters
Possible side effects (for suggested dosages)	Restlessness, nausea and insomnia
Relative controindication	Pregnancy and lactation (high dosages of vitamins B1 and B6)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Várkonyi T et al. Minerva Med. 2017;108(5):419–437. Peters TJ et al. Alcohol Alcohol. 2006;41(6):636–42.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Peripheral or diabetic neuropathies associated with a plasma vitamin D deficiency, osteopenia
Oral bioavailability	Ergocalciferol (vitamin D2) is apparently absorbed with similar efficiency to cholecalciferol (vitamin D3) 25-hydroxyvitamin D (25OHD) is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol The amount of fat with which vitamin D is ingested does not seem to significantly modify the bioavailability of vitamin D3 Hypochlorhydria decreases vitamin D bioavailability
Supposed main mechanism of action	Not definitively determined
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–3000 IU of cholecalciferol /day (400 IU = 10 mcg)
Duration of treatment	Cyclic (usually 30–90 days)/Long-term (depending on the disease)
Main expected effect	Improvement of signs and symptoms

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	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Secundary positive effects	Improvement of vitamin C deficiency, depressive symptoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption, tyrosinemia symptoms
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Haemocromatosis, previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (vitamin D could increase the effects), diltiazem, verapamil, (vitamin D could decrease the effects) thiazide diuretics (elevated serum calcium), proton pump inhibitors, sucrose polyesters and tetrahydrolipstatin (probably diminish vitamin D absorption)
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Shehab D et al. Med Princ Pract. 2015;24(3):250–6. Agmon-Levin N et al. J Autoimmun. 2012;39(3):234–9.

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Diabetic and peripheral neuropathies
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant and neurotrophic activity
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	600–900 mg/day
Duration of treatment	Cyclic (at least 4 months)/Long-term (depending on the disease)
Main expected effect	Improvement of neuropathic signs and symptoms
Secundary positive effects	Improvement of cholesterolemia, arterial stiffness, endothelial function (reduction of the serum levels of hsCRP, advanced glycation end products, metalloproteinases and cell adhesion molecules) and oxidative stress
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation, bleeding disorders, head and neck cancer, prostate cancer, heart attack, stroke, angioplasty and diabetes

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Possible pharmacokinetic interactions of clinical interest	Warfarin (risk of bleeding), cyclosporine (Vitamin E might enhance the bioavailability of this drug), medications substrate of CYP450 (Vitamin E might enhance the hepatic clearance)
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	Salehi Z, Roayaei M. Int J Prev Med. 2015;6:104. Manzella D et al. Am J Clin Nutr. 2001; 73(6):1052–7.

Nutraceuticals Active on Heart Function

	Beetroot and organic nitrates
Main source	*Beta vulgaris* Organic nitrates dietary supplements
Main indication	NYHA I-IV heart failure, Mild-to-moderate hypertension
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Nitric oxide (NO) donor
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	10–13 mmol of NO_3^- The title and the extract standardization are important requirements for the effectiveness
Treatment duration	Long-term
Main expected effect	Improvement of exercise performance [Six-Minute Walking Distance (6MWD)], reduction of blood pressure and heart failure symptoms
Secundary positive effects	Improvement of arterial stiffness
Possible side effects (for suggested dosages)	Halytosis, nausea, smelly transpiration, diarrhea
Relative controindication	Pregnancy and lactation (few data available at high dosages)
Possible pharmacokinetic interactions of clinical interest	NO donor drugs (eg. Nitroglycerin and isosorbide) and antihypertensive drugs
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals
Suggested recent bibliography	Lara J et al. Eur J Nutr. 2016;55(2):451–459. Siervo M et al. J Nutr. 2013;143(6):818–26.

	L-carnosine
Main source	Dietary supplements
Main indication	NYHA I-IV heart failure
Oral bioavailability	Definitive data not available in humans L-carnosine is absorbed in the intestine by a peptide transporter (PEPT): increasing the dosages and saturated the transporters, bioavailability decreases

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https://doi.org/10.1007/978-3-319-73642-6_3

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	L-carnosine
Supposed main mechanism of action	Improvement of functionality and dynamism of cardiac-muscle cells, antioxidant activity, sensitizing of Ca^{++} channels, Na/K-ATPase activation and prevention of membrane depolarization, reduction of oxidative stress, plasma levels of proinflammatory cytokines and synthesis of fibronectin and type IV collagen
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	500–1000 mg/day
Treatment duration	Long-term
Main expected effect	Improvement of functional capacity, left ventricular ejection fraction (LVEF) and quality of life (EQ-5D test and VAS score)
Secundary positive effects	Improvement of exercise performance [Six-Minute Walking Distance (6MWD)], muscle contractility and reduction of fatigue
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals
Suggested recent bibliography	Lombardi C et al. Clin Med Insights Cardiol. 2014;8:39–44. McCarty MF, Di Nicolantonio JJ. Open Heart. 2014;1(1): e000119.

	Coenzyme Q10
Main source	Dietary supplements
Main indication	NYHAI-IV heart failure
Oral bioavailability	Highly variable and not completely determined but in general: Bioavailability ubiquinol > ubiquinone Bioavailability of powder < suspension < emulsion Bioavailability of particles (mm) < particles (μm) < particles (nm) Bioavailability in fasted state < fed state
Supposed main mechanism of action	Improvement of functionality and dynamism of cardiac-muscle cells, antioxidant activity, sensitizing of Ca^{++} channels, inductor of the synthesis of ATP, reduction of oxidative stress and lipid peroxidation
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	>200 mg/day
Treatment duration	Long-term

	Coenzyme Q10
Main expected effect	Improvement of left ventricular ejection fraction (LVEF) and left atrial diameter Reduction of Major Adverse Cardiovascular Events (MACE) and mortality
Secundary positive effects	Improvement of migraine, myalgia, fibromyalgia, post-training recovery
Possible side effects (for suggested dosages)	Mild stomach upset, loss of appetite, nausea and diarrhea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data)
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals
Suggested recent bibliography	Mortensen SA et al. JACC Heart Fail. 2014;2(6):641–9. Fotino AD et al. Am J Clin Nutr 2013;97:268–75.

	D-ribose
Main source	Dietary supplements
Main indication	NYHAI-IV heart failure
Oral bioavailability	88–100%
Supposed main mechanism of action	Inducer of the synthesis of ATP
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	5–10 g/day
Treatment duration	Long-term
Main expected effect	Improvement of tissue Doppler velocity (E'), ratio of early diastolic filling velocity (E) to early annulus relaxation velocity (E') and maximum predicted VO2 values
Secundary positive effects	Improvement of myoadenylate deaminase deficiency, athletic performance
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps, headache, diarrhea, hypoglicemia
Relative controindication	Pregnancy and lactation (>1.8–2 g/day)
Possible pharmacokinetic interactions of clinical interest	Antidiabetes drugs (D-ribose increases the hypoglicemic effect)
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals
Suggested recent bibliography	Cicero AFG, Colletti A. Curr Pharm Des. 2017;23(8): 1265–72. Bayram M et al. Ther Adv Cardiovasc Dis. 2015;9(3):56–65.

	Essential amino acids
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of these nutraceuticals.
Main indication	NYHA-I/IV heart failure
Oral bioavailability	Variable: increasing the dosages and saturated the transporters, bioavailability decreases
Supposed main mechanism of action	Improvement of functionality and dynamism of cardiac-muscle cells, sensitizing of Ca^{++} channels, Na/K-ATPase activation and prevention of membrane depolarization
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	20–30 g/day
Treatment duration	Cyclic (30–90 days)
Main expected effect	Improvement of functional capacity, left ventricular ejection fraction (LVEF) and quality of life (EQ-5D test and VAS score)
Secundary positive effects	Improvement of exercise performance [Six-Minute Walking Distance (6MWD)], muscle contractility and reduction of fatigue
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Levodopa (reduction of drug bioavailability)
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals
Suggested recent bibliography	Cicero AFG, Colletti A. Curr Pharm Des. 2017;23(8):1265–72. McCarty MF, Di Nicolantonio JJ. Open Heart. 2014;1(1): e000119.

	Hawthorn
Main source	*Crataegus monogyna, Crataegus oxyacantha*
Main indication	NYHA-I/II heart failure
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Positive inotropic effect, inhibition of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), activation of Inositol 1,4,5-triphosphate (IP3) pathway benzodiazepine-like activity
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–1200 mg/day of dry extract (oligomeric procyanidins 15–20%) The title and the standardization of oligomeric procyanidins (15–20%) could be important to recognize the most effective extracts
Treatment duration	Long-term

	Hawthorn
Main expected effect	Improvement of maximal workload (MWL), left ventricular ejection fraction (LVEF) and pressure-heart rate product increase (PHRPI) at 50 W ergometric exercise Improvement of typical symptoms like reduced exercise tolerance, shortness of breath, exertional dyspnea, weakness, fatigue, and palpitations
Secundary positive effects	Improvement of anxiety [Hamilton Anxiety Rating Scale (HAM-A)], insomnia, high blood pressure
Possible side effects (for suggested dosages)	Mild headache, dizziness, stomach upset, sweating, nausea, fatigue, palpitations, insomnia, agitation (paradoxical effect)
Relative controindication	Pregnancy and lactation (not enough information available), heart disease (hawthorn could interact with many prescription drugs: its prescription it must be made only by healthcare providers)
Possible pharmacokinetic interactions of clinical interest	Digoxin, beta-blockers, calcium channel blockers, phosphodiesterase-5-inhibitors, sildenafil, tadalafil, vardenafil: it increases the pharmacological effects. Nitrates: hawthorn could increase the risk of dizziness and lightheadedness
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals
Suggested recent bibliography	Orhan IE. Curr Med Chem. 2016 Sep 18. [Epub ahead of print] Eggeling T et al. Phytomedicine. 2011;18(14):1214–9.

	Iron
Main source	Red meat, White meat, Eggs, Spinach In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Iron deficiency, anemia, coughts caused ACE inhibitors, learning problems, heart failure (30–50% of subjects with Long-term heart failure have iron deficiency)
Oral bioavailability	1–25% of nonheme iron, > in fasted state Calcium, copper, manganese, phosphorous, phytates, fibers and alcohol migh decrease its bioavailability, while Vitamin C can improve it
Supposed main mechanism of action	Constituent of hemoglobin and myoglobin, cofactor in several enzymatic reactions
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	10–100 mg/day of elemental iron
Main expected effect	Improvement of anemia
Secundary positive effects	Improvement of exercise capacity, heart failure symptoms, left ventricular ejection fraction, quality of life, depressive symptoms [Edinburgh Postnatal Depression Scale], coughts caused by ACE-inhibitors, attention deficit-hyperactivity disorder (ADHD)

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	Iron
Possible side effects (for suggested dosages)	Diarrhea, constipation, stomach upset, nausea Side effects could be mitigated if the iron is taken with food or with polysaccharides or enteric coated complex: however, in the fed state the bioavailability of this micronutrient is considerably reduced.
Relative controindication	Pregnancy and lactation (>50 mg/day few data available), stomach/intestinal ulcers, intestinal inflammation (iron might increase these conditions), Hemochromatosis
Possible pharmacokinetic interactions of clinical interest	Levodopa, methyldopa, levotyroxine, mycophenolate mofetil, quinolone, penicillamine and tetracycline antibiotics and bisphosphonates (drecreased drug effectiveness)
Possible additive or synergistic nutraceuticals	Multimineral supplements, heart function improving nutraceuticals
Suggested recent bibliography	Pozzo J et al. Arch Cardiovasc Dis. 2017;110(2):99–105. von Hardenberg A, Maack C. Handb Exp Pharmacol. 2017; 243:491–514.

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Main source	Dietary supplements Dairy products and derivatives
Main indication	NYHA-I/II heart failure, intestinal dysbiosis
Oral bioavailability	*Lactobacilli* and *Bifidobacteria* colonize the intestinal lumen *Saccharomyces* it's a fermenter yeast, but does not colonize the intestinal lumen In order to obtain the maximum effectiveness, probiotics should be taken before the main meal with a lipid vehicle (eg. yogurt or milk).
Supposed main mechanism of action	Modulation of HPA (hypothalamic–pituitary–adrenal) axis, restore intestinal eubiosis and reduction of systemic inflammatory markers [eg. Trimethylamine N-oxide (TMAO), high-sensitivity C-reactive protein (hs-CRP)]
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>3.5 UFC (live)/day
Treatment duration	Long-term
Main expected effect	Reduction of plasma TMAO, uric acid and hs-CRP levels, improvement of left ventricular ejection fraction (LVEF) and left atrial diameter
Secundary positive effects	Improvement of mood, depressive symptoms and anxiety [Improvement of Leiden Index of Depression Sensitivity (LEIDS-r), Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D)], bowel health, regulation of cholesterolemia, blood pressure, immune system, chemoprevention, prevention of urinary infections and improvement of its symptoms (eg. burning, pain)
Possible side effects (for suggested dosages)	Mild and transient gastrointestinal side effects

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Relative controindication	Heart function improving nutraceuticals
Possible pharmacokinetic interactions of clinical interest	Not determined: it is possible that probiotics interfere with the molecules subject to intestinal enzymatic metabolism (eg. polyphenols, berberine)
Possible additive or synergistic nutraceuticals	Prebiotics
Suggested recent bibliography	Costanza AC et al. Int J Cardiol. 2015;179:348–50. Wilson TW et al. J Am Coll Cardiol. 2014;64(18):1908–14.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*) In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of these nutraceuticals.
Main indication	NYHA-I/IV heart failure, especially in patients with hypertriglyceridemia
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > re-esterified triglycerides > free fatty acids > ethyl esters
Supposed main mechanism of action	Improvement of functionality and dynamism of cardiac-muscle cells, decrease of synthesis and release of inflammatory cytokines
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	1–6 g/day of eicosapentanoic and/or docosahexaenoic acid The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Treatment duration	Long-term
Main expected effect	Improvement of membrane viscosity, left ventricular ejection fraction (LVEF) and left atrial diameter, reduction of Brain Natriuretic Peptide (BNP) plasma levels
Secundary positive effects	Cardiovascular disease prevention, antiproarrhytmic effect, antinflammatory effect, macula protection, brain protection, mood stabilization
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time
Relative controindication	Use of anticoagulants
Possible pharmacokinetic interactions of clinical interest	Warfarin (possible increasing effect for use of high dosages)
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals, Lipid-lowering nutraceuticals
Suggested recent bibliography	Watanabe Y, Tatsuno I. Expert Rev. Clin Pharmacol. 2017;10(8): 865–873. Wen YT et al. Nutr Metab Cardiovasc Dis. 2014;24(5):470–5.

	Vitamin B1 (thiamine)
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Brain function, Wernicke Korsakoff syndrome, NYHA I-IV heart failure, thiamine deficiency
Oral bioavailability	Low (3–7%)
Supposed main mechanism of action	Cofactor in several enzymatic reactions (eg. in the pentose phosphate cycle and in the Krebs cycle) involved in the energy metabolism and in that of carbohydrates and aminoacids
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	20–30 mg/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of brain and heart function [Left Ventricular Ejection Fraction (LVEF)]
Secundary positive effects	Improvement of cognitve function and dysmenorrhea
Possible side effects (for suggested dosages)	Mild skin irritations
Relative controindication	Pregnancy and lactation (>25 mg/day)
Possible pharmacokinetic interactions of clinical interest	Alcohol (reduction of thiamine bioavailability)
Possible additive or synergistic nutraceuticals	Multivitamins, heart function improving nutraceuticals
Suggested recent bibliography	Wong AP et al. Am J Cardiovasc Dis. 2016;6(3):81–92. Jain A et al. J Card Fail. 2015;21(12):1000–7.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	NYHAI-IV heart failure, osteopenia
Oral bioavailability	Ergocalciferol (vit. D2) is apparently absorbed with similar efficiency to cholecalciferol (vit. D3), however 25-hydroxyvitamin D (25OHD) is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol. The amount of fat with which vit. D is ingested does not seem to significantly modify the bioavailability of vit. D3. Hypochlorhydria and achlorhydria decrease vitamin D bioavailability
Supposed main mechanism of action	Inhibition of angiotensin II receptors
Level of support	Randomized clinical trials
Population tested	Adults, elderly

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Dose ranges	400–3000 IU of cholecalciferol /day (400 IU = 10 mcg)
Treatment duration	Long-term
Main expected effect	Improvement of left ventricular ejection fraction (LVEF), Tumor Necrosis Factor (TNF)-alpha, plasma levels of 25-hydroxyvitamin D
Secundary positive effects	Improvement of depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], vitamin C deficiency, age-related vision loss, albuminuria, osteoarthritis, physical performance, and iron absorption, immunostimulation
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, headache and severe diarrhea
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (increased effects), diltiazem, verapamil (decreased efficacy), thiazide diuretics (elevated serum calcium), proton pump inhibitors, sucrose polyesters and tetrahydrolipstatin (diminish vit. D absorption)
Possible additive or synergistic nutraceuticals	Multivitamins, heart function improving nutraceuticals
Suggested recent bibliography	Trehan N et al. Crit Pathw Cardiol. 2017;16(3):109–118. Jiang WL et al. Clin Cardiol. 2016;39(1):56–61.

Nutraceuticals Active on Blood Pressure

	Beetroot
Main source	*Beta vulgaris and organic nitrates*
Main indication	High blood pressure
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Improvement of endothelial nitric oxide (NO) availability
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	250 ml of beetroot juice (10–12 mmol of NO3)
Treatment duration	Long-term
Main expected effect	Reduction of systolic (5–15 mmHg) and diastolic (3–10 mmHg) blood pressure
Secundary positive effects	Improvement of endothelial function [flow-mediated dilation (FMD)] and arterial stiffness [augmentation index (AI), pulse wave velocity (PWV)], exercise performance
Possible side effects (for suggested dosages)	Halytosis, nausea, smelly transpiration, diarrhea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals, blood pressure lowering nutraceuticals
Suggested recent bibliography	Ashor AW et al. J Hypertens. 2017;35(7):1353–1359. Siervo M et al. Nitric Oxide. 2015;47:97–105.

	Calcium
Main source	Milk, yogurt, and fortified foods In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Hypocalcemia with or without mild hypertension, pre-eclampsia

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https://doi.org/10.1007/978-3-319-73642-6_4

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	Calcium
Oral bioavailability	5–50% Bioavailability is variable, depending on the kind of fortified foods and not only by the content of calcium per unit [eg. spinach (115 mg Ca/125 ml) 5% vs bok choy (79 mg Ca/125 ml) 50/55% vs cheddar cheese (300 mg Ca/40 g) 32%]. The best-absorbed form of calcium are salts like carbonate (in fed state) or phosphate (in fed/fasted state). Calcium gluconate and lactate are absorbed well by pregnant women also in fasted state. Hypochlorhydria decreases calcium bioavailability. Vitamin D, sugars (in particular lactose), some amino acids (lysine, arginine) and increase of the intraluminal pH may increase calcium bioavailability
Supposed main mechanism of action	Calcium plays a key role in physiology and biochemistry of the cell, particularly in signal transduction pathways
Level of support	Meta-analysis of randomized clinical trials
Population tested	Pregnant women
Dose ranges	500–3000 mg/day
Treatment duration	Long-term
Main expected effect	Improvement of calcemia and blood pressure (pregnant women only)
Secundary positive effects	Improvement of hyperkalemia, osteopenia, premenstrual syndrome, hyperparathyroidism
Possible side effects (for suggested dosages)	Mild stomach upset, belching or bloating, nausea, diarrhea
Relative controindication	Pregnancy and lactation (not enough information available with high dosages), hyperphosphatemia or hypophosphatemia, hypothyroidism, poor kidney function, hypercalcemia
Possible pharmacokinetic interactions of clinical interest	Ceftriaxone (increased toxicity), quinolone and tetracycline antibiotics, bisphosphonates, L-thyroxine, sotalol, calcium channel blockers (reduced effectiveness), calcipotriene, estrogens and thiazide diuretics (increased risk of hypercalcemia), digoxin (reduced therapeutic range)
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	An LB et al. Int J Nurs Pract. 2015;21 Suppl 2:19–31. Hofmeyr GJ et al. Cochrane Database Syst Rev. 2014;6:CD001059.

	Cocoa and dark chocolate
Main source	*Theobroma cacao L.*
Main indication	Mild-to-moderate depression, Cognitive decline and high blood pressure

	Cocoa and dark chocolate
Oral bioavailability	The bioavailability of polyphenols is widely variable: cold roasted cocoa > hot roasted cocoa and cold chocolate cold worked > dark chocolate hot worked Detary fat intake, form and dose ingested, gut transit time, fecal degration rate and intestinal eubiosis could also influence the bioavailability of cocoa-polyphenols
Supposed main mechanism of action	Improvement of nitric oxide (NO) endothelial concentrations, reduction of oxidative stress
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	250–1000 mg/day of dry extract total polyphenols The title and the standardization of total flavonoids could be important to recognize the most effective extracts
Treatment duration	Long-term
Main expected effect	Reduction of systolic (2–10 mmHg) and diastolic (1–5 mmHg) blood pressure
Secundary positive effects	Improvement of blood pressure, insulin-resistance, arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)], cognitive function and mood
Possible side effects (for suggested dosages)	Mild-gastrointestinal side effects
Relative controindication	Gastroesophageal reflux disease (GERD), migraine
Possible pharmacokinetic interactions of clinical interest	Adenosine (antagonism effect), clozapine, phenylpropanolamine, theophylline, MAO inhibitors (improvement of the effects), ergotamine (improvement of caffeine-cocoa availability), estrogens (reduction of caffeine-cocoa availability), litium (improvement of bioavailability)
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	Ried K et al. Cochrane Database Syst Rev. 2017;4:CD008893. Cicero AF, Colletti A. High Blood Press Cardiovasc Prev. 2015;22(3):203–13.

	Coenzyme Q10
Main source	Dietary supplements
Main indication	High blood pressure, NYHA-I/IV heart failure
Oral bioavailability	Highly variable and not completely determined but in general: Bioavailability ubiquinol > ubiquinone Bioavailability of powder < suspension < emulsion Bioavailability of particles (mm) < particles (μm) < particles (nm) Bioavailability in fasted state < fed state
Supposed main mechanism of action	Improvement of functionality and dynamism of cardiac-muscle cells, antioxidant activity, sensitizing of Ca^{++} channels, inductor of the synthesis of ATP, reduction of oxidative stress and lipid peroxidation

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	Coenzyme Q10
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	> 200 mg/day
Treatment duration	Long-term
Main expected effect	Improvement of left ventricular ejection fraction (LVEF) and left atrial diameter Reduction of Major Adverse Cardiovascular Events (MACE) and mortality
Secundary positive effects	Improvement of blood pressure (in hypertensive patients), migraine, myalgia, fibromyalgia, post-training recovery
Possible side effects (for suggested dosages)	Mild stomach upset, loss of appetite, nausea, diarrhea
Relative controindication	Pregnancy and lactation (not enough information available)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals, Blood pressure lowering nutraceuticals
Suggested recent bibliography	Ho MJ et al. Cochrane Database Syst Rev. 2016;3:CD007435. Mortensen SA et al. JACC Heart Fail. 2014;2(6):641–9.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*) In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of these nutraceuticals.
Main indication	Cardiovascular disease prevention and hypertriglyceridemia
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Decreased synthesis and release of inflammatory cytokines, activation of endothelial NO synthase, increased synthesis of vasodilating prostaglandins, insulin-resistance reduction, vascular tone regulation by parasympathetic nervous system stimulation, and suppression of the renin–angiotensin–aldosterone system
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	2–4 g/day of eicosapentanoic and/or docosahexaenoic acid The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Treatment duration	Long-term
Main expected effect	Dose-dependent reduction of plasma triglycerides and blood pressure (1–5 mmHg, both systolic and diastolic one)

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Secundary positive effects	Improvement of arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)], anti-proarrhytmic and antinflammatory effects, macula protection, brain protection, mood stabilization
Possible side effects (for suggested dosages)	Mild aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Warfarin (possible increasing effect for use of high dosages)
Possible additive or synergistic nutraceuticals	Heart function improving nutraceuticals, Blood pressure lowering nutraceuticals, Lipid-lowering nutraceuticals
Suggested recent bibliography	Wen YT et al. Nutr Metab Cardiovasc Dis. 2014;24(5):470–5. Pase MP et al. Br J Nutr. 2011;106:974–80.

	Garlic
Main source	*Allium sativum*
Main indication	High blood pressure
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Improvement of nitric oxide (NO), H2S and bradykinin production, Angiotensin-converting enzyme (ACE) inhibition, calcium channel blocking, reduction of catecholamine sensitivity.
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	600–900 mg/day The title and the standardization of S-allylcysteine and ajoene (0.4–1%) could be important to recognize the most effective extracts
Treatment duration	Long-term
Main expected effect	Reduction of systolic (10–15 mmHg) and diastolic (8–10 mmHg) blood pressure
Secundary positive effects	Improvement of sexual dysfunction, arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)]
Possible side effects (for suggested dosages)	Halytosis, aftertaste. heartburn, bloating, nausea, smelly transpiration, diarrhea, mild risk of bleeding
Relative controindication	Pregnancy and lactation (at high dosages not enough data available), bleeding disorder, stomach or digestion problems, low blood pressure
Possible pharmacokinetic interactions of clinical interest	Isoniazid (garlic could reduce its absorption), Non-Nucleoside Reverse Transcriptase Inhibitors, birth control pills, cyclosporine and saquinavir (garlic might decrease their effectiveness), medications CYP2E1 substrates as acetaminophen, chlorzoxazone, theophylline (garlic is a CYP2E1 inhibitor), medications CYP3A4 substrates as some statins, azole antifungines, fexofenadine, triazolam (garlic is a CYP3A4 inducer), anticoagulant/antiplatelet drugs (garlic might increase their effectiveness), NSAIDs (garlic might increase their antiaggregant effects)

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	Garlic
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	Schwingshackl L et al. Phytomedicine. 2016;23(11):1127–33. Xiong XJ et al. Phytomedicine. 2015;22(3):352–61.

	L-arginine
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	High blood pressure, preeclampsia management
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Nitric oxide donator, modulation of HPA (hypothalamic–pituitary–adrenal) axis, 5-HT4 (5-hydroxytryptamine 4) receptor antagonist
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, pregnant women
Dose ranges	4–24 g/day
Treatment duration	Long-term, preeclampsia duration
Main expected effect	Reduction of systolic (5–10 mmHg) and diastolic (2–5 mmHg) blood pressure
Secundary positive effects	Improvement of anxiety, athletic performance, arterial stiffness, heart failure, erectile dysfunction and male infertility
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects (diarrhea and stomach cramps)
Relative controindication	Pregnancy and lactation (not enough data available in humans) Kidney disease, recent heart attack
Possible pharmacokinetic interactions of clinical interest	Nitrates (increases blood flow, dizziness and lightheadedness), hypotensive drugs (eg. captopril, analapril, losartan, valsartan, diltiazem, amlodipine, furosemide), sildenafil
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	Dong JY et al. Am Heart J. 2011;162(6):959–65. Dorniak-Wall T et al. J Hum Hypertens. 2014;28(4):230–5.

	Lactotripeptides (Isoleucine-Proline-Proline/ Valine-Proline-Proline)
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of these nutraceuticals.
Main indication	Mild hypertension
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Angiotensin Converting Enzyme (ACE) inhibition

	Lactotripeptides (Isoleucine-Proline-Proline/ Valine-Proline-Proline)
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	10–100 mg/day
Treatment duration	Long-term
Main expected effect	Reduction of systolic (1–6 mmHg) and diastolic (1–5 mmHg) blood pressure in Caucasians, significantly more evident in Asian subjects
Secundary positive effects	Improvement of arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)]
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects (diarrhea and stomach cramps)
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	Chanson-Rolle A et al. PLoS One. 2015;10(11):e0142235. Cicero AF et al. Am J Hypertens. 2013;26(3):442–9.

	Lycopene
Main source	Tomato In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild hypertension
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant, free radical scavenger
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	10–40 mg/day
Treatment duration	Long-term
Main expected effect	Reduction of systolic (1–10 mmHg) and diastolic (1-s3 mmHg) blood pressure
Secundary positive effects	Mild improvement of cholesterolemia, positive effects on benign prostate hypertrophy
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	Li X, Xu J. Nutrients. 2013;5(9):3696–712. Ried K, Fakler P. Maturitas. 2011;68:299–310.

	Magnesium
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	High blood pressure
Oral bioavailability	20–50%. Calcium, iron, copper, manganese, phosphorous and alcohol might decrease its bioavailability. Magnesium aspartate, citrate, chloride and lactate are more bioavailable than magnesium hydroxide, oxide, and sulfate
Supposed main mechanism of action	Calcium-channel blocking action, prostaglandin-E increase and nitric oxide synthesis improvement, antagonist of N-methyl-D-aspartate (NMDA) receptor and modulation of hypothalamic–pituitary–adrenal axis; Cofactor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis, responsible of several processes including hormone receptor binding, muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability, neurotransmitter release
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–1500 mg/day
Treatment duration	Long-term
Main expected effect	Reduction of systolic (3–6 mmHg) and diastolic (2–5 mmHg) blood pressure
Secundary positive effects	Improvement of depressive symptoms, attention deficit-hyperactivity disorder, chronic fatigue syndrome, premenstrual syndrome, myalgia, cramps, headache, fibromyalgia, osteoporosis, high blood pressure
Possible side effects (for suggested dosages)	Mild diarrhea, stomach upset, nausea, heartbeat
Relative controindication	Pregnancy (>350 mg/day), kidney failure
Possible pharmacokinetic interactions of clinical interest	Per large doses with quinolone and antibiotics and bisphosphonates (decreased drug effectiveness), calcium channel blockers (increased drugs effect), muscle relaxants (increased risk of side effects], potassium sparing diuretics (risk of hypermagnesemia)
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	Zhang X et al. Hypertension. 2016;68(2):324–33. Houston MC. J Clin Hyperten. 2011;13:843–7.

	Melatonin (5-Methoxy-N-Acetyltryptamine)
Main source	Dietary supplements
Main indication	Insomnia, nocturnal high blood pressure
Oral bioavailability	30–50%
Supposed main mechanism of action	Melatonin receptors (MT1, MT2) agonist, improvement of NO metabolism and endothelial function

	Melatonin (5-Methoxy-N-Acetyltryptamine)
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1–10 mg/day
Treatment duration	Long-term
Main expected effect	Reduction of night systolic (5–10 mmHg) and diastolic (1–5 mmHg) blood pressure. Controlled-release melatonin use is associated to significantly higher decrease of night blood pressure level
Secundary positive effects	Improvement of sleeping disorders, immune-system modulation
Possible side effects (for suggested dosages)	Mild stomach cramps, headache, depression, sleepiness, dizziness, irritability
Relative controindication	Pregnancy and lactation (melatonin might interfere with ovulation), bleeding disorders, depression, diabetes, seizure disorders
Possible pharmacokinetic interactions of clinical interest	Sedative medications [(eg. Benzodiazepines, barbiturates) sleepiness and drowsiness], verapamil, caffeine and flumazenil (may decrease the effectiveness of melatonin), fluvoxamine and birth control pills as ethinyl estradiol or norethindrone (may increase the effectiveness and side effects of melatonin), nifedipine (melatonin may decrease the effectiveness of nifedipine), anticoagulant/antiplatelet drugs (increase risk of bleeding), immunosuppresants (melatonin might increase the immune system), anti-diabetic agent (melatonin might increase blood sugar)
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals, sleep quality improving nutraceuticals
Suggested recent bibliography	Rodella LF et al. Front Biosci. 2013;5:119–29. 94. Grossman E et al. Vasc Health Risk Manag. 2011;7:577–84.

	Pycnogenol
Main source	*Pinus pinaster*
Main indication	Mild high blood pressure
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Improvement of nitric oxide (NO) production, renal cortical blood flow and endothelial function, reduction of myeloperoxidase activity improves and levels of high-sensitivity C-reactive protein (hs-CRP)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>100 mg/day
Treatment duration	Long-term
Main expected effect	Reduction of systolic (1–10 mmHg) and diastolic (1–5 mmHg) blood pressure
Secundary positive effects	Improvement of vascular stiffness, athletic performance, asthma and allergies

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	Pycnogenol
Possible side effects (for suggested dosages)	Mild dizziness, gastrointestinal impairment, headache, mouth ulcers
Relative controindication	Pregnancy and lactation Patients with auto-immune diseases (pycnogenol seems to increase the immune system)
Possible pharmacokinetic interactions of clinical interest	Immunosuppressants (pycnogenol seems to increase the immune system)
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	Cicero AF, Colletti A. High Blood Press Cardiovasc Prev. 2015;22(3):203–13. Maimoona A et al. J Ethnopharmacol. 2011;133:261–77.

	Potassium
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild hypertension, hypokalemia
Oral bioavailability	90%
Supposed main mechanism of action	Increased sodium/potassium ATPase, natriuresis, baroreflex sensitivity modulation, decreased sensitivity to catecholamines and angiotensin II, improved function of the sympathetic nervous system and insulin sensitivity, reduction of intracellular sodium, NADPH oxidase, asymmetric dimethylarginine and lowers production of Tumor Growth Factor-beta
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1000–3000 mg/day
Treatment duration	Long-term
Main expected effect	Reduction of systolic (5–10 mmHg) and diastolic (1–5 mmHg) blood pressure
Secundary positive effects	Improvement of hypercalciuria
Possible side effects (for suggested dosages)	Mild stomach cramps, diarrhea, stomach upset, nausea, intestinal bloating
Relative controindication	Pregnancy and lactation (>500 mg/day) Patients with severe renal impairment or those on medications that significantly increase renal potassium retention (potassium-sparing diuretics)
Possible pharmacokinetic interactions of clinical interest	ACE inhibitors and Angiotensin receptor blockers (ARBs), indomethacin, tacrolimus, cyclosporine, potassium-sparing diuretics (increased potassium retention)

	Potassium
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	McDonough AA et al. Am J Physiol Endocrinol Metab. 2017;312(4):E348-E356. Houston MC. Curr Hypertens Rep. 2011;13:309–17.

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Main source	Dietary supplements Dairy products and derivatives
Main indication	Mild hypertension, especially if associated with intestinal dysbiosis
Oral bioavailability	*Lactobacilli* and *Bifidobacteria* colonize the intestinal lumen *Saccharomyces* it's a fermenter yeast, but doesn't colonize the intestinal lumen
Supposed main mechanism of action	Unclear/Multiple: restore intestinal eubiosis and fermentation of short-chain fatty acids with hypotensive activities
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>3.5 UFC (live)/day The administration of probiotic strains, to obtain the maximum effectiveness, should be take before the main meal with a lipid vehicle (eg. yogurt or milk)
Treatment duration	Long-term
Main expected effect	Improvement of blood pressure 1–10 mmHg (systolic), 1–5 mmHg (diastolic)
Secundary positive effects	Improvement of bowel health, prevention of cardiovascular risk (regulation of cholesterolemia, inflammatory marker), regulation of the immune system, chemoprevention, prevention of urinary infections and improvement of its symptoms (eg. burning, pain), regulation of mood, depressive symptoms and anxiety [Improvement of Leiden Index of Depression Sensitivity (LEIDS-r), Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D)]
Possible side effects (for suggested dosages)	Mild and transient gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Not determined: it is possible that probiotics interfere with the molecules subject to intestinal enzymatic metabolism (eg. polyphenols, berberine)
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals, heart function improving nutraceuticals
Suggested recent bibliography	Robles-Vera I, et al. Curr Hypertens Rep. 2017;19(4):26. Khalesi S, et al. Hypertension. 2014;64(4):897–903.

	Resveratrol
Main source	Grape, Red wine In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild hypertension
Oral bioavailability	Less than 1% (extensive first pass liver metabolism)
Supposed main mechanism of action	Anti-oxidant, stimulation of endothelial production of nitric oxide (NO), inhibition of vascular inflammation and prevention of platelet aggregation
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>150 mg/day
Treatment duration	Long-term
Main expected effect	Reduction of systolic (1–10 mmHg) and diastolic (1–5 mmHg) blood pressure
Secundary positive effects	Reduction of vascular inflammation, improvement in cognitive function (elderly patients) and insulin-resistance
Possible side effects (for suggested dosages)	Mild and transient gastrointestinal side effects
Relative controindication	Pregnancy and lactation (few data available), bleeding disorders, hormone-sensitive condition such as breast cancer, uterine cancer, ovarian cancer, uterine fibroids, endometriosis (resveratrol might act like estrogen)
Possible pharmacokinetic interactions of clinical interest	Medications substrate of cytochrome P450 3A4 as lovastatin, ketoconazole, itraconazole, fexofenadine, triazolam (resveratrol is an inhibitor of CYP3A4), anticoagulant/antiplatelet (resveratrol might slow blood clotting) as aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin
Possible additive or synergistic nutraceuticals	Blood pressure lowering nutraceuticals
Suggested recent bibliography	Liu Y et al. Clin Nutr. 2015;34(1):27–34. Li H, Xia N. Nitric Oxide. 2012;26(2):102–10.

	Vitamin C (Ascorbic acid)
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Mild hypertension
Oral bioavailability	50–90% (above 1 g may be less than 50%)

	Vitamin C (Ascorbic acid)
Supposed main mechanism of action	Increase of Na/K ATPase, superoxide dismutase, cyclic GMP, nitric oxide, prostaglandins (PG)-I2 and sympathovagal balance, induction of sodium water diuresis, decrease of adrenal steroid production, activation of potassium channels, reduction of cytosolic calcium and serum aldehydes, decrease the binding affinity of the AT1 receptor by angiotensin II by disrupting the ATR1 disulfide bridges
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–1000 mg/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Reduction of systolic (3–10 mmHg) and diastolic (1–4 mmHg) blood pressure, particularly in hypertensive subjects
Secundary positive effects	Improvement of arterial stiffness, depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], vitamin C deficiency, age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption, tyrosinemia
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (> 1.8–2 g/day) Hemochromatosis, previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, iron, estrogens (vitamin C could increase their effects), fluphenazine, warfarin, protease inhibitors (vitamin C could decrease their effects)
Possible additive or synergistic nutraceuticals	Multivitamins, blood pressure improving nutraceuticals
Suggested recent bibliography	Cicero AF, Colletti A. High Blood Press Cardiovasc Prev. 2015;22(3):203–13. Juraschek SP et al. Am J Clin Nutr. 2012;95:1079–88.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplements In order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical.
Main indication	Cardiovascular prevention, hypovitaminosis D, osteopenia
Oral bioavailability	Ergocalciferol (vit. D2) is apparently absorbed with similar efficiency to cholecalciferol (vit. D3), however 25-hydroxyvitamin D (25OHD) is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol. The amount of fat with which vit. D is ingested does not seem to significantly modify the bioavailability of vit. D3 Hypochlorhydria decreases vitamin D bioavailability

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	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Supposed main mechanism of action	Inhibition of angiotensin II receptors
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–3000 IU of cholecalciferol/day (400 IU = 10 mcg)
Treatment duration	Long-term
Main expected effect	Restoration of plasma vitamin D levels
Secundary positive effects	Improvement of depressive symptoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], vitamin C deficiency, age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (increased effects), diltiazem, verapamil (decreased efficacy), thiazide diuretics (elevated serum calcium), proton pump inhibitors, sucrose polyesters and tetrahydrolipstatin (diminish vit. D absorption)
Possible additive or synergistic nutraceuticals	Multivitamins, Blood pressure improving nutraceuticals
Suggested recent bibliography	Stojanović M, Radenković M. Cardiovasc Ther. 2015;33(3):145–54. Kunutsor SK et al. Eur J Epidemiol. 2014;29(1):1–14.

Nutraceuticals Active on Capillaries and Veins

	Bilberry
Main source	*Vaccinum myrtillus*
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), venous ulcers, stasis dermatitis, hemorrhoidal disease
Oral bioavailability	< 1%
Supposed main mechanism of action	Structural support of venous walls, increased glycosaminoglycan metabolism (vasal trophism), reduction of capillary filtration and antinflammatory activity
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	80–320 mg/day of dry extract
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone, postpartum varicose veins condition, reduction of venous capacitance, distensibility, and stasis
Secundary positive effects	Reduction in the release of inflammatory mediators
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Toledo RR et al. Ann Vasc Surg. 2017;38:212–219. Asada T et al. J Agric Food Chem. 2012; 60(42):10634–40.

	Black grape
Main source	*Vitis vinifera*
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), venous ulcers, stasis dermatitis, hemorrhoidal disease
Oral bioavailability	Very low

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https://doi.org/10.1007/978-3-319-73642-6_5

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	Black grape
Supposed main mechanism of action	Strong antioxidant activity, inhibition of xanthine oxidase, iron and copper ion chelation from damaged tissues, increased release of prostacyclin, antagonism against elastase, collagenase, hyaluronidases and other enzymes involved in extra vascular connectivity damage
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	80–320 mg/day of Oligomeric Proantho Cyanidins (OPC)
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone, signs and symptoms, postpartum varicose veins condition, reduction of venous capacitance, distensibility, and stasis
Secundary positive effects	Reduction in the release of inflammatory mediators
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Nassiri-Asl M et al. Phytother Res. 2016;30(9):1392–403. Scallon C et al. Cochrane Database Syst Rev. 2013;5:CD006477.

	Centella
Main source	*Centella asiatica*
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), venous ulcers, stasis dermatitis, hemorrhoidal disease
Oral bioavailability	Good
Supposed main mechanism of action	Increased cellular proliferation and collagen synthesis at the wound site, synthesis and release of tropocollagen and mucopolysaccharide acids in the connective tissue (enhancement of the connective tissue of the venous walls), inhibition of the inflammatory process
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	60–120 mg/day of asiaticosides The title and the standardization of triterpenoids (in particular asiaticosides) could be important to recognize the most effective extracts

	Centella
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone [RF (flux at rest) and RAS (rate of ankle swelling)] and lymphatic drainage, reduction of venous capacitance (reduction of capillary filtration), distensibility, and stasis Improvement in signs and symptoms
Secundary positive effects	Reduction in the release of inflammatory mediators, as oxygen free radicals and prostaglandins
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Sedative medications (as clonazepam, lorazepam, phenobarbital, zolpidem: centella might increase sleepiness and drowsiness)
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Martinez-Zapata MJ et al. Cochrane Database Syst Rev. 2016;4:CD003229. Chong NJ et al. Evid Based Complement Alternat Med. 2013; 2013: 627182.

	Diosmin
Main source	Dietary supplement
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), venous ulcers, stasis dermatitis, hemorrhoidal disease
Oral bioavailability	Good The micronization of the flavone fraction from 20 to 2 μM, increases the intestinal absorption and bioavailability of the substance
Supposed main mechanism of action	Prolongation of the vasoconstrictor effect of norepinephrine on the vein wall, improvement of lymphatic contractions and the total number of functional lymphatic capillaries and reduction of intralymphatic pressure, reduction of capillary hyperpermeability and enhancement of capillary resistance by protecting the microcirculation from damaging processes, reduction of the expression of endothelial adhesion molecules (ICAM1, VCAM1), and inhibition of the adhesion, migration, and activation of leukocytes at the capillary level
Level of support	Meta-analysis of randomized clinical trials (most of them in combination with hesperidin)
Population tested	Adults, elderly
Dose ranges	50–1300 mg/day
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)

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	Diosmin
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone and lymphatic drainage, reduction of venous capacitance, distensibility, and stasis
Secundary positive effects	Reduction in the release of inflammatory mediators, as oxygen free radicals and prostaglandins (PGE2, PGF2a)
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Vidhya R et al. Biomed Rep. 2016;5(3):283–288. Scallon C et al. Cochrane Database Syst Rev. 2013;5: CD006477.

	Hamamelis
Main source	*Hamamelis virginiana*
Main indication	Chronic venous insufficiency, hemorrhoidal disease
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Strong antioxidant activity, waterproof the external layers of the skin and mucosae, vasoconstrictor effect on small superficial vessels, improvement of tissue regeneration in case of superficial burn or wound, inhibition of 5-lipoxygenase, angiotensin converting enzyme, hyaluronidase activation, glucosyl-transferases, protein kinase C
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–300 mg/day of dry extract The title and the standardization of tannins (10%) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone, signs and symptoms
Secundary positive effects	Reduction in the release of inflammatory mediators
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.

	Hamamelis
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Scallon C et al. Cochrane Database Syst Rev. 2013;5: CD006477. MacKay D et al. Altern Med Rev. 2001;6(2):126–40.

	Hesperidin
Main source	Dietary supplement
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), venous ulcers, stasis dermatitis, hemorrhoidal disease
Oral bioavailability	Good
Supposed main mechanism of action	Prolungation of the vasoconstrictor effect of norepinephrine on the vein wall, improvement of lymphatic contractions and the total number of functional lymphatic capillaries and reduction of intralymphatic pressure, reduction of capillary hyperpermeability and enhancement of capillary resistance by protecting the microcirculation from damaging processes, reduction of the expression of endothelial adhesion molecules (ICAM1, VCAM1), and inhibition of the adhesion, migration, and activation of leukocytes at the capillary level
Level of support	Meta-analysis of randomized clinical trials (most of them in combination with diosmin)
Population tested	Adults, elderly
Dose ranges	50–1300 mg/day The micronization of the flavone fraction from 20 to 2 μM, increases the intestinal absorption and bioavailability of the substance
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone and lymphatic drainage, reduction of venous capacitance, distensibility, and stasis
Secundary positive effects	Reduction in the release of inflammatory mediators, as oxygen free radicals and prostaglandins (PGE2, PGF2a)
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Vidhya R et al. Biomed Rep. 2016; 5(3): 283–288. Scallon C et al. Cochrane Database Syst Rev. 2013; 5:CD006477.

	Hippocastanum
Main source	*Aesculus hippocastanum*
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), venous ulcers, stasis dermatitis
Oral bioavailability	Low (the amorphous form (bioavailability 10%) is 200 times more soluble than the crystalline form)
Supposed main mechanism of action	Reduction of number and diameter of venous capillaries
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–150 mg/day of escin
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone, signs and symptoms, reduction of venous capacitance, distensibility, and stasis
Secundary positive effects	Reduction in the release of inflammatory mediators
Possible side effects (for suggested dosages)	Mild headache, nausea, veritigo, pruritus
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Lithium (alteration of pharmacokinetic profile), anticoagulant (hyppocastanum might slow blood clotting), aminoglycosides (increased risk of nephrotoxicity)
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Scallon C et al. Cochrane Database Syst Rev. 2013; 5:CD006477. Suter A et al. Adv Ther. 2006;23(1):179–90.

	Nattokinase
Main source	*Glycine max* Dietary supplement
Main indication	Prevention of superficial and deep vein thrombosis
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Fibrinolytic agent, tissue plasminogen activator (tPA) activator
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–300 mg/day of nattokinase 2000 F.U. (Fibrinolytic Unit)
Duration of treatment	Cyclic
Main expected effect	Reduction of vascular inflammation, incidence of vein thrombosis, and peripheral edema
Secundary positive effects	Reduction in the release of inflammatory mediators, fibrinogen, factor VII and VIII, blood pressure
Possible side effects (for suggested dosages)	At high dosages: hepatotoxicity
Relative controindication	Pregnancy and lactation (not enough data available in humans)

	Nattokinase
Possible pharmacokinetic interactions of clinical interest	Anticoagulant therapy (mildly increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Gavish I et al. Intern Emerg Med. 2011;6(2):113–6. Hsia CH et al. Nutr Res. 2009;29(3):190–6.

	Pycnogenol
Main source	*Pinus pinaster*, *Pinus maritima*
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), venous ulcers, stasis dermatitis, hemorrhoidal disease
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Unclear (pycnogenol has potent antioxidant activity, anti-inflammatory actions, improves endothelial function, reduces platelet aggregation, promotes wound healing)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	50–360 mg/day
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone, signs and symptoms, postpartum varicose veins condition, reduction of venous capacitance, distensibility, and stasis
Secundary positive effects	Reduction in the release of inflammatory mediators, improvement of allergies, asthma, athletic performance, mental function, retinal diseases, hypertension (inclusive data)
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Immunosuppressants (as azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate, tacrolimus, sirolimus, prednisone, corticosteroids: pycnogenol seems to increase the immune system)
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Belcaro G et al. Int J Angiol. 2017;26(1):12–19. Toledo RR et al. Ann Vasc Surg. 2017;38:212–219.

	Ruscus
Main source	*Ruscus aculeatus*
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), venous ulcers, stasis dermatitis, hemorrhoidal disease
Oral bioavailability	Bioavailability of ruscogenins: 5%

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	Ruscus
Supposed main mechanism of action	Agonist activity on alpha-1 and 2 adrenergic receptors of smooth muscle cells of the venous walls, improvement of the release of norepinephrine on the vein wall
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–200 mg/day of dry extract The title and the standardization of ruscogenins (5–10%) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)
Main expected effect	Reduction of inflammation, pain and stiffness, improvement of venous tone and lymphatic drainage, reduction of venous capacitance, distensibility, and stasis
Secundary positive effects	Reduction in the release of inflammatory mediators, as oxygen free radicals and prostaglandins
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Alpha-adrenergic antagonists (ruscus might reduce the therapeutic effect) and agonists (ruscus might intensify the therapeutic effect)
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Jawien A et al. Int Angiol. 2017;36(1):31–41. Masullo M et al. Planta Med. 2016;82(18):1513–1524.

	Sweet clover
Main source	*Melilotus officinalis*
Main indication	Chronic venous insufficiency including spider and varicose veins, leg swelling (edema), lymphoedema**,** venous ulcers, stasis dermatitis
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Exact mechanisms of action are still unclear: we highlight an increase of capillary resistance, reduction of vascular permeability, improvement of lymphatic circulation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–300 mg/day of dry extract The title and the standardization of coumarins (coumarin, melilotin, melilotic acid, melilotoside) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (at least 1 month of treatment)/Long-term (depending on disease severity)

	Sweet clover
Main expected effect	Reduction of inflammation, improvement of venous tone and lymphatic drainage, reduction of venous capacitance, distensibility, and stasis
Secundary positive effects	Reduction in the release of inflammatory mediators
Possible side effects (for suggested dosages)	At high dosages: hepatotoxicity
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Other venoprotective nutraceuticals
Suggested recent bibliography	Scallon C et al. Cochrane Database Syst Rev. 2013;5: CD006477. Yarnell E et al. Alter Compl Ther. 2009;15(1):24–30.

Nutraceuticals Active on Lipid Metabolism

	Artichoke
Main source	*Cynara scolymus, Cynara cardunculus*
Main indication	Mild-to moderate hypercolesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of HMGCoA reductase
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	1–3 g/day
Duration of treatment	Long-term
Main expected effect	– 10% LDL-C plasma level
Secundary positive effects	Improvement of liver transaminases, Fasting Plasma Glucose and HDL levels
Possible side effects (for suggested dosages)	Mild and transient gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Berberine, Phytosterols
Main recent comprehensive references	Sahebkar A et al. Crit Rev Food Sci Nutr. 2017 Jun 13:1–8. doi: 10.1080/10408398.2017.1332572. Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005.

	β-glucan
Main source	Dietary supplements
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Prolonged gastric emptying time, inhibiton of hepatic cholesterol synthesis, increase satiety and faecal excretion of cholesterol and bile salts
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, children, elderly
Dose ranges	3–25 g/day
Treatment duration	Long-term

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https://doi.org/10.1007/978-3-319-73642-6_6

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	β-glucan
Main expected effect	−5–15% LDL-C plasma level
Secundary positive effects	Improvement of nitric oxide (NO) release
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Red yeast rice, berberine, other lipid-lowering nutraceuticals
Suggested recent bibliography	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Ho HV et al. Eur J Clin Nutr. 2016;70(11):1239–1245.

	Berberine
Main source	*Coptis* (*Coptis chinensis*, *Coptis japonica*), *Hydrastis* (*Hydrastis canadensis*), *Berberis* (*Berberis aristata*, *Berberis vulgaris*, *Berberis croatica*)
Main indication	Mild-to-moderate hypercholesterolemia, hyperglycemia
Oral bioavailability	<2% Alternative approaches to increase the bioavailability of berberine have been studied, using permeability enhancers (sodium caprate, sodium deoxycholate and chitosan), P-gp inhibitors (silymarin), or modified release dosage form (nanoemulsions, micelles, liposomes, nanoparticles) with satisfactory results
Supposed main mechanism of action	Activation of Adenosin-Monophosphate-Kinase-alpha (AMPK) and the expression of LDL receptors, inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, children, elderly
Dose ranges	500–1500 mg/day
Duration of treatment	Long-term
Main expected effect	15–20% LDL
Secundary positive effects	Reduction of ApoB, Triglycerides (TG), high sensitivity C-Reactive Protein (hsCRP), Interleukin (IL)-6, Monocyte Chmotactic Protein (MCP), Matrix Metallo-Proteinase (MMP), vascular adhesion molecules, Fasting Plasma Glucose, HbA1c, Homeostasis Model Assessment Index (HOMA-index) and blood pressure
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnacy and lactation
Possible pharmacokinetic interactions of clinical interest	Cyclosporine and medications Cytochrome P450 3A4 (CYP3A4) substrates (berberine might reduce the metabolism of these drugs)
Possible additive or synergistic nutraceuticals	Red yeast rice, sylimarin, phytosterols

	Berberine
Main recent comprehensive references	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Cicero AF, Baggioni A. Adv Exp Med Biol. 2016;928:27–45.

	Bergamot
Main source	*Citrus bergamia*
Main indication	Mild-to-moderate hypercholesterolemia, hyperglicemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of HMG-CoA reductase and Sterol O-acyltransferase (ACAT), reduction of the oxidation of LDL-C and intestinal absorption of cholesterol, activation of Adenosin-Monophosphate-Kinase-alpha (AMPK-α), LDL receptor gene transcription via protein kinase C and peroxisome proliferator-activated receptors gamma (PPAR-γ)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	Bergamot 1000 mg/day [bergamot derived polyphenolic fraction (BPF)] The title and the standardization of neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin and poncirin could be important to recognize the most effective extracts
Duration of treatment	Long-term
Main expected effect	−10−20% LDL-C plasma level
Secundary positive effects	Improvement of small dense (sd)-LDL, inflammatory markers as hsCRP and TNF-α
Possible side effects (for suggested dosages)	Mild and transient gastrointestinal side effects
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Photosensitizing drugs as amitriptyline, ciprofloxacin, norfloxacin, lomefloxacin, ofloxacin, levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin, trimethoprim/sulfamethoxazole, tetracycline, methoxsalen and trioxsalen (bergamot might also increase the sensitivity to sunlight)
Possible additive or synergistic nutraceuticals	Red yeast rice, Artichoke, Berberine, Phytosterols
Main recent comprehensive references	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Mikhailidis DP, et al. Curr Vasc Pharmacol. 2011;9(5):531–2.

	Chitosan
Main source	Dietary supplements (husks of blonde psyllium seed)
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Prolonged gastric emptying time, inhibiton of hepatic cholesterol synthesis (via the short-chain fatty acid byproducts of fiber fermentation), increase satiety and faecal excretion of cholesterol and bile salts (stimulating 7-α-hydroxylase)

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	Chitosan
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	1–6 g/day
Duration of treatment	Long-term
Main expected effect	−5% LDL-C plasma level
Secundary positive effects	Improvement of glyemia, HOMA index, body weight
Possible side effects (for suggested dosages)	Transient side effects such as abdominal pain, diarrhea, constipation occurred in rare cases at doses ranging between 1 and 6 g/day
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Red Yeast Rice
Main recent comprehensive references	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Kim HJ et al. Food Funct. 2014;(10):2662–9.

	Curcumin
Main source	*Curcuma longa*
Main indication	Mild hypercholesterolemia, especially in insulin-resistant patients
Oral bioavailability	Very low (< 1%)
Supposed main mechanism of action	Inhibition of the expression of NPC1L1 transporter, increases the efflux of cholesterol via expression of ABCA1, enhances cell-surface LDL receptor level and promotes LDL uptake through the downregulation of the expression of PCSK9
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	Standard curcumin: >1 g/day (usually 1.5 g/day) Curcumin in specific pharmaceutical forms (with biopharmaceutical strategies as micelles or nanoemulsions): >400/500 mg/day
Duration of treatment	Long-term
Main expected effect	−5% LDL-C plasma level
Secundary positive effects	Improvement of cardiovascular disease risk factors [Reduction of inflammatory markers (eg. COX, vascular endothelial grow factor, tumor necrosis factor-alpha (TNF-alpha), interleukins (IL-23,-17,-1β,-4), improvement of glutathione plasma concentrations and NrF-2] and insulin-resistance, prevention and/or treatment of headaches, arthritis, joint pain, stomach pain, irritable bowel syndrome, inflammatory bowel diseases, fibromyalgia, immune system dysfunction, bladder inflammation, cognitive decline. Improvement of depressive symptoms [Hamilton Depression Rating Scale (HAM-D)] and reduction of serum and salivary stress markers such as cortisol and interleuchins

	Curcumin
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps and/or upset, diarrhea, dizziness
Relative controindication	Pregnancy and lactation, Gilbert's disease or gallbladder problems, infertility, iron deficiency, bleeding problems, hormone-sensitive conditions (breast cancer, uterine cancer, ovarian cancer, uterine fibroids or endometriosis)
Possible pharmacokinetic interactions of clinical interest	Inhibition of CYP450 (in particular CYP2C9) Possible interactions with anticoagulant and antiplatelet drugs (aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin), diclofenac, ibuprofen, naproxen and other NSAIDs.

Possible additive or synergistic nutraceuticals	Guggul and chlorogenic acid
Main recent comprehensive references	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Panahi Y et al. J Cardiovasc Pharmacol. 2016;68(3):223–9.

	Gamma-oryzanol
Main source	Rice brain oil
Main indication	Mild-to moderate hypercolesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of HMG-CoA reductase and reduction of the intestinal cholesterol absorption
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	300 mg/day
Duration of treatment	Long-term
Main expected effect	−5% LDL-C plasma level
Secundary positive effects	Improvement of ApoB and HDL levels
Possible side effects (for suggested dosages)	None, beyond individual intolerance to the product
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Red Yeast Rice
Main recent comprehensive references	Jolfaie NR et al. Horm Metab Res 2016;48(7):417–26. Cicero AF, Gaddi A. Phytother Res. 2001;15(4):277–89.

	Glucomannan
Main source	*Amorphophallus konjac*
Main indication	Mild-to moderate hypercolesterolemia

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	Glucomannan
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Prolonged gastric emptying time, inhibiton of hepatic cholesterol synthesis, increase satiety and faecal excretion of cholesterol
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Children, Elderly
Dose ranges	3–25 g/day
Duration of treatment	Long-term
Main expected effect	−5−15% LDL-C plasma level
Secundary positive effects	Improvement of nitric oxide (NO) release
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Reduction of bioavailability of vitamin E, calcium and other minerals while it does not hinder the absorption of water-soluble vitamins. For these reasons, it is recommended to take the medication 1 h before or at least 4 h after taking glucomannan
Possible additive or synergistic nutraceuticals	Red Yeast Rice, Plant sterols
Main recent comprehensive references	Onakpoya I et al. J Am Coll Nutr. 2014;33(1):70–8. Sood N et al. Am J Clin Nutr. 2008;88(4):1167–75.

	Green tea extracts
Main source	*Camellia sinensis*
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Activation of Adenosin-Monophosphate-Kinase-alpha (AMPK) and inhibition of HMG-CoA reductase and the ileal apical sodium-dependent bile acid transporter, enhancement the hepatic LDL receptors expression and the biliary excretion of cholesterol
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	250 to 1200 mg/day of green tea extract / 170 to 850 mg/day of epigallocatechin-3-gallate (EGCG)
Duration of treatment	Long-term
Main expected effect	−5−10% LDL-C plasma level
Secundary positive effects	Improvement of arterial stiffnees [Flow Mediated Dilation (FMD), Pulse Wave Velocity (PWV)], glycemia and reduction of blood pressure
Possible side effects (for suggested dosages)	Mild grastointestinal disorders
Relative controindication	Pregnancy and lactation (High doses of green tea can cause a deficiency of iron and folate due to its capacity to bind and reduce their intestinal absorption)

	Green tea extracts
Possible pharmacokinetic interactions of clinical interest	Warfarin, Pentobarbital, Dipyridamole (decrease their effectiveness), Theophylline, Adenosine (synergistic actions with caffeine), Riluzole, Phenylpropanolamine, MAO inhibitors, Clozapine (green tea increase the effects and side effects of these drugs)
Possible additive or synergistic nutraceuticals	Curcumin, guggul, pantethine, soybean plant sterols, delta-tocotrienol, phytolens
Main recent comprehensive references	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Onakpoya I et al. Nutr Metab Cardiovasc Dis. 2014;24(8):823–36.

	Monacolin K
Main source	Red yeast rice
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	Good, enhanced by intake with food
Supposed main mechanism of action	Reversible inhibition of the liver 3-Hydroxy-3-Methyl-Glutaryl Coenzyme A reductase (HMGCoA-R)
Level of support	Meta-analyses of several randomized clinical trials
Population tested	Adults, Children, Elderly
Dose ranges	3–10 mg/day
Treatment duration	Long-term
Main expected effect	−15−25% LDL-C plasma level
Secundary positive effects	Mild decrease in TG and increase in HDL-C, reduction of biomarkers of vascular inflammation and matrix metalloproteinases levels, improvement of flow-mediated dilation, reduction in the risk of cardiovascular events in secondary prevention
Possible side effects (for suggested dosages)	Myalgia, Increase in Creatin-phosfo-kinase (CPK) levels, reversible increase in liver transaminases Low quality products could contains citrinin, a nephrotoxic alkaloid: pay attention to use citrinin-free products only
Relative controindication	Previous intolerance to low dosed first level statins (for instance, Pravastatin 20 mg, Simvastatin 10 mg), known myopathies
Possible pharmacokinetic interactions of clinical interest	Strong CYP3A4 inhibitors (azolic antimycotics, macrolydes, some antiretrovirals, amiodarone, diltiazem, verapamil, isoniazid)
Possible additive or synergistic nutraceuticals	Soluble fibers, Phytosterols, Berberine, other lipid-lowering nutraceuticals; mild myalgia associated with red yeast rice use could be sometime prevented or managed with supplementation of Coenzyme Q10 (>100 mg/day)
Suggested recent bibliography	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005 Li Y et al. PLoS One. 2014;9(6):e98611.

	Nuts
Main source	*Juglans regia*
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	Good

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	Nuts
Supposed main mechanism of action	Reversible inhibition of the liver 3-Hydroxy-3-Methyl-Glutaryl Coenzyme A reductase (HMGCoA-R)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	30 g/day
Duration of treatment	Long-term
Main expected effect	−5% LDL-C plasma level
Secundary positive effects	Mild decrease in TG and increase in HDL-C, reduction of biomarkers of vascular inflammation and matrix metalloproteinases levels, improvement of flow-mediated dilation
Possible side effects (for suggested dosages)	Body weight increase
Relative controindication	Nuts allergies
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Polyunsaturated fatty acids
Main recent comprehensive references	Orem A et al. J Clin Lipidol. 2013;7(2):123–31. Katz DL et al. J Am Coll Nutr. 2012;31(6):415–23.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*)
Main indication	Mild-to moderate hypertriglyceridemia
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Reduction of available substrate for the synthesis of new tryglycerides, the activity of tryglycerides-synthetizing enzymes (diacylgylcerol acyltranferase or phosphatidic acid phosphohydrolase), improvement of β-oxidation of fatty acids, reduction of the endogenous synthesis of fatty acids and the increase of synthesis of phospholipids
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	2–6 g/day of eicosapentanoic and/or docosahexaenoic acid
Duration of treatment	Long-term
Main expected effect	−25–30% triglycerides plasma level (dose-dependent)
Secundary positive effects	Cardiovascular disease prevention, anti-proarrhytmic and antinflammatory effects, macula protection, brain protection, mood stabilization
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Relative controindication	Not reported
Possible pharmacokinetic interactions of clinical interest	Warfarin (Dose-related increase in bleeding time)
Possible additive or synergistic nutraceuticals	Red yeast rice, psyllium, gamma-oryzanol, garlic,
Main recent comprehensive references	Leslie MA et al. Lipids Health Dis. 2015;14:53. Taghizadeh M et al. J Clin Lipidol. 2016;10(2):386–93.

	Plant sterols and stanols
Main source	Vegetable oils, nuts, seeds, legumes and some fat spreads Dietary supplements
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	<2%
Supposed main mechanism of action	Reduction of intestinal absorption of exogenous cholesterol (they compete in the solubilised micelle formation)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Children, Elderly
Dose ranges	400–3000 mg
Treatment duration	Long-term
Main expected effect	−8–12% LDL-C plasma level
Secundary positive effects	Mild decrease in TG and increase in HDL-C, reduction of biomarkers of vascular inflammation as hsCRP
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Familial sitosterolemia (extremely rare genetic disease)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Red yeast rice, berberine, other lipid-lowering nutraceuticals
Suggested recent bibliography	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Ras RT et al. Br J Nutr. 2014;112(2):214–9.

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Main source	Dietary supplements Dairy products and derivatives
Main indication	Cardiovascular prevention (mild hypertension, hypercolesterolemia, heart failure NYHA I-II), intestinal dysbiosis
Oral bioavailability	*Lactobacilli* and *Bifidobacteria* colonize the intestinal lumen *Saccharomyces* it's a fermenter yeast, but doesn't colonize the intestinal lumen

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	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Supposed main mechanism of action	Reduction of the enterohepatic circulation of bile salts through bile salts hydrolase (BSH) activity, interaction with the formation of micelles, the transport pathways of cholesterol and/or lipoprotein (as NPC1L1 gene expression) and cholesteryl esters, production of organic short fatty acids, modification of bowel pH
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	>3.5 UFC (live)/day To obtain the maximum effectiveness, probiotic strains should be taken before the main meal with a lipid vehicle (eg. yogurt or milk)
Duration of treatment	Long-term
Main expected effect	Reduction of cholesterolemia (−5/−10% LDL) in patients with dysbiosis and or bowel disorders
Secundary positive effects	Improvement of bowel health, prevention of cardiovascular risk (regulation of blood pressure, inflammatory marker as hsCRP), regulation of the immune system, chemoprevention, prevention of urinary infections and improvement of its symptoms (eg. burning, pain). Regulation of mood, depressive symptoms and anxiety [Improvement of Leiden Index of Depression Sensitivity (LEIDS-r), Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D)]
Possible side effects (for suggested dosages)	Mild gastrointenstinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Prebiotics, red yeast rice
Main recent comprehensive references	Cho YA, Kim J. Medicine. 2015;94(43):e1714. Shimizu M et al. PLoS One. 2015;10(10):e0139795.

	Psyllium
Main source	Dietary supplements (husks of blonde psyllium seed)
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	None
Supposed main mechanism of action	Prolonged gastric emptying time, inhibiton of hepatic cholesterol synthesis (via the short-chain fatty acid byproducts of fiber fermentation), increase satiety and faecal excretion of cholesterol and bile salts (stimulating 7-α-hydroxylase)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Children, Elderly
Dose ranges	3–20 g/day

	Psyllium
Duration of treatment	Long-term
Main expected effect	−5−15% LDL-C plasma level (dose-related)
Secundary positive effects	Improvement of glyemia, HOMA index, body weight, irritable bowel syndrome (IBS)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Slowed or reduced absorption of co-assumed drugs: Its assumption has to be done far from other drugs
Possible additive or synergistic nutraceuticals	Plant sterols
Main recent comprehensive references	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Ribas SA et al. Br J Nutr. 2015;113(1):134–41.

	Soy and lupin proteins
Main source	*Glycine max, Lupinus polyphyllus*
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Expression downregulation of the hepatic transcription factor of sterol regulatory element binding protein (SREBP-1), regulation of SREBP-2, reduction of cholesterol synthesis, improvement of ApoB receptor activity and enhancement of the faecal excretion of bile salts
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	25–100 g/day
Duration of treatment	Long-term
Main expected effect	−3−10% LDL-C plasma level
Secundary positive effects	Improvement of arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)]
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation, breast cancer, endometrial cancer, kidney failure, urinary bladder cancer, hypothyroidism (only for soy), cystic fibrosis
Possible pharmacokinetic interactions of clinical interest	Warfarin (soy has been reported to decrease the effectiveness of warfarin), tamoxifen (soy might decrease the effectiveness of tamoxifen), estrogens (taking soy along with estrogen pills might decrease the effects of estrogen pills), MAOIs (fermented soy products contain tyramine: MAOIs can decrease the breakdown of tyramine)
Possible additive or synergistic nutraceuticals	Plant sterols, red yeast rice, bitter gourd chlorella, licorice, pantethine, green tea extract, delta-tocotrienol and phytolens
Main recent comprehensive references	Tokede A et al. Br J Nutr. 2015;114(6):831–43. Lammi C et al. J Agric Food Chem. 2014;62(29):7151–9.

	Spirulin
Main source	*Arthrospira platensis*
Main indication	Mild-to moderate hypercolesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	1–8 g/day
Duration of treatment	Long-term
Main expected effect	−5% LDL-C plasma level
Secundary positive effects	Improvement of triglycerides and HDL levels
Possible side effects (for suggested dosages)	None, beyond individual intolerance to the product
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Plant sterols
Main recent comprehensive references	Serban MC et al. Clin Nutr. 2016;35(4):842–51. Lee EH et al. Nutr Res Pract. 2008;2(4):295-300.

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Main source	Dietary supplements
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Activation of peroxisome proliferator-activated receptor (PPAR-α, PPAR-β, and PPAR-γ), inhibition of HMG-CoA reductase
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	400–800 IU/day
Duration of treatment	Long-term
Main expected effect	−5% LDL-C plasma level
Secundary positive effects	Improvement of arterial stiffness and endothelial function (reduction of the serum levels of hsCRP, advanced glycation end products, metalloproteinases and cell adhesion molecules)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Preganncy and lactation, bleeding disorders, head and neck cancer, prostate cancer, heart attack, stroke, angioplasty and diabetes
Possible pharmacokinetic interactions of clinical interest	Warfarin (risk of bleeding), Cyclosporine (Vitamin E might enhance the bioavailability of this drug), Medications substrate of CYP450 (Vitamin E might enhance the hepatic clearance)

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Possible additive or synergistic nutraceuticals	Vitamin C, Pantethine, soybean plant sterols, green tea extract
Main recent comprehensive references	Ashor AW et al. Br J Nutr. 2015;113(8):1182–94. Loffredo L et al. Nutr Metab Cardiovasc Dis. 2015;25(4):354–63.

Nutraceuticals Active on Glucose Metabolism

	2-*Cis*,4-*trans*-abscisic acid (ABA)
Main source	Fruits and vegetables (eg. Avocado, citrus, soybean, apple) Dietary supplements
Main indication	Hyperglycemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Interaction with with insulin release and glucagon-like peptide-1 (GLP-1), activation of glucose transporter-4 (GLUT-4)
Level of support	Preclinical studies, open label clinical trials
Population tested	Adults
Dose ranges	1 μg/kg body weight
Duration of treatment	Long-term
Main expected effect	Improvement of Fasting Plasma Glucose (FPG) and insulinemia
Secundary positive effects	ABA reduces adipose tissue inflammation and improves immuno-modulation
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Zocchi E et al. Front Nutr. 2017; 4: 24. Bassaganya-Riera J et al. Curr Med Chem. 2010;17(5):467–78.

	Alpha-lipoic acid
Main source	Dietary supplements
Main indication	Hyperglycemia, peripheral neuropathies
Oral bioavailability	Approximately 30%
Supposed main mechanism of action	Antioxidant, role in IR/PI3K/Akt-dependent activation of glucose uptake in skeletal muscle

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https://doi.org/10.1007/978-3-319-73642-6_7

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	Alpha-lipoic acid
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–1200 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of Fasting Plasma Glucose (FPG) Post-Prandial Glycemia (PPG), HbA1c and insulinemia
Secundary positive effects	Improvement of cholesterolemia, oxidative stress, reactive oxygen species (ROS), nerve conduction velocity and positive neuropathic symptoms, glucose and ascorbate handling, levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) and endothelial nitric oxide synthase (eNOS) activity, activation of Phase II detoxification via the transcription factor Nrf2, and lower expression of matrix metallopeptidase 9 (MMP-9) and vascular cell adhesion protein 1 (VCAM-1) through repression of NF-kappa-B, reduction of malondialdehyde (MDA), hsCRP (high sensible C reactive protein) and body weight
Possible side effects (for suggested dosages)	Mild to moderate rash
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Chemotherapy (the antioxidant properties of alpha-lipoic acid may reduce chemotherapeutic efficacy) thyroid disease (taking alpha-lipoic acid might interfere with treatments for under-active or over-active thyroid), excessive consumption of alcohol/thiamine deficiency
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	De Rosa G et al. Int J Mol Sci. 2016; 17(11):1802–1810. Rochette et al. Can J Physiol Pharmacol. 2015;93(12):1021–7.

	Banaba
Main source	*Lagerstroemia speciosa*
Main indication	Hyperglycemia, weight loss
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Interaction with insulin release, activation of glucose transporter-4 (GLUT-4) and Adenosin-Monophosphate-Kinase-alpha (AMPK), reduction of gluconeogenesis and inhibition of the hydrolysis of starches and sucrose
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1000 mg/day (1% corosolic acid) The title and the standardization of corosolic acid (1% of dry extract) could be important to identify the most effective extracts

	Banaba
Duration of treatment	Long-term
Main expected effect	Improvement of Fasting Plasma Glucose (FPG) and Post-Prandial Glycemia (PPG)
Secundary positive effects	Improvement of arterial stiffness (preliminary data) and mild weight loss
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Cicero AF et al. Phytomedicine. 2016;23(11):1134–44. Ríos JL et al. Planta Med. 2015;81(12–13):975–94.

	Berberine
Main source	Coptis (*Coptis chinensis*, *Coptis japonica*), Hydrastis (*Hydrastis canadensis*), Berberis (*Berberis aristata*, *Berberis vulgaris*, *Berberis croatica*)
Main indication	Hyperglycemia, hypercholesterolemia
Oral bioavailability	<2% Alternative approaches to increase the bioavailability of berberine have been studied, using permeability enhancers (sodium caprate, sodium deoxycholate and chitosan), P-gp inhibitors (silymarin), or modified release dosage form (nanoemulsions, micelles, liposomes, nanoparticles) with satisfactory results
Supposed main mechanism of action	Activation of Adenosin-Monophosphate-Kinase-alpha (AMPK)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Children, Elderly
Dose ranges	500–1500 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of Fasting Plasma Glucose (FPG), HbA1c, Homeostasis Model Assessment Index (HOMA-index)
Secundary positive effects	Reduction of low-density lipoprotein (LDL), ApoB, Triglycerides (TG), high sensitivity C-Reactive Protein (hsCRP), Interleukin (IL)-6, Monocyte Chemotactic Protein (MCP), Matrix Metallo-Proteinase (MMP), vascular adhesion molecules, and blood pressure
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Cyclosporine and medications Cytochrome P450 3A4 (CYP3A4) substrates (berberine might reduce the metabolism of these drugs)

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	Berberine
Possible additive or synergistic nutraceuticals	Red yeast rice and different glucose lowering nutraceuticals
Suggested recent bibliography	Lan J et al. J Ethnopharmacol. 2015;161:69–81. Pirillo A et al. Atherosclerosis. 2015;243(2):449–61.

	Bergamot
Main source	*Citrus bergamia*
Main indication	Hyperglicemia in metabolic syndrome
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of HMG-CoA reductase and Sterol O-acyltransferase (ACAT), reduction of the oxidation of LDL-C and intestinal absorption of cholesterol, activation of Adenosin-Monophosphate-Kinase-alpha (AMPK-α), LDL receptor gene transcription via protein kinase C and peroxisome proliferator-activated receptors gamma (PPAR-γ)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	Bergamot 1000 mg/day [bergamot derived polyphenolic fraction (BPF)] The title and the standardization of neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin and poncirin could be important to recognize the most effective extracts
Duration of treatment	Long-term
Main expected effect	Improvement of fasting plasma glucose and LDL-C plasma level
Secundary positive effects	Improvement of small dense (sd)-LDL, inflammatory markers as hsCRP and TNF-α
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Photosensitizing drugs as amitriptyline, ciprofloxacin, norfloxacin, lomefloxacin, ofloxacin, levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin, trimethoprim/sulfamethoxazole, tetracycline, methoxsalen and trioxsalen (bergamot might also increase the sensitivity to sunlight)
Possible additive or synergistic nutraceuticals	Berberine, banaba
Main recent comprehensive references	Cicero AF et al. Arch Med Sci. 2017; 13(5): 965–1005. Mikhailidis DP et al. Curr Vasc Pharmacol. 2011;9(5):531–2.

	Bitter gourd
Main source	*Momordica charantia L.*
Main indication	Hyperglycemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Insulin sensitizers
Level of support	Randomized clinical trials
Population tested	Adults
Dose ranges	4–5 g/day of lyophilized extract The title and the standardization of charantin could be important to identify the most effective extracts
Duration of treatment	Long-term
Main expected effect	Improvement of Fasting Plasma Glucose (FPG) and regulation of cholesterolemia
Secundary positive effects	Regulation of blood pressure and triglycerides
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Cicero AF et al. Phytomedicine. 2016;23(11):1134–44. Ota A, Ulrih NP. Front Pharmacol. 2017;8:436.

	Cassia
Main source	*Cassia angustifolia*
Main indication	Hyperglycemia, weight loss, constipation
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Reduction of sugars availability
Level of support	Randomized clinical trials
Population tested	Adults
Dose ranges	10–30 mg/day
Duration of treatment	Cyclic
Main expected effect	Improvement of Post Prandial Glycemia (PPG)
Secundary positive effects	Laxative and body weight loss
Possible side effects (for suggested dosages)	Diarrhea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Digoxin, diuretics (cassia might increase potassium excretion)
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Varghese GK et al. Pharm Biol. 2013;51(3):345–9. Khader SZA et al. Integr Med Res. 2017;6(2):131–140.

	Chitosan
Main source	Dietary supplements
Main indication	Hyperglycemia, dyslipidemia, weight loss
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of intestinal α-glucosidase, improvement of glucose transporter-4 (Glut4) translocation to the cell surface
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1–6 g/day
Duration of treatment	Long-term
Main expected effect	Improvement of Post Prandial Glycemia (PPG), HbA1c
Secundary positive effects	Regulation of cholesterolemia and body weight loss
Possible side effects (for suggested dosages)	Mild abdominal pain, diarrhea, constipation
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Yu S et al. Biofactors. 2017;43(1):90–99. Hernàndez-Gonzàlez SO et al. Nutr Res. 2010; 30(6):392–395

	Chlorogenic acid
Main source	Green coffee, black tea
Main indication	Hyperglycemia
Oral bioavailability	<30% (chlorogenic acid is metabolized in caffeic acid in the intestine)
Supposed main mechanism of action	Improvement of the kinase activity of insulin receptor β and Adenosin-Monophosphate-Kinase-alpha (AMPK), glucose transporter-4 (Glut4) translocation to the cell surface, the activity of downstream effectors of insulin signaling pI3-kinase and Akt, stimulation of insulin secretion and the secretion of glucagon-like peptide-1 (GLP-1), inhibition of the activity of α-Glucosidase and upregulation of expression of hepatic peroxisome proliferator-activated receptor alpha (PPAR-α)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–500 mg/day The title and the standardization of chlorogenic acid could be important to identify the most effective extracts of green coffee
Duration of treatment	Long-term
Main expected effect	Improvement of Fasting Plasma Glucose (FPG), Post Prandial Glycemia (PPG), HbA1c
Secundary positive effects	Regulation of cholesterolemia, lipid peroxidation, blood pressure, arterial stiffness, weight, inflammation [inhibition of the production of TNF-α and interleukin 6 (IL-6), IL-10, IL-4, IL-2, IL-12], brain and liver protection

	Chlorogenic acid
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Berberine, banaba
Suggested recent bibliography	Tajik N et al. Eur J Nutr. 2017;doi:https://doi.org/10.1007/s00394-017-1379-1. Cicero AF, Colletti A. Phytomedicine. 2016;23(11):1134–44.

	Chromium
Main source	Dietary supplements
Main indication	Chromium deficiency, hyperglycemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Improvement of the kinase activity of insulin receptor β and Adenosin-Monophosphate-Kinase-alpha (AMPK), glucose transporter-4 (Glut4) translocation to the cell surface, the activity of downstream effectors of insulin signaling pI3-kinase and Akt. Chromium also down-regulates Protein tyrosine phosphatase 1B (PTP-1B)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–200 mcg/day Chromium picolinate appears to be the most bioavailable form
Duration of treatment	Long-term
Main expected effect	Improvement of chromium deficiency, Fasting Plasma Glucose (FPG), HbA1c, Homeostasis Model Assessment Index (HOMA-index)
Secundary positive effects	Reduction of cholesterolemia and triglycerides
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation, kidney and/or liver disease
Possible pharmacokinetic interactions of clinical interest	Levothyroxine (chromium might reduce the bioavailability of this drug), nonsteroidal anti-inflammatory drugs (they increase chromium bioavailability)
Possible additive or synergistic nutraceuticals	Berberine, banaba
Suggested recent bibliography	Yin RV, et al. Nutr J. 2015;14:14. Suksomboon N, et al. J Clin Pharm Ther. 2014;39(3):292–306.

	Cinnamon
Main source	*Cinnamon zeylanicum, Cinnamon aromaticum*
Main indication	Hyperglycemia, Metabolic syndrome
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of alpha-glucosidase enzyme, improvement of glucose transporter-4 and -1 (Glut4 and Glut1) translocation to the cell surface, insulin sensitizers, activation of peroxisome proliferator-activated receptors (PPARs)-alpha and gamma.
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1–6 g/day of dry extract The title and the standardization of cinnamic acid, cinnamate and cinnamaldehyde could be important to identify the most effective extracts
Duration of treatment	Long-term
Main expected effect	Improvement of Fasting Plasma Glucose (FPG), HbA1c, Homeostasis Model Assessment Index (HOMA-index)
Secundary positive effects	Improvement of blood pressure, cholesterolemia and triglycerides
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Cicero AF, et al. Phytomedicine. 2016;23(11):1134–44. Costello RB, et al. J Acad Nutr Diet. 2016;116(11):1794–1802.

	Curcumin
Main source	*Curcuma longa*
Main indication	Mild hypercholesterolemia, hyperglicemia and vascular inflammation
Oral bioavailability	Very low (< 1%)
Supposed main mechanism of action	Modulation of hypothalamic–pituitary–adrenal axis, stimulation of synpasin I, cAMP responsive element-binding protein and Brain-Derived neurotrophic factor, MAO inhibition and regulation of Nrf2 transcription gene, reduction of the tumor necrosis factor-α (TNF-α) serum levels, inhibition of nuclear factor-kappa B (NF-κB) activation and protein carbonyl, lipid peroxidation and lysosomal enzyme activities, induction of peroxisome proliferator-activated receptor-gamma (PPAR-γ) and nuclear factor erythroid-2-related factor-2 (Nrf2) activations.
Level of support	Randomized clinical trials
Population tested	Adults, elderly

	Curcumin
Dose ranges	Curcumin: >1 g/day (usually 1.5 g/day) Curcumin in specific pharmaceutical forms improving the curcumin bioavailability (for instance micelles or nanoemulsions): >400/500 mg/day
Duration of treatment	Long-term
Main expected effect	Regulation of glycemia and vascular stiffness
Secundary positive effects	Improvement of cardiovascular disease risk factors [Reduction of inflammatory markers, plasma glutathione concentrations, insulin-resistance], prevention and/or treatment of any inflammation related disease
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps and/or upset, diarrhea, dizziness
Relative controindication	Pregnancy and lactation, Gilbert's disease or gallbladder problems, infertility, iron deficiency, bleeding problems, hormone-sensitive conditions (breast cancer, uterine cancer, ovarian cancer, uterine fibroids or endometriosis)
Possible pharmacokinetic interactions of clinical interest	Inhibition of CYP2C9; possible interactions with anticoagulant, antiplatelet and anticoagulant drugs, NSAIDs
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Zhang D et al. `Evid Based Complement Alternat` Med. 2013; 2013: 636053. Miaomiao et al. Biomed Res Int. 2017; 2017: 1516985.

	Fenugreek
Main source	*Trigonella foenum-graecum L.*
Main indication	Hyperglycemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Insulin sensitizers
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–1000 mg/day
Duration of treatment	Long-term
Main expected effect	Reductions of post-prandial glycemia, HOMA-insulin resistance index, insulinemia
Secundary positive effects	Mild improvement of cholesterolemia
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Rare and mild with standard suggested dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.

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	Fenugreek
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Neelakantan N, et al. Nutrition Journal 2014; 13(1): 7. Mohamadi N, et al. J Diet Suppl. 2017; 17:1–16.

	Glucomannan
Main source	*Amorphophallus konjac, Aloe vera*
Main indication	Mild-to-moderate hypercholesterolemia, hyperglycaemia, metabolic syndrome
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Prolonged gastric emptying time, inhibition of hepatic cholesterol synthesis, increase satiety and faecal excretion of cholesterol
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, children, elderly
Dose ranges	3–25 g/day
Duration of treatment	Long-term
Main expected effect	Reductions of post-prandial glycemia, HOMA-insulin resistance index, body mass index and low-density lipoprotein (LDL)
Secundary positive effects	Improvement of nitric oxide (NO) release
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Reduction of bioavailability of vitamin E, calcium and other minerals while it does not hinder the absorption of water-soluble vitamins. For these reasons, it is recommended to take the medication 1 h before or at least 4 h after taking glucomannan
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Sood N, et al. Am J Clin Nutr. 2008;88(4):1167–75. Jenkins AL, et al. Eur J Nutr. 2017 Jul 7.

	Gymnema
Main source	*Gymnema silvestre*
Main indication	Hyperglycemia, weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Increased secretion of insulin from the pancreas and promotion of islet cell regeneration, reduction of glucose absorption in the intestine
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, children, elderly

	Gymnema
Dose ranges	200–400 mg/day The title and the standardization of gymnemic acids could be important to identify the most effective extracts
Duration of treatment	Long-term
Main expected effect	Reductions of post-prandial glycemia, HOMA-insulin resistance index, body mass index (BMI) and low-density lipoprotein (LDL)
Secundary positive effects	Improvement of cholesterolemia
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Rare and mild with standard suggested dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Ota A, Ulrih NP. Frontiers in Pharmacology. 2017;8:436. Martínez-Abundis E et al. World J Diabetes. 2016;7(7):142–52.

	Magnesium
Main source	Dietary supplements
Main indication	Psychophysical stress, hypomagnesemia
Oral bioavailability	20–50%, variable Calcium, iron, copper, manganese, phosphorous and alcohol might decrease its bioavailability Magnesium aspartate, citrate, chloride and lactate are more bioavailable than magnesium hydroxide, oxide, and sulfate
Supposed main mechanism of action	Regulation of receptors with tyrosine-kinase activity (insulin receptos) and insulin-mediated cellular glucose uptake, phosphorylation of insulin receptor kinase Cofactor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis, responsible of several processes including hormone receptor binding, gating of calcium channels, muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability, neurotransmitter release
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	200–400 mg/day
Treatment duration	Cyclic/Long-term (depending on the disease control)
Main expected effect	Improvement of magnesemia and glycemic control (fasting and postprandial states)
Secundary positive effects	Improvement of depressive symptoms, anxiety and perceived stress, inflammation, attention deficit-hyperactivity disorder, Chronic fatigue syndrome, premenstrual syndrome, myalgia, cramps, headache, fibromyalgia, osteoporosis, high blood pressure
Possible side effects (for suggested dosages)	Mild diarrhea, stomach upset, nausea, heartbeat

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	Magnesium
Relative controindication	Pregnancy (>350 mg/day: few data available), kidney failure, heart block, bleeding disorders (inconclusive data), restless leg syndrome (inconclusive data)
Possible pharmacokinetic interactions of clinical interest	Per large doses with quinolone and antibiotics and bisphosphonates (decreased effectiveness of drugs), calcium channel blockers (increased effect of drus), muscle relaxants (increased risk of side effects], potassium sparing diuretics (risk of hypermagnesemia)
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Fang X et al. Nutrients. 2016; 8(11): 739. Barbagallo M et al. World J Diabetes. 2015; 6(10): 1152–1157.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA/ALA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*)
Main indication	Fasting glycemia reduction, cardiovascular disease prevention
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Improvement of functionality and dynamism of neuronal cells Reduction of the release and synthesis of inflammatory cytokines
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	1–4 g/day
Treatment duration	Long-term (cerebrovascular disease prevention)/Cyclic (usually 30–90 days)
Main expected effect	Improvement of Fasting Plasma Glucose (FPG), Homeostatic Model Assessment (HOMA) index, Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)
Secundary positive effects	Cardiovascular prevention, triglyceride lowering effect, anti-proarrhytmic and antinflammatory effects, macula protection, brain protection, mood stabilization
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Warfarin (possible increasing effect for use of high dosages)
Possible additive or synergistic nutraceuticals	Antioxidant, lipid-lowering and antinflammatory nutraceuticals
Suggested recent bibliography	De Rosa G, et al. Biofactors 2016; 42(3):316–322. Hy Wu J, et al. Br J Nutr. 2012; 107(0 2): S214–S227.

	Phaseolamin
Main source	*Phaseolus vulgaris*
Main indication	Hyperglycemia, weight loss
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of alpha-amylase activity
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	0,5–3 g/day of dry extract
Treatment duration	Long-term
Main expected effect	Improvement of Fasting Plasma Glucose (FPG), Homeostatic Model Assessment (HOMA) index, Insulin Resistance (IR)
Secundary positive effects	Weight loss
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Barret et al. Nutr J. 2011; 10: 24. De Gouveir MN et al. J Med Food. 2014; 17(8): 915–920.

	Psyllium
Main source	Dietary supplements (husks of blonde psyllium seed)
Main indication	Mild-to-moderate hypercholesterolemia, blood sugars control
Oral bioavailability	Not orally absorbed
Supposed main mechanism of action	Prolonged gastric emptying time, inhibiton of hepatic cholesterol synthesis (via the short-chain fatty acid byproducts of fiber fermentation), increase satiety and faecal excretion of cholesterol and bile salts (stimulating 7-α-hydroxylase)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, children, elderly
Dose ranges	3–20 g/day
Duration of treatment	Long-term/Cyclic
Main expected effect	Improvement of Post Prandial Glycemia (PPG), Fasting Plasma Glucose (FPG), HOMA index
Secundary positive effects	Improvement of cholesterolemia, body weight, irritable bowel syndrome (IBS)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages

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	Psyllium
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other glucose lowering nutraceuticals
Suggested recent bibliography	Ota A, Ulrih NP. Frontiers in Pharmacology. 2017;8:436. Gibb RD, et al. Am J Clin Nutr. 2015;102(6):1604–14.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplements
Main indication	Vitamin D deficiency, osteopenia, cardiovascular prevention
Oral bioavailability	Ergocalciferol (vit. D2) is apparently absorbed with similar efficiency to cholecalciferol (vit. D3), however 25-hydroxyvitamin D (25OHD) is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol. The amount of fat with which vit. D is ingested does not seem to significantly modify the bioavailability of vit. D3. Hypochlorhydria decreases vitamin D bioavailability
Supposed main mechanism of action	Not definitively determined
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	400–3000 IU of cholecalciferol /day (400 IU = 10 mcg)
Treatment duration	Long-term (plausible suspension in summer time)
Main expected effect	Improvement of fasting plasma glucose (FPG), homeostatic model assessment (HOMA) index, HbA1c, insulin resistance (IR) especially in people with baseline levels of vitamin D deficiency
Secundary positive effects	Improvement of depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], vit. C deficiency, age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption, tyrosinemia, heart failure symptoms, cognitive decline (preliminary data)
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (increased effects), diltiazem, verapamil (decreased efficacy), thiazide diuretics (elevated serum calcium), proton pump inhibitors, sucrose polyesters and tetrahydrolipstatin (diminish vit. D absorption)

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Possible additive or synergistic nutraceuticals	Not investigated on diabetes prevention
Suggested recent bibliography	Wu C et al. Metabolism. 2017;73:67–76 Giri D et al. BMC Res Notes. 2017;10(1):465.

Nutraceuticals for Body Weight Modulation

	Caralluma
Main source	*Caralluma fimbriata*
Main indication	Weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of hunger
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	1 gr/day of dry extract
Treatment duration	Cyclic (at least 60 days)
Main expected effect	Mild body weight decrease, improvement of waist circumference
Secundary positive effects	Related to body weight loss
Possible side effects (for suggested dosages)	Stomach upset, intestinal gas, constipation, and stomach pain
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Ekta A, et al. Perspect Clin Res. 2015;6(1):39–44. Kuriyan G, et al. Appetite. 2007; 48:338–44.

	Capsaicin
Main source	Plants of genus *Capsicum*
Main indication	Weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Activation of transient receptor potential vanilloid 1 receptor (TRPV1), improvement of satiety and energy expenditure and increased lipolysis of the brown adipose tissue
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	50–300 mg/day

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https://doi.org/10.1007/978-3-319-73642-6_8

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	Capsaicin
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	Mild weight reduction
Secundary positive effects	Improvement of pain and analgesic effect, platelet anti-aggregating effect
Possible side effects (for suggested dosages)	Stomach irritation and upset, sweating, flushing, and runny nose
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Janssens PL, et al. Appetite. 2014;77:44–9. Snitker, et al. Am J Clin Nutr. 2009;89:45–50.

	Chitosan
Main source	Dietary supplements (husks of blonde psyllium seed)
Main indication	Mild-to-moderate hypercholesterolemia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Prolonged gastric emptying time, inhibiton of hepatic cholesterol synthesis (via the short-chain fatty acid byproducts of fiber fermentation), increase satiety and faecal excretion of cholesterol and bile salts (stimulating 7-α-hydroxylase)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1–6 gr/day
Duration of treatment	Long-term
Main expected effect	Mild body weight reduction (−1–5%)
Secundary positive effects	Improvement of glyemia, HOMA index
Possible side effects (for suggested dosages)	Transient abdominal pain, diarrhea, or constipation (rare and dose-dependent)
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Kim HJ, et al. Food Funct. 2014(10):2662–9. Lengfield H, et al. Obes Res. 1999;60(suppl1):O132.

	Cissus
Main source	*Cissus quadrangolaris*
Main indication	Weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of alpha-glucosidase and pancreatic lipase
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	150–300 mg/day
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	Weight reduction (−5–9% in 10 weeks)
Secundary positive effects	Improvement of cholesterolemia and glycemia
Possible side effects (for suggested dosages)	None, beyond individual intolerance to the product
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	*Irvingia gabonensis* and other nutraceuticals acting on body weight
Suggested recent bibliography	Kuate D, et al. Nat Prod Commun. 2015;10(7):1281–6. Oben JE, et al. Lipids Health Dis. 2008;7:12.

	Citrus aurantium
Main source	*Citrus aurantium var. amara L.*
Main indication	Body weight modulation
Oral bioavailability	Not definitive data available in humans
Supposed main mechanism of action	P-Sinephrine have a stimulating effect on beta 3 receptors and therefore a lipolytic and thermogenic action
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	10–50 mg/day of synephrine The main pharmacologically active compound of Citrus is p-synephrine (para synephrine or ossedrine)
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	1–5 Kg in 60 days of treatment
Secundary positive effects	Related to body weight loss
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Preganncy and lactation, children under the age of 12

	Citrus aurantium
Possible pharmacokinetic interactions of clinical interest	MAO inhibitors, caffeine and stimulant drugs, dextromethorphan (taking bitter orange with these medications used for depression might cause serious side effects including fast heartbeat, high blood pressure, seizures and nervousness), midazolam, felodipine, indinavir, and drugs substrate of cytochrome P450 3A4 (bitter orange might increase the effects and side effects of these durgs), antiarrhythmic drugs (bitter orange might increase the speed of heartbeat)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Shara M, et al. Phytother Res. 2016;30(5):842–7. Sidney JS, et al. Int J Med Sci. 2012; 9(7): 527–538.

	Chlorogenic acid
Main source	Green coffee, black tea
Main indication	Hyperglycemia, weight loss
Oral bioavailability	<30% (chlorogenic acid is metabolised in caffeic acid in the intestine)
Supposed main mechanism of action	Improvement of the kinase activity of insulin receptor β and Adenosin-Monophosphate-Kinase-alpha (AMPK), glucose transporter-4 (Glut4) translocation to the cell surface, the activity of downstream effectors of insulin signaling pI3-kinase and Akt, stimulation of insulin secretion and the secretion of glucagon-like peptide-1 (GLP-1), inhibition of the activity of α-Glucosidase and upregulation of expression of hepatic peroxisome proliferator-activated receptor alpha (PPAR-α)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–500 mg/day The title and the standardization of chlorogenic acid could be important to identify the most effective extracts
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	Reduction of weight (−1–8%)
Secundary positive effects	Improvement of Fasting Plasma Glucose (FPG), post prandial glycemia (PPG), HbA1c, regulation of cholesterolemia, lipid peroxidation, blood pressure, arterial stiffness, inflammation [inhibition of the production of TNF-α and interleukin 6 (IL-6), IL-10, IL-4, IL-2, IL-12], brain and liver protection
Possible side effects (for suggested dosages)	None identified for standard dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans), anemia, anxiety disorders, bleeding disorders, heart conditions, diarrhea, glaucoma, irritable bowel syndrome (IBS), osteoporosis
Possible pharmacokinetic interactions of clinical interest	Other nutraceuticals acting on body weight

	Chlorogenic acid
Possible additive or synergistic nutraceuticals	Prebiotics
Suggested recent bibliography	Tajik N, et al. Eur J Nutr. 2017 Apr 8. doi: https://doi.org/10.1007/s00394-017-1379-1. Beam JR, et al. Nutrition. 2015;31(2):292–7.

	Fucoxanthin
Main source	*Undaria pinnatifida*, *Hijika fusiformis, Myagropsis myagroides*, *Dictyota coriacea*, *Himanthalia elongata*, *Petalonia binghamiae*, *Turbinaria turbinate*, *Laminaria japonica*, *Phaeodactylum tricornutum*, *Odontella aurita*, *Isochrysis*
Main indication	Weight control
Oral bioavailability	15–45% Fucoxanthin absorption is enhanced in the presence of fatty acids
Supposed main mechanism of action	Reduction of white adipose tissue (activation of Uncoupling Protein 1 (UCP1) and stimulation of β3-adrenergic receptor), reduction of gene expression of the fat-regulating enzymes malic enzyme (ME), Glucose-6-Phosphate Dehydrogenase (G6PD) and fatty acid synthetase (FAS), activation of 5' AMP-activated protein kinase (AMPK)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	2–5 mg/day
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	Weight reduction (−5 Kg in 16 weeks)
Secundary positive effects	Reduction of liver enzymes (ALT, AST GGT) and liver fat after prolonged usage, circulating leptin levels, improvement of metabolic rate, circulating adiponectin levels, reduction high sensible protein C reactive (hsCRP), circulating levels of interleukin (IL) and tumor necrosis factor-alpha (TNF-α)
Possible side effects (for suggested dosages)	Stomach irritation and upset, sweating, headache
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Wan-Loy C, Siew-Moi P. Mar Drugs. 2016;14(12). pii: E222. Abidov et al. Diabetes Obes Metab. 2010;12:72–81.

	Garcinia
Main source	*Garcinia cambogia*
Main indication	Weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of adenosine triphosphate citrate lyase (reduction of fatty acids synthesis), pancreatic alpha-amylase and intestinal alpha-glucosidase
Level of support	Randomized lable clinical trials
Population tested	Adults, elderly
Dose ranges	1500 mg/day of dry extract The title and the standardization of hydroxycitric acid could be important to recognize the most effective extracts
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	Weight reduction (1–5 kg)
Secundary positive effects	Improvement of exercise performance (preliminary data), glycemia (preliminary data)
Possible side effects (for suggested dosages)	Nausea, digestive tract discomfort and headache
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Yamada T, et al. Appl Microbiol Biotechnol. 2007;75:977:82. Sullivan C, et al. Am J Clin Nutr. 1997:30;767–776.

	Glucomannan
Main source	*Amorphophallus konjac*
Main indication	Mild-to-moderate hypercholesterolemia, weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Prolonged gastric emptying time, inhibiton of hepatic cholesterol synthesis, increase satiety and faecal excretion of cholesterol
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, children, elderly
Dose ranges	3–25 g/day
Duration of treatment	Long-term
Main expected effect	Mild reduction of body weight associated to LDL-C reduction
Secundary positive effects	Improvement of nitric oxide (NO) release
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Reduction of bioavailability of vitamin E, calcium and other minerals: for these reasons, it is recommended to take the medication 1 h before or at least 4 h after taking glucomannan

	Glucomannan
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Onakpoya I, et al. J Am Coll Nutr. 2014;33(1):70–8. Sood N, et al. Am J Clin Nutr. 2008;88(4):1167–75.

	Green tea
Main source	*Camellia sinensis*
Main indication	Weight control
Oral bioavailability	Intestinal uptake of green tea catechins is low, less than 2%
Supposed main mechanism of action	Inhibition of Catechol-O-Methyltransferase (COMT), NADPH oxidase, activation of glucose transporter-4 (GLUT-4) and improvement of thermogenesis
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–1200 mg/day of catechins The title and the standardization of epigallocatechin-3-gallate (EGCG), epi-gallocatechin (EGC), epicatechin gallate (ECG) and epicatechin (EC) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (at least 60 days)/Long-term
Main expected effect	Weight reduction (−3–8%)
Secundary positive effects	Improvement of arterial stiffness, insulin sensitivity, insulin secretion and glycemia, cholesterolemia, triglyceridemia, adiponectin levels, cognitive performance, mood, memory, fatigue, oxygen uptake, skin quality, maximal oxygen consumption (VO2 max), reduction of exercise-induced oxidation, muscle soreness, carbohydrate absorption, lipid oxidation
Possible side effects (for suggested dosages)	Stomach upset, constipation, headache, nervousness, sleep disorders, diarrhea, irritability, irregular heartbeat, tremors, dizziness, tinnitus (for very high commonly not used dosages)
Relative controindication	Anemia (a decrease in iron absorption associated with green tea catechins has been observed), anxiety disorders, bleeding disorders, heart conditions, diarrhea, glaucoma, irritable bowel syndrome (IBS), osteoporosis
Possible pharmacokinetic interactions of clinical interest	Ephedrine, fluconazole, alcohol, MAOIs, nicotine (these drugs can increase side effects of caffeine), quinolone antibiotics and contraceptive drugs, cimetidine, clozapine, mexiletine, terbinafine, verapamil, estrogens (these drugs might slow caffeine metabolism), lithium (green tea might increase lithium clearance), adenosine, warfarin (green tea decrease the effectiveness of warfarin), theophylline
Possible additive or synergistic nutraceuticals	NOPE and other nutraceuticals acting on body weight
Suggested recent bibliography	Yang CS, et al. Mol Nutr Food Res. 2016;60(1):160–74. Huang J, et al. Eur J Clin Nutr. 2014;68(10):1075–87.

	Griffonia
Main source	*Griffonia simplicifolia*
Main indication	Weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Reduction of appetite (increased serotonin levels)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	55–90 mg/day of 5-HTP (5-hydroxytryptophan)
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	Reduction of weight (1–6 kg) in subjects with 25–30 of body mass index (BMI)
Secundary positive effects	Improvement of mood and depressive symptoms [Improvement of Leiden Index of Depression Sensitivity (LEIDS-r), Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D)]
Possible side effects (for suggested dosages)	Mild heartburn, stomach pain, nausea, diarrhea, drowsiness, sexual problems, eosinophilia-myalgia syndrome (EMS) (Very rare)
Relative controindication	Pregnancy and lactation (not enough data available in humans), children
Possible pharmacokinetic interactions of clinical interest	Antidepressant drugs [eg. Fluoxetine, paroxetine, sertraline, clomipramine, amitriptyline, imipramine, MAOIs) (taking 5-HTP along with medications for depression], carbidopa, dextromethorphan, meperidine, pentazocine, tramadol
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Rondanelli M, et al. Eat Weight Disord. 2012;17(1):e22–8. Emanuele E, et al. Neuro Endocrinol Lett. 2010;31(5):663–6.

	Guarana and caffeine
Main source	*Paullinia cupana* Caffeine (Dietary supplements)
Main indication	Body weight modulation
Oral bioavailability	Good (caffeine >95%)
Supposed main mechanism of action	Enhancement of cyclic AMP (adenosine 5′-cyclic monophosphate) pathway, cAMP synthesis and reduction of cAMP degradation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–200 mg/day of caffeine
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	1–5 Kg in 60 days of treatment (if associated to a correct lifestyle)
Secundary positive effects	Improvement of muscle contractility, antiemicranic and analgesic action (reduction of release of adenosine-mediated pain mediators and activation of noradrenergic routes), positive inotropic and chronotropic effect, temporary increase of blood pressure, improvement of acid secretion at gastric level (action on H2 receptors), mobilization of abdominal fat reserves

	Guarana and caffeine
Possible side effects (for suggested dosages)	Dose-related insomnia, nervousness and restlessness, stomach irritation, nausea, increased heart rate and blood pressure, rapid breathing, tremors, delirium, diuresis. Large guaranà doses might cause headache, anxiety, agitation, tinnitus, stranguria, stomach cramps and irregular heartbeats
Relative controindication	Preganncy and lactation, children under the age of 12, diarrhea, irritable bowel syndrome (IBS), anxiety
Possible pharmacokinetic interactions of clinical interest	Ephedrine, amphetamines, quinolone antibiotics, verapamil, cimetidine, disulfiram, estrogens, fluvoxamine, MAOIs, theophylline, nicotine (increase in side effects of caffeine), riluzole, lithium, phenylpropanolamine, clozapine (increase in side effects of these drugs)
Possible additive or synergistic nutraceuticals	Ephedrine and other nutraceuticals acting on body weight
Suggested recent bibliography	Lima NDS, et al. Nutrients. 2017 Jun 20;9(6). pii: E635. Heckman MA, et al. J Food Sci. 2010;75(3):R77–87.

	N-oleyl-phosphatidylethanolamine (NOPE)
Main source	Dietary supplements
Main indication	Weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	GPR119 agonist receptors [increased glucagon-like peptide-1 (GLP-1) production]
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	150–250 mg/day
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	Reduction of weight (−3/4 Kg in association with EGCG)
Secundary positive effects	Improvement of mood
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Epigallocatechin gallate (EGCG) and other nutraceuticals acting on body weight
Suggested recent bibliography	Mangine GT, et al. Lipids Health Dis. 2012 Oct 4;11:127. Rondanelli M, et al. Brit J Nutr. 2009;101(3):457–64.

	Irvingia
Main source	*Irvingia gabonensis*
Main indication	Weight control
Oral bioavailability	Definitive data not available in humans

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	Irvingia
Supposed main mechanism of action	Inhibition of pancreatic alpha-amylase, prolonged gastric emptying time, increase satiety and faecal excretion of cholesterol and bile salts
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–200 mg/day
Duration of treatment	Cyclic/Chronic
Main expected effect	Weight reduction (−10/12% in 10 weeks in association with Cissus)
Secundary positive effects	Improvement of cholesterolemia, triglyceridemia and glycemia
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	*Cissus quadrangularis* and other nutraceuticals acting on body weight
Suggested recent bibliography	Martínez-Abundis E et al. World J Diabetes. 2016;7(7):142–52. Oben JE et al. Lipids Health Dis. 2008;7:12.

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Main source	Dietary supplements Dairy products and derivatives
Main indication	Mild overweight in patients with intestinal dysbiosis
Oral bioavailability	*Lactobacilli* and *Bifidobacteria* colonize the intestinal lumen *Saccharomyces* it's a fermenter yeast, but doesn't colonize the intestinal lumen
Supposed main mechanism of action	Definitive data not available in humans/Multiple: restore intestinal eubiosis and fermentation of short-chain fatty acids with hypotensive activities
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>3.5 UFC (live)/day The administration of probiotic strains, to obtain the maximum effectiveness, should be taken before the main meal with a lipid vehicle (eg. yogurt or milk)
Treatment duration	Long-term
Main expected effect	Reduction of body weight (1–4 Kg in 4 weeks)

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Secundary positive effects	Improvement of bowel health, prevention of cardiovascular risk (regulation of cholesterolemia, blood pressure, inflammatory marker), regulation of the immune system, chemoprevention, prevention of urinary infections and improvement of its symptoms (eg. burning, pain), regulation of mood, depressive symptoms and anxiety [Improvement of Leiden Index of Depression Sensitivity (LEIDS-r), Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D)]
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Prebiotics and other nutraceuticals acting on body weight
Suggested recent bibliography	Robles-Vera I, et al. Curr Hypertens Rep. 2017;19(4):26. Kobyliak N, et al. Nutr Metab (Lond). 2016;13:14.

	Psyllium
Main source	Dietary supplements (husks of blonde psyllium seed)
Main indication	Mild-to-moderate hypercholesterolemia, modulation of weight
Oral bioavailability	None
Supposed main mechanism of action	Prolonged gastric emptying time, inhibiton of hepatic cholesterol synthesis (via the short-chain fatty acid byproducts of fiber fermentation), increase satiety and faecal excretion of cholesterol and bile salts (stimulating 7-α-hydroxylase)
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Children, Elderly
Dose ranges	3–20 g/day
Duration of treatment	Long-term
Main expected effect	Mild weight loss
Secundary positive effects	Improvement of glyemia, HOMA index, irritable bowel syndrome (IBS)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects, mainly bloating
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Inhibition of absorption of some drugs, vitamins and minerals, avoidable if assumed far from meals and drug assumption
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting on body weight
Suggested recent bibliography	Ribas SA, et al. Br J Nutr. 2015;113(1):134–41. Wei ZH, et al. Eur J Clin Nutr. 2009;63(7):821–7.

	Rhodiola
Main source	*Rhodiola rosea*
Main indication	Psyhcophysical stress, weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Adaptogen, inhibition of Catechol-O-methyltransferase (COMT), increased transport of 5-hydroxytriptofan through the hematoencephalic barrier, modulation of HPA (hypothalamic–pituitary–adrenal) axis
Level of support	Randomized clinical trials
Population tested	Adults
Dose ranges	340–680 mg/day of dry extract The title and the standardization of salidroside, rhodioloside, rosavin and tyrosol could be important to recognize the most effective extracts
Treatment duration	Cyclic (usually 60 days)
Main expected effect	Regulation of body weight
Secundary positive effects	Improvement of mood memory, cognition and depressive symptoms [Hamilton Depression Rating Scale (HAM-D), Mini Mental State Examination (MMSE), Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)], reduction of physical and mental fatigue, anxiety and modulation of immune system
Possible side effects (for suggested dosages)	Gastrointestinal symptoms, insomnia, nervousness
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Rhodiola is an inhibitor of CYP3A4 and CYP2C19 (*in vitro*) even if it does not interfere with the warfarin metabolism (CYP2C9)
Possible additive or synergistic nutraceuticals	No clinically relevant interaction has been yet confirmed
Suggested recent bibliography	Amsterdam JD, Panossian AG. Phytomedicine. 2016; 23(7):770–83. Hung SK et al. Phytomed. 2011;18:235–44.

	Yohimbine
Main source	*Pausinystalia yohimbe*
Main indication	Weight control
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Non-selective antagonist of alpha2-adrenergic receptors
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	0.2–5 mg/Kg/day
Duration of treatment	Cyclic (at least 60 days)
Main expected effect	Weight reduction (−1/5 Kg in 3–4 weeks)

	Yohimbine
Secundary positive effects	Improvement of exercise performance (preliminary data), erectile dysfunction (preliminary data)
Possible side effects (for suggested dosages)	Arrhytmias, polyuria, kidney failure, bloating, dyspepsia, excitation, irritability, tremor, sleep problems, anxiety or agitation, high blood pressure, dizziness, headache, seizure, rash. High doses can also cause dyspnoea, hypotension, and arrhytmias
Relative controindication	Pregnancy and lactation (not enough data available in humans), children, bleeding conditions (taking yohimbe might increase the risk of bleeding in people with bleeding disorders), schizophrenia, prostate problems (Yohimbe might make the symptoms of benign prostatic hyperplasia (BPH) worse), post-traumatic stress disorder (PTSD), liver and kidney disease, high or low blood pressure, heart disease, chest disease, anxiety, depression
Possible pharmacokinetic interactions of clinical interest	Mao inhibitors (MAOIs) (taking yohimbe along with MAOIs might increase the effects and side effects of yohimbe and MAOIs), clonidine (taking yohimbe along with clonidine might decrease the effectiveness of these drugs), tricyclic antidepressants (taking yohimbe along with these medications used for depression might cause heart problems), naloxone (taking naloxone along with yohimbine might increase the chance of side effects such as anxiety, nervousness,trembling, and hot flashes), phenothiazines (taking yohimbe along with phenothiazines might increase the effects and side effects of yohimbine), stimulant drugs (eg. diethylpropion, epinephrine, phentermine, pseudoephedrine) (taking yohimbe along with stimulant drugs might cause serious problems including increased heart rate and high blood pressure)
Possible additive or synergistic nutraceuticals	Prebiotics, probiotics
Suggested recent bibliography	Pittler MH et al. Obes Rev. 2005;6(2):93–111. Pittler MH, Ernst E. Am J Clin Nutr. 2004;79(4):529–36.

Nutraceuticals Active on Digestive System

	Alginic acid (Sodium, magnesium, aluminum, calcium, potassium alginate)
Main source	Dietary supplements
Main indication	Symptomatic treatment of epigastralgia associated with dyspepsia and esophagitis
Oral bioavailability	0% (the conjugated salts are absorbed as free cations)
Supposed main mechanism of action	Mechanical protective "barrier effect"
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	500–1000 mg/day
Treatment duration	Cyclic (usually 30–90 days)/Symptomatic
Main expected effect	Improvement of Gastroesophageal Reflux Disease (GERD), Nonerosive Reflux Disease (NERD) and dyspepsia symptomatology
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages Long-term aluminum consumption (aluminum alginate) could be linked to an increase in neurodegenerative diseases and cancer Depending on the conjugated salt, in Long-term administration it is possible an increase of the risk of hypercalemia, hypernatriemia and hypermagnesemia
Relative controindication	None, beyond individual intolerance to the product
Possible pharmacokinetic interactions of clinical interest	Oral drugs (alginate may interfere with the absorption of oral medications by the formation of a "sticky gel")
Possible additive or synergistic nutraceuticals	Magnesium hydroxide, bromelain, sodium bicarbonate
Suggested recent bibliography	Sun J et al. Aliment Pharmacol Ther. 2015; 42(7):845–54. Corvaglia L et al. Aliment Pharmacol Ther. 2011;33(4):466–70.

A.F.G. Cicero, A. Colletti, *Handbook of Nutraceuticals for Clinical Use*,
https://doi.org/10.1007/978-3-319-73642-6_9

	Aloe
Main source	*Aloe vera*
Main indication	Constipation, dyspepsia, inflammatory bowel disease (IBD)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of PG-E2 synthesis, inhibition of various transcription factors and LOX and COX activity
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	200–400 ml/day
Duration of treatment	Long-term/Cyclic/Symptomatic
Main expected effect	Improvement of constipation and irritable bowel disease (Simple Clinical Colitis Activity Index and histological scores)
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Abdominal cramps, diarrhea
Relative controindication	Pregnancy and lactation, diabetes, allergy to plants of the Liliaceae family
Possible pharmacokinetic interactions of clinical interest	Aloe latex is a laxative, it may reduce the absorption and therefore the effectiveness of some drugs that are taken orally Aloe improves the absorption of both the vitamin C and E Potential interactions have been suggested for *Aloe vera* and drugs that may alter electrolyte balance, such as thiazide diuretics and corticosteroids. Possible hypokalemia-related arrhythmia suggests a potential herb–drug interaction with cardiac glycosides
Possible additive or synergistic nutraceuticals	Laxative nutraceuticals
Main recent comprehensive references	Langhorst J et al. J Crohns Colitis. 2015;9(1):86–106. Langmead L et al. Aliment Pharmacol Ther. 2004;19(7):739–47.

	Andrographis
Main source	*Andrographis paniculata*
Main indication	Inflammatory bowel disease (IBD)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of T cell proliferation and T_H1/T_H17 responses
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1200–1800 mg/day
Duration of treatment	Long-term/Cyclic
Main expected effect	Improvement of Irritable Bowel Disease (Simple Clinical Colitis Activity Index and histological scores)
Secundary positive effects	Improvement of common cold, reduction of the fever and sore throat due to tonsillitis
Possible side effects (for suggested dosages)	Abdominal cramps, hematochezia, hematuria, rash

	Andrographis
Relative controindication	Pregnancy and lactation, fertility problems (inconclusive data), Auto-immune diseases" such as multiple sclerosis (MS), lupus (systemic lupus erythematosus, SLE) and rheumatoid arthritis (RA) (andrographis might increase the symptoms of auto-immune diseases), increased bleeding risk conditions
Possible pharmacokinetic interactions of clinical interest	Immunosuppressants (andrographis might reduce their efficacy) and anticoagulant or antiplatelet drugs (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Not investigated
Main recent comprehensive references	Triantafyllidi A et al. Ann Gastroenterol. 2015;28(2):210–220. Gabrielian F et al. Phytomedicine. 2002;9(7):589–97.

	Anthraquinones
Main source	*Senna alexandrina, Rhamnus purshiana, Rhamnus frangula*, *Aloe vera, Rheum rhabarbarum*
Main indication	Acute and long-term constipation
Oral bioavailability	Very low
Supposed main mechanism of action	Na^+/K^+-ATPase pump inhibition, increased release of autacoids and prostaglandins
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	10–50 mg/day of anthraquinone glycosides
Treatment duration	Cyclic (usually 1–2 weeks)
Main expected effect	Improvement of constipation
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Stomach cramps, diarrhea, abdominal colic, hemorrhoid, reversible colon melanosis, discoloration of the urine
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Oral drugs (anthraquinones may interfere with the absorption of oral medications)
Possible additive or synergistic nutraceuticals	Laxative nutraceuticals
Suggested recent bibliography	Gordon M et al. Cochrane Database Syst Rev. 2016;8:CD009118. Cirillo C et al. Phytother Res. 2015; 29(10):1488–93.

	Artichoke
Main source	*Cynara scolymus, Cynara cardunculus*
Main indication	Dyspepsia, Irritable Bowel Syndrome
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Gastric emptying promotion

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	Artichoke
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	1–3 g/day
Duration of treatment	Cyclic (30–90 days)
Main expected effect	Improvement of dyspepsia and Irritable Bowel Syndrome symptoms, quality of life in subjects with Irritable Bowel Syndrome (total quality-of-life (QOL) score)
Secundary positive effects	Improvement of LDL and HDL cholesterol, liver transaminases, fasting plasma glucose
Possible side effects (for suggested dosages)	Transient gastrointestinal effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	*Zingiber officinalis*, curcumin, cholorogenic acid, dandelion, rosemary
Suggested recent bibliography	Holtmann G et al. Aliment Pharmacol Ther. 2003;18(11–12):1099–105. Lazzini S et al. Eur Rev Med Pharmacol Sci. 2016;20(1):146–9.

	Boswellia
Main source	*Boswellia serrata*
Main indication	Chron's disease, irritable bowel syndrome (IBS)
Oral bioavailability	Variable. Compared to the fasted state, the administration of boswellic acids concomitantly with a high-fat meal led to several-fold increased areas under the plasma concentration-time curves as well as peak concentrations of boswellic acids.
Supposed main mechanism of action	Interaction on 5-LOX, leukocyte elastase, topoisomerase 1 and 2, and IkappaB kinases
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	2400–3600 mg/day of dry extract The title and the standardization of boswellic acids could be important to recognize the most effective extracts
Duration of treatment	3–12 months
Main expected effect	Improvement of Crohn's disease and irritable bowel disease symptoms
Secundary positive effects	Benefits on ulcerative colitis, bronchial asthma and peritumoral cerebral edema. In patients with arthritis: reduction of pain, reduction of cartilage degradation, improvement of physical activity. In patients with long-term colitis: improvement and sometimes remission of the disease.

	Boswellia
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin, antiplatelet and anticoagulant medications (boswellia increases the risk of bleeding)
Possible additive or synergistic nutraceuticals	Curcumin
Suggested recent bibliography	Triantafyllidi A et al. Ann Gastroenterol. 2015;28(2): 210–220. Gerhardt H et al. Z Gastroenterol. 2001;39(1):11–7.

	Capsaicin
Main source	Plants of genus *Capsicum*
Main indication	Dyspepsia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	50–300 mg/day
Duration of treatment	Symptomatic
Main expected effect	Improvement of heartburn and dyspepsia symptoms
Secundary positive effects	Weight reduction, pain and analgesic effects
Possible side effects (for suggested dosages)	Stomach irritation and upset, sweating, flushing, and runny nose
Relative controindication	Pregnancy and lactation (few data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data)
Possible additive or synergistic nutraceuticals	Not investigated
Main recent comprehensive references	McCarty MF, et al. Open Heart. 2015; 2(1): e000262. Rodriguez-Stanley S, et al. Aliment Pharmacol Ther. 2000;14(1):129–34.

	Carbonates (calcium, magnesium, sodium, potassium carbonate)
Main source	Dietary supplements
Main indication	Symptomatic treatment of epigastralgia associated with dyspepsia and gastroesophageal reflux
Oral bioavailability	0% (the conjugated salts are absorbed as free cations)
Supposed main mechanism of action	Antacid effect

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	Carbonates (calcium, magnesium, sodium, potassium carbonate)
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	300–5000 mg/day
Treatment duration	Cyclic (usually 30–90 days)/ Symptomatic
Main expected effect	Improvement of Gastroesophageal Reflux Disease *(*GERD*)* and Nonerosive Reflux Disease (NERD) related symptoms
Secundary positive effects	None, beyond individual intolerance to the product
Possible side effects (for suggested dosages)	Stomach cramps, flatulence, belching, nausea. Depending on the conjugated salt, in long-term administration it is possible an increase of the risk of hypercalemia, hypernatriemia and hypermagnesemia
Relative controindication	Pregnancy and lactation (not enough data in humans)
Possible pharmacokinetic interactions of clinical interest	Oral drugs (carbonate may interfere with the absorption of oral medications for the reduction of gastric pH)
Possible additive or synergistic nutraceuticals	Alginates
Suggested recent bibliography	Tighe M et al. Cochrane Database Syst Rev 2014;11:CD008550. Pellicano R et al. Minerva Gastroenterol Dietol. 2009;55(3):227–35.

	Chamomile
Main source	*Matricaria chamomilla, German chamomile*
Main indication	Dyspepsia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Benzodiazepine-like activity (apigenin)
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	220–1100 mg/day of dry extract (apigenin titration 1–1.5%) The title and the standardization of flavonoids (as rutin) and terpenoids (as farnesene) could be important to recognize the most effective extracts
Treatment duration	Symptomatic/cyclic
Main expected effect	Improvement of anxiety sypmtoms (latency, quality and duration of sleep) and dyspepsia
Secundary positive effects	Improvement of mucositis
Possible side effects (for suggested dosages)	Allergies

	Chamomile
Relative controindication	Pregnancy and lactation (not enough information available as supplement), hormone sensitive cancers conditions (some chemicals in chamomile act like estrogen), allergies to ragweed or related plants
Possible pharmacokinetic interactions of clinical interest	Per high dosages with contraceptive drugs and estrogens (chamomile might have some estrogen-like effects), sedative medications as benzodiazepines, zolpidem or barbiturates (sleepiness and drowsiness), alcohol (sleepiness and drowsiness), tamoxifen (decrease the effectiveness), warfarin (increase the effectiveness), medications substrates of CYP1A2 and 3A4 (could increase the effectiveness)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Singh O et al. Pharmacogn Rev 2011; 5(9): 82–95. Srivastava JK et al. Mol Med Report. 2010; 3(6): 895–901.

	Cumin
Main source	*Nigella sativa*
Main indication	Dyspepsia, diarrhea, bowel spasms, irritable bowel syndrome (IBS), patients on drug therapy for the eradication of *H. pylori*
Oral bioavailability	Definitive data not available in humans (dihydrothymoquinone, and terpenes could be responsible for the effects of the plant)
Supposed main mechanism of action	Suppression of inflammatory mediators and oxidative stress: inhibition the synthesis of 5-lipoxygenase, eicosanoid generation through inhibition of both lipoxygenase and LTC4 synthase pathways
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	50–300 mg/day
Duration of treatment	Symptomatic/Cyclic
Main expected effect	Improvement of gastrointestinal symptoms (diarrhea, spasms, dyspepsia)
Secundary positive effects	Improvement in endothelial dysfunction, glucose metabolism, lipid profile and blood pressure, Headache prophylaxix
Possible side effects (for suggested dosages)	None, beyond individual intolerance to the product
Relative controindication	Pregnancy and lactation (not enough data available in humans) Increased bleeding risk conditions
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Gholamnezhad Z. J Ethnopharmacol. 2016;190:372–86. Pandey S et al. PLoS One. 2015; 10(12): e0144469.

	Curcumin
Main source	*Curcuma longa*
Main indication	Dyspepsia
Oral bioavailability	Very low (< 1%)
Supposed main mechanism of action	Modulation of hypothalamic–pituitary–adrenal axis, stimulation of synpasin I, cAMP responsive element-binding protein and Brain-Derived neurotrophic factor, MAO inhibition and regulation of Nrf2 transcription gene
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	Curcumin: >1 g/day (usually 1.5 g/day) Curcumin in specific pharmaceutical forms improving the curcumin bioavailability (for instance micelles or nanoemulsions): >400/500 mg/day
Duration of treatment	Cyclic (usually 30–90 days)/Long-term
Main expected effect	Improvement of Chron's symptomatology (Crohn's Disease Activity Index), reduction of interleukin-1, C-reactive protein, tumor necrosis factor-alpha and enzyme prenylated protein methyltransferase
Secundary positive effects	Improvement of depressive symptoms [Hamilton Depression Rating Scale (HAM-D)] and reduction of serum and salivary stress markers such as cortisol and interleukins, cardiovascular disease risk factors [Reduction of inflammatory markers, improvement of glutathione plasma concentrations and NrF-2, regulation of insulin-resistance and cholesterolemia], prevention and/or treatment of headaches, arthritis, joint pain, stomach pain, ulcerative colitis, diarrhea, irritable bowel syndrome, fibromyalgia, immune system dysfunction, bladder inflammation, cognitive function
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps and/or upset, diarrhea, dizziness
Relative controindication	Pregnancy and lactation (only as Dietary supplement), Gilbert's disease or gallbladder problems, infertility, iron deficiency, bleeding problems, hormone-sensitive conditions (breast cancer, uterine cancer, ovarian cancer, uterine fibroids or endometriosis)
Possible pharmacokinetic interactions of clinical interest	Inhibition of CYP450 (in particular CYP2C9) Possible interactions with anticoagulant and antiplatelet drugs (aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin), diclofenac, ibuprofen, naproxen and other NSAIDs.
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Schneider A et al. Complement Ther Med. 2017;33:32–38. Taylor LA et al. Altern Med Rev 2011;16(2):152–6.

	Fennel
Main source	*Foeniculum vulgare*
Main indication	Dyspepsia, irritable bowel syndrome (IBS)
Oral bioavailability	Definitive data not available in humans

	Fennel
Supposed main mechanism of action	Spasmolytic and anti-inflammatory activity
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	Unclear
Duration of treatment	Cyclic (30–90 days)
Main expected effect	Improvement of dyspepsia and IBS symptoms [Visual Analogue Scale (VAS), Irritable Bowel Syndrome-symptom severity score (IBS-SSS)], quality of life in subjects with IBS (total quality-of-life (QOL) score)
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	None, beyond individual intolerance to the product
Relative controindication	None, beyond individual intolerance to the product
Possible pharmacokinetic interactions of clinical interest	None identified for standard dosages
Possible additive or synergistic nutraceuticals	Curcumin
Suggested recent bibliography	Portincasa P, et al. J Gastrointestin Liver Dis. 2016(2):151–7. Shamkant B, et al. Biomed Res Int. 2014; 2014: 842,674.

	Ginger
Main source	*Zingiber officinale*
Main indication	Nausea and vomiting (especially in association with antiretroviral drugs and after surgical treatments)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Increased gastric tone and motility due to anticholinenergic (M3) and antiserotonergic (5HT3) actions, increased gastric emptying, dose-dependent; inhibition of cyclooxygenase 2, interleukin-1β, tumor necrosis factor-alpha, inducible nitric oxide synthase, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and matrix metalloproteinases expression, neutralization of free radicals and oxidative stress
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	200–2500 mg/day of dry extract The title and the standardization of gingerols + shogaols (1–4%) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (usually 30–90 days)/ Symptomatic
Main expected effect	Reduction of nausea and vomiting (especially when due to chemotherapy, antiretroviral drugs or after surgical treatments), abdominal pain, improvement dyspepsia and irritable bowel syndrome (preliminary data)

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	Ginger
Secundary positive effects	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation, reduction of painful menstrual periods, morning sickness and dizziness, improvement of headache, alcohol hangover, chronic obstructive pulmonary disease
Possible side effects (for suggested dosages)	Mild heartburn, diarrhea, general stomach discomfort and extra menstrual bleeding
Relative controindication	Bleeding disorders
Possible pharmacokinetic interactions of clinical interest	Warfarin, aspirin, clopidogrel, dalteparin, heparin, phenprocoumon, and others anticoagulant and antiplatelet drugs (Ginger might slow blood clotting)
Possible additive or synergistic nutraceuticals	Artichoke
Suggested recent bibliography	Lete I et al. Integr Med Insights. 2016; 11: 11–17. Marx W et al. Crit Rev Food Sci Nutr. 2017;57(1):141–146.

	Hydroxides (aluminium, calcium, magnesium, sodium, potassium hydroxide)
Main source	Dietary supplements
Main indication	Symptomatic treatment of epigastralgia associated with dyspepsia and esophagitis
Oral bioavailability	0% (the conjugated salts are absorbed as free cations)
Supposed main mechanism of action	Buffer action
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	200–800 mg/day
Treatment duration	Cyclic (usually 30–90 days)/ Symptomatic
Main expected effect	Improvement of Gastroesophageal Reflux Disease *(*GERD*)*, Nonerosive Reflux Disease (NERD) and dyspepsia symptomatology
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Stomach cramps, flatulence, belching, nausea; depending on the conjugated salt, in Long-term administration it is possible an increase of the risk of hypercalemia, hypernatriemia and hypermagnesemia
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Oral drugs (carbonate may interfere with the absorption of oral medications for the reduction of gastric pH)
Possible additive or synergistic nutraceuticals	Alginates, carbonates
Suggested recent bibliography	Sun J, et al. Aliment Pharmacol Ther. 2015; 42(7): 845–854. Tran T et al. AP&T. 2007; 25(2):143–153.

	Lactulose
Main source	Dietary supplement
Main indication	Constipation, hepatic encephalopathy
Oral bioavailability	Very low
Supposed main mechanism of action	Lactulose is the substrate of the bacterial colon microflora that degrades it by producing hydrogen, methane, lowering the faecal pH, releasing short chain fatty acids, and reclaiming water
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	15–60 ml/day
Treatment duration	Cyclic (usually 30–90 days)/ Symptomatic
Main expected effect	Improvement of constipation
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Stomach cramps, flatulence, belching, nausea
Relative controindication	Pregnancy and lactation (not enough data in humans)
Possible pharmacokinetic interactions of clinical interest	Oral drugs (lactulose may interfere with the absorption of oral medications)
Possible additive or synergistic nutraceuticals	Sorbitol
Suggested recent bibliography	Treepongkaruna S et al. BMC Pediatr. 2014; 14: 153. Di Palma JA et al. Rev Gastroenterol Disord. 2004;4(Suppl. 2):S34-S42.

	Melissa
Main source	*Melissa officinalis, Melissa graveolens, Melissa calamintha, Melissa romana, Melissa glandulosa, Melissa glomerata, Melissa montana*
Main indication	Definitive data not available in humans
Oral bioavailability	Not determined
Supposed main mechanism of action	Benzodiazepine-like activity, inhibition of monoamine oxidase (MAO-A) (preliminary data), neuro-sedative and spasmolytic effect (attributed to anti-thyroid activity)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	300–600 mg/day of dry extract (rosmarinic acid 35–40 mg/g of dry extract) The title and the standardization of rosmarinic acid (35–40 mg/g of dry extract) could be important to identify the most effective extracts
Treatment duration	Symptomatic/Cyclic (usually 30–90 days)
Main expected effect	Improvement of anxiety [Hamilton Anxiety Rating Scale (HAM-A)] and stress
Secundary positive effects	Improvement of cold sores, dyspepsia and insomnia
Possible side effects (for suggested dosages)	Mild headache, dizziness, stomach upset, nausea, wheezing

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	Melissa
Relative controindication	Pregnancy and lactation (not enough information available)
Possible pharmacokinetic interactions of clinical interest	Sedative medications as benzodiazepines, zolpidem or barbiturates (sleepiness and drowsiness), alcohol (sleepiness and drowsiness)
Possible additive or synergistic nutraceuticals	*Cynara scolymus*
Suggested recent bibliography	Moeko NS et al. PLoS One. 2015; 10(5): e0126422. Gasbarrini G et al. J Biol Regul Homeost Agents. 2010;24(1):93–8

	Mint
Main source	*Mentha piperita*
Main indication	Dyspepsia, Irritable Bowel Syndrome (IBS)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Spasmolytic and anti-inflammatory action
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	90 mg/day of mint oil
Treatment duration	Symptomatic/Cyclic
Main expected effect	Reduction of dyspepsia and IBS symptoms scores, improvemet of quality of life
Secundary positive effects	Improvement of headache, migraine, breastfeeding discomfort, relaxing the colon during medical exams, including barium enemas
Possible side effects (for suggested dosages)	Diarrhea, nausea
Relative controindication	Pregnancy and lactation (not enough information available)
Possible pharmacokinetic interactions of clinical interest	Cyclosporine, Medications substrate of CYP 2C19, 1A2, 2C9, 3A4 (alteration of pharmacokinetic profiles)
Possible additive or synergistic nutraceuticals	Caraway oil
Suggested recent bibliography	Knonche A et al. J Ethnopharmacol. 2017;206:267–273. Mikaili P, et al. Anc Sci Life. 2013; 33(2): 131–138.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*)
Main indication	Inflammatory bowel disease
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Improvement of functionality and dynamism of cells, substrates for anti-inflammatory eicosanoid production and for the synthesis of resolvins, maresins and protectins

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	2–4 g/day of eicosapentanoic and/or docosahexaenoic acid
Treatment duration	Long-term
Main expected effect	Attenuation of the inflammatory responses in Irritable Bowel Disease, reducing oxidative stress, production of tumor necrosis factor-α and proinflammatory cytokines, working as chemopreventive agents, and decreasing the expression of adhesion molecules
Secundary positive effects	Cardiovascular prevention, mood stabilization, triglyceride lowering effect, anti-proarrhytmic and antinflammatory effects, macula protection, brain protection
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time. The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Relative controindication	None, beyond individual intolerance to the product
Possible pharmacokinetic interactions of clinical interest	Warfarin (possible increasing effect for use of high dosages)
Possible additive or synergistic nutraceuticals	Lipid-lowering and antinflammatory nutraceuticals
Suggested recent bibliography	Barbalho SA et al. Ann Gastroenterol. 2016; 29(1): 37–43. Farrukh A et al. World J Clin Cases. 2014; 2(7): 250–252.

	Pycnogenol
Main source	*Pinus pinaster*
Main indication	Inflammatory bowel disease
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Improvement of nitric oxide (NO) production, renal cortical blood flow and endothelial function, reduction of myeloperoxidase activity improves and levels of high-sensitivity C-reactive protein (hs-CRP), inhibition of myeloperoxidase (MPO) activity
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>100 mg/day
Treatment duration	Long-term
Main expected effect	Improvement of Chron's disease
Secundary positive effects	Reduction of blood pressure, hs-CRP levels and vascular inflammation, improvement of vascular stiffness, athletic performance, asthma and allergies, mental function (preliminary data), retina disease (preliminary data)
Possible side effects (for suggested dosages)	Mild dizziness, gut problems, headache, and mouth ulcers

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	Pycnogenol
Relative controindication	Pregnancy and lactation Patients with auto-immune diseases (pycnogenol seems to increase the immune system)
Possible pharmacokinetic interactions of clinical interest	Immunosuppressants (pycnogenol seems to increase the immune system)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Mochizuki M, Hasegawa N. Phytother Res. 2004;18(12):1027–8. Maimoona A et al. J Ethnopharmacol. 2011;133:261–77.

	Prebiotics
Main source	Soluble fibers [inulin, fructooligosaccharides (FOS) and galactoligosaccharides (GOS), pectins, gums, mucilages, polyols, beta-glucans, *arabinoxylan*oligosaccharides (AXOS)] and insoluble fibers (cellulose and lignin)
Main indication	Constipation, hemorrhoid, diverticulitis, irritable bowel syndrome (IBS)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Osmotic effect, intestinal bacterial fermentation and eubiosis restoration
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, Children, Elderly
Dose ranges	>20 g/day
Duration of treatment	Cyclic
Main expected effect	Improvement of constipation (daily evacuation number)
Secundary positive effects	Improvement of glycemia, body weight, cholesterolemia, irritable bowel syndrome (IBS), hemorrhoids and diverticulitis
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Digoxin, warfarin, metformin, penicillin, clindamycin and tetracycline (alterations of pharmacokinetic profiles)
Possible additive or synergistic nutraceuticals	Probiotics
Main recent comprehensive references	Rao SS et al. Aliment Pharmacol Ther. 2015;41(12):1256–70. Yang J et al. World J Gastroenterol. 2012; 18(48):7378–83.

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Main source	Dietary supplements Dairy products and derivatives
Main indication	Gastrointestinal dysbiosis, patients on drug therapy for the eradication of *H. pylori*
Oral bioavailability	*Lactobacilli* and *Bifidobacteria* colonize the intestinal lumen *Saccharomyces* is a fermenter yeast, but doesn't colonize the intestinal lumen The administration of probiotic strains, to obtain the maximum effectiveness, should be taken before the main meal with a lipid vehicle (eg. yogurt or milk)
Supposed main mechanism of action	Restore intestinal eubiosis
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>3.5 UFC (live)/day
Treatment duration	Long-term (Long-term dysbiosis)/Cyclic (usually 30–90 days)
Main expected effect	Improvement of intestinal symptoms, acute infectious diarrhoea, antibiotic-associated diarrhoea, *Clostridium difficile*-associated diarrhea, pouchitis and *Helicobacter pylori* infection eradication, constipation, abnominal discomfort, irritable bowel syndrome, inflammatory bowel disease, diverticular diseases
Secundary positive effects	Improvement of bowel health, mild improvement of some cardiovascular risk factors (cholesterolemia, blood pressure, inflammatory marker), regulation of the immune system, prevention of urinary infections and improvement of its symptoms. Regulation of mood, depressive symptoms and anxiety [Improvement of Leiden Index of Depression Sensitivity (LEIDS-r), Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D)]
Possible side effects (for suggested dosages)	Minors (mostly of gastrointestinal nature)
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Not determined: it is possible that probiotics interfere with molecules subject to intestinal enzymatic metabolism (eg. polyphenols, berberine)
Possible additive or synergistic nutraceuticals	Prebiotics
Suggested recent bibliography	Derwa I et al. Aliment Pharmacol Ther. 2017;46(4):389–400. Domingo JJ. Gastroenterol Hepatol. 2017;40(6):417–429.

	Resveratrol
Main source	Dietary supplement
Main indication	Irritable Bowel Disease
Oral bioavailability	Less than 1% (extensive first pass liver metabolism)

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	Resveratrol
Supposed main mechanism of action	Anti-oxidant, stimulation of endothelial production of nitric oxide (NO), inhibition of vascular inflammation and prevention of platelet aggregation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>150 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of Irritable Bowel Disease symptomatology and quality of life (Simple Clinical Colitis Activity Index Questionnaire (SCCAIQ), Inflammatory Bowel Disease Questionnaire-9 (IBD Q-9), serum level of malondialdehyde (MDA), superoxide dismutase (SOD), and total anti-oxidant capacity (TAC))
Secundary positive effects	Improvement of blood pressure 1–10 mmHg (systolic), 1–5 mmHg (diastolic), reduction of vascular inflammation and improvement of athletic performance (preliminary data)
Possible side effects (for suggested dosages)	Minors (mostly of gastrointestinal nature)
Relative controindication	Pregnancy and lactation (few data available), bleeding disorders, hormone-sensitive condition such as breast cancer, uterine cancer, ovarian cancer, uterine fibroids, endometriosis (resveratrol might act like estrogen)
Possible pharmacokinetic interactions of clinical interest	Medications substrate of cytochrome P450 3A4 as lovastatin, ketoconazole, itraconazole, fexofenadine, triazolam (resveratrol is an inhibitor of CYP3A4), anticoagulant/antiplatelet (resveratrol might slow blood clotting) as aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin
Possible additive or synergistic nutraceuticals	Not investigated
Main recent comprehensive references	Lu Y et al. Inflamm Bowel Dis. 2017; doi: https://doi.org/10.1097/MIB.0000000000001108. Samsamikor M et al. Arch Med Res. 2016;47(4):304–9.

	Sorbitol
Main source	Dietary supplement
Main indication	Constipation
Oral bioavailability	Very low
Supposed main mechanism of action	Osmotic agent
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	5–20 g/day
Treatment duration	Cyclic (usually 30–90 days)/ Symptomatic
Main expected effect	Improvement of constipation
Secundary positive effects	Not clinically relevant

	Sorbitol
Possible side effects (for suggested dosages)	Stomach cramps, flatulence, belching, nausea, diarrhea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Oral drugs (lactulose may interfere with the absorption of oral medications)
Possible additive or synergistic nutraceuticals	Sorbitol
Suggested recent bibliography	Gonzalez-Martinez MA et al. J Clin Gastroenterol. 2014;48(1): 21–28. Portalatin M et al. Clin Colon Rectal Surg. 2012; 25(1):12–9.

	Vitamin C (ascorbic acid)
Main source	Dietary supplements
Main indication	Irritable Bowel Disease
Oral bioavailability	50–90% (above 1 g may be less than 50%)
Supposed main mechanism of action	Unclear
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–1000 mg/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of Irritable Bowel Disease symptomatology
Secundary positive effects	Improvement of arterial stiffness, depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], vitamin C deficiency, age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption, tyrosinemia, reduction of blood pressure, 3–10 mmHg (systolic), 1–4 mmHg (diastolic)
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Haemochromatosis, previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, iron, estrogens (vitamin C could increase the effects), fluphenazine, warfarin, protease inhibitors (vitamin C could drecrease the effects)
Possible additive or synergistic nutraceuticals	Vitamin E
Suggested recent bibliography	Masri OA et al. World J Gastroenterol. 2015;21(17):5191–209. Yan H et al. Int J Clin Exp Med. 2015; 8(11): 20,245–20,253.

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Main source	Dietary supplements
Main indication	Irritable Bowel Disease
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	400–800 IU/day
Duration of treatment	Long-term
Main expected effect	Improvement of Irritable Bowel Disease symptomatology
Secundary positive effects	Improvement of cholesterolemia, arterial stiffness and endothelial function (reduction of the serum levels of hsCRP, advanced glycation end products, metalloproteinases and cell adhesion molecules)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation, bleeding disorders, head and neck cancer, prostate cancer, heart attack, stroke, angioplasty and diabetes
Possible pharmacokinetic interactions of clinical interest	Warfarin (risk of bleeding), Cyclosporine (Vitamin E might enhance the bioavailability of this drug), Medications substrate of CYP450 (Vitamin E might enhance the hepatic clearance)
Possible additive or synergistic nutraceuticals	Vitamin C
Suggested recent bibliography	Masri OA et al. World J Gastroenterol. 2015;21(17):5191–209. Scalera A et al. World J Gastroenterol. 2013;19(33):5402–420.

Nutraceuticals Active on Urinary Tract

	Cranberry
Main source	*Vaccinum macrocarpon*
Main indication	Urinary tract infection
Oral bioavailability	Anthocyanins: less than 1%
Supposed main mechanism of action	Reduction of pH of urinary tract and adhesion of fimbriated bacteria to bladder urothelium and urethra (agglutination of bacterial fimbriae and inhibition of bacterial biofilm formation)
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	Proanthocyanidins A (PACs A) >70 mg/day The title and the standardization of proanthocyanidins A could be important to recognize the most effective extracts
Treatment duration	Acute (10–15 days) or cyclic (usually 10–15 days each 3 month)
Main expected effect	Reduction of incidence of urinary tract infections (particularly in individuals with recurrent urinary tract infections)
Secundary positive effects	Reduction of the administration of antibiotics
Possible side effects (for suggested dosages)	Mild stomach upset, diarrhea
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Warfarin (increased risk of bleeding), CYP2C9 substrates (as amitriptyline, diazepam, zileuton, celecoxib, diclofenac, fluvastatin, glipizide, ibuprofen, irbesartan, losartan, phenytoin, piroxicam, tamoxifen, tolbutamide, torsemide)
Possible additive or synergistic nutraceuticals	*Arctostaphylos uva-ursi*, *L. rhamnosus*
Suggested recent bibliography	Luis A et al. J Urol. 2017;198(3):614–621. Rossi et al. J Clin Gastroenterol. 2010;44 Suppl 1:S61–2.

	D-Mannose
Main source	Dietary supplement
Main indication	Urinary tract infection
Oral bioavailability	Very good (in fasted state, D-mannose is absorbed almost completely)
Supposed main mechanism of action	Bacteriostatic effect

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	D-Mannose
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	2 g/day
Treatment duration	Acute or Cyclic (at least 30 days)
Main expected effect	Reduction of the incidence of urinary tract infections (particularly in individuals with recurrent urinary tract infections)
Secundary positive effects	Reduction of the administration of antibiotics (preliminary data)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation, diabetes type II
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Cranberry, solidago
Suggested recent bibliography	Kranjčec B et al. World J Urol. 2014 Feb;32(1):79–84. Duane RH et al. Rev Urol. 2013; 15(2): 41–48.

	Grapefruit
Main source	*Citrus paradisi*
Main indication	Prevention of kidney stones
Oral bioavailability	Definitive data are not available in humans
Supposed main mechanism of action	Increased urinary excretion of citrate, calcium and magnesium
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	1 cup/day
Treatment duration	Acute or Cyclic (at least 30 days)
Main expected effect	Reduction of the incidence of kidney stones
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Grapefruit is a potent inhibitor of CYP 450 thus potentially increasing the plasma concentration of a large part of drugs and xenobiotics
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Kranjčec B et al. World J Urol. 2014;32(1):79–84. Robinson MR et al. J Urol. 2009; 18(13);145–50.

	Ortosiphon
Main source	*Orthosiphon aristatus, Orthosiphon ferrugineus*
Main indication	Urinary tract infection
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Natriuretic
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>150 mg/day
Treatment duration	Acute or Cyclic (usually 10–15 days)
Main expected effect	Increased volume of urinary fluid
Secundary positive effects	Reduction of postprandial glycemia (PPG) (preliminary data)
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans), fluid retention caused by heart or kidney problems
Possible pharmacokinetic interactions of clinical interest	Lithium, natriuretics
Possible additive or synergistic nutraceuticals	Cranberry, solidago
Suggested recent bibliography	Frumenzio E et al. Arch Ital Urol Androl. 2013;85(4):197–9. Duane RH et al., Rev Urol. 2013; 15(2): 41–48.

	Phyllanthus
Main source	*Phyllanthus niruri*
Main indication	Kidney stones
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Litogenesis inhibitor
Level of support	Open label clinical trials
Population tested	Adults, Elderly
Dose ranges	500–1200 mg/day
Treatment duration	Cyclic (at least 30 days)
Main expected effect	Reduction of kidney stones formation
Secundary positive effects	Coleretic effect
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Van Exel NJ, et al. Eur Urol. 2006;49 (1):92–102. Kramer G, et al. Curr Opin Urol. 2000; 10:35–8.

	Piloselle
Main source	*Hieracium pilosella*
Main indication	Urinary tract infection
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of lipoxygenase, diuretic activity
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	>15 mg/day of vitexin The title and the standardization of vitexin could be important to recognize the most effective extracts
Treatment duration	Acute or Cyclic (usually 10–15 days)
Main expected effect	Increased volume of urinary fluid, reduction of urinary inflammation
Secundary positive effects	Coleretic effect
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Cranberry, solidago
Suggested recent bibliography	Gawrońska-Grzywacz M et al. J Sep Sci. 2007;30(5):746–50. Duane RH et al. Rev Urol. 2013; 15(2): 41–48.

	Potassium/Magnesium citrate
Main source	Dietary supplements
Main indication	Kidney stones
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Citrate reduces urinary supersaturation of calcium salts by forming soluble complexes with calcium ions and by inhibiting crystal growth and aggregation, increases the activity of some macromolecules in the urine (eg.Tamm-Horsfall protein) that inhibit calcium oxalate aggregation and it seems able to reduce the expression of urinary osteopontin
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	>500 mg/day
Treatment duration	Cyclic
Main expected effect	Increase urinary citrate and reduce stone formation rates
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Mild dizziness, drowsiness, nausea

	Potassium/Magnesium citrate
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	MAO inhibitors (possibly fatal drug interaction), guaifenesin and dextromethorphan
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Caudarella R, et al. Arch Ital Urol Androl. 2009;81(3):182–7. Kramer G, et al. Curr Opin Urol. 2000; 10:35–8.

	Uva ursi
Main source	*Arctostaphylos uva-ursi*
Main indication	Urinary tract infection
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antimicrobial and diuretic effect
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>200 mg/day of arbutin The title and the standardization of arbutin could be important to recognize the most effective extracts
Treatment duration	Acute or Cyclic (usually 10–15 days)
Main expected effect	Reduction of genitourinary inflammation and infections
Secundary positive effects	Reduction of antibiotics consumption vs *Staphylococcus* and *E. coli* infections
Possible side effects (for suggested dosages)	Mild nausea and stomach discomfort, harmless greening of the urine
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Lithium Arbutin is thought to increase inhibitory action of prednisone and dexamethasone on contact dermatitis, allergic reactions, hypersensitivity and arthritis
Possible additive or synergistic nutraceuticals	Cranberry, solidago
Suggested recent bibliography	Duane RH et al. Rev Urol. 2013; 15(2): 41–48. Head K et al. Altern Med Rev. 2008;13(3):227–44.

	Vitamin A
Main source	Dietary supplements
Main indication	Urinary tract infection (adjuvant to antibiotic therapy)
Oral bioavailability	10–70%
Supposed main mechanism of action	Not definitively determined
Level of support	Randomized clinical trials

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	Vitamin A
Population tested	Adults, elderly
Dose ranges	200,000 IU/day Iron and zinc deficiencies may alter the absorption and metabolism of vitamin A
Treatment duration	Cyclic (at least 30 days)
Main expected effect	Reduction of the incidence of urinary tract infections
Secundary positive effects	Improvement of vitamin a deficiency, malaria symptoms, cataracts, diarrhea related to HIV, measles complications, oral leukoplakia, complications after and during pregnancy in malnourished women, retinitis pigmentosa
Possible side effects (for suggested dosages)	Fatigue, irritability, mental changes, anorexia, stomach discomfort, nausea, mild fever, excessive sweating
Relative controindication	Pregnancy and lactation (<10,000 units per day), Type V hyperlipoproteinemia, excessive use of alcohol and liver disease
Possible pharmacokinetic interactions of clinical interest	Tetracycline antibiotics (icreased risk of intracranial hypertension) and warfarin (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Vitamin C
Suggested recent bibliography	Duane RH et al. Rev Urol. 2013; 15(2): 41–48. Yilmaz A et al. Pediatr Int. 2007; 49: 310–3.

	Vitamin C (Ascorbic acid)
Main source	Dietary supplements
Main indication	Urinary tract infection
Oral bioavailability	50–90% (above 1 g may be less than 50%)
Supposed main mechanism of action	Acidification of the urine, modulation of immune system
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	200–2500 mg/day
Treatment duration	Cyclic (usually 30–90 days)
Main expected effect	Improvement of immune system (antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis, and delayed-type hypersensitivity), reduction of incidence of urinary tract infections
Secundary positive effects	Improvement of vitamin C deficiency, depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption and tyrosinemia, reduction of urinary nitrites to reactive nitrogen oxides
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache

	Vitamin C (Ascorbic acid)
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Blood-iron disorders, previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, iron, estrogens (vitamin C could increase the effects), fluphenazine, warfarin, protease inhibitors (vitamin C could drecrease the effects)
Possible additive or synergistic nutraceuticals	Cranberry, *Arctostaphylos uva-ursi*, *L. rhamnosus*, folic acid, ferrous sulphate
Suggested recent bibliography	Montorsi et al. Eur Urol. 2016;70(6):912–915. Duane RH et al. Rev Urol. 2013;15(2):41–48.

Nutraceuticals Active on Genital Apparatus

	Astragalus
Main source	*Astragalus glycyphyllos, Astragalus lentiginosus, Astragalus trichopodus, Astragalus canadensis, Astragalus lemmonii, Astragalus didymocarpus, Astragalus miguelensis, Astragalus pachypus, Astragalus nuttallii Astragalus pulsiferae, Astragalus purshii, Astragalus nevinii, Astragalus agrestis, Astragalus tener*
Main indication	Idiopathic infertility
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined (astragalus contains zinc and folic acid, essential micronutrients to ensure normal spermatozoa functionality)
Level of support	Open label clinical trials
Population tested	Adults, Elderly
Dose ranges	400–1200 mg/day of dry extract
Duration of treatment	Cyclic (>30 days)
Main expected effect	Improvement of sperm motility
Secundary positive effects	Modulation of the immune system
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (at high dosages not enough data available), auto-immune diseases
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	*Serenoa repens, Pygeum africanum, Urtica dioica*, zinc, selenium, lycopene
Suggested recent bibliography	Yao DF, Mills JN. Asian J Androl. 2016;18(3):410–8. Kim W et al. J Tradit Complement Med. 2015;6(3):294–8.

	Cordyceps
Main source	*Cordyceps sinensis*
Main indication	Erectile dysfunction (ED), idiopathic infertility
Oral bioavailability	Definitive data not available in humans

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https://doi.org/10.1007/978-3-319-73642-6_11

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	Cordyceps
Supposed main mechanism of action	Not definitively determined (cordyceps contains vitamin B1, 2, 12, E, K, C, essential amino acids, polyamides, polysaccharides, cordyptic acid, fatty acids, proteins, galactosan, alkaloids, steroids, guanidine, oleic, linoleic, linolenic, palmitic and stearic acids, uridine and many other micronutrients)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–1000 mg/day The title and the standardization of beta-glucans could be important to recognize the most effective extracts
Duration of treatment	Long-term
Main expected effect	Improvement of libido, sexual performance, motility, functionality and sperm count
Secundary positive effects	Improvement of exercise performance (preliminary data), VO2 max, testosterone/cortisol ratio (overtraining), antioxidant and ergogenic muscle capacity, regulation of immune system
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been confirmed
Possible additive or synergistic nutraceuticals	*Serenoa repens, Pygeum africanum, Urtica dioica*, zinc, selenium, lycopene
Suggested recent bibliography	Hardeep ST et al. 3 Biotech. 2014; 4(1): 1–12. Chang Y et al. Am J Chin Med. 2008;36(5):849–59.

	Cucurbita
Main source	*Cucurbita pepo*
Main indication	Benign prostatic hypertrophy (BPH)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined (antinflammatory activity)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–1000 mg/day of seeds extract
Duration of treatment	Long-term
Main expected effect	Improvement of LUTS (Lower Urinary Tract Symptoms), quality of life and BPH symptomatology [international prostate function score (IPSS)]
Secundary positive effects	Not reported

	Cucurbita
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been confirmed
Possible additive or synergistic nutraceuticals	*Serenoa repens, Pygeum africanum, Urtica dioica*, zinc, selenium, lycopene
Suggested recent bibliography	Pagano E, et al. Phytother Res. 2014;28(7):949–55. Dreikorn K, et al. Urologe A. 2002; 41(5):447–51.

	Garlic
Main source	*Allium sativum*
Main indication	Erectile dysfunction (ED) in patients with high blood pressure
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Improvement of nitric oxide (NO), H2S and bradykinin production, Angiotensin-converting enzyme (ACE) inhibition, calcium channel blocking, reduction of catecholamine sensitivity
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	600–900 mg/day The title and the standardization of S-allylcysteine and ajoene (0.4–1%) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (>30 days)
Main expected effect	Reduction of blood pressure 10–15 mmHg (systolic) and 8–10 mmHg (diastolic) and improvement of erectile function
Secundary positive effects	Improvement of sexual dysfunction, arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)], prevention of prostate cancer, colon and rectal cancer, exercise performance (preliminary data)
Possible side effects (for suggested dosages)	Halytosis, heartburn, nausea, bloating, body odor, diarrhea, mildly increased risk of bleeding
Relative controindication	Pregnancy and lactation (at high dosages not enough data available), bleeding disorder, stomach or digestion problems, hypotension
Possible pharmacokinetic interactions of clinical interest	Isoniazid (garlic could reduce its absorption), Non-Nucleoside Reverse Transcriptase Inhibitors, birth control pills, cyclosporine and saquinavir (garlic might decrease the effectiveness of these drugs), CYP2E1 substrates as acetaminophen, chlorzoxazone, theophylline (garlic is an inhibitor of CYP2E1), CYP3A4 substrates as lovastatin, azole antimycotics fexofenadine, triazolam (garlic is an inducer of CYP3A4), anticoagulant/antiplatelet drugs and FANS (garlic might increase the bleeding time when associated to these drugs)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Sirtori CR, et al. Ann Med. 2015;47(6):447–56. Nishimatsu H, et al. Aging Male. 2014;17(2):112–6.

	Ginkgo
Main source	*Ginkgo biloba L.*
Main indication	Idiopathic infertility
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Adaptogen
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	80–400 mg/day of dry extract The title and the standardization of ginkosides could be important to recognize the most effective extracts
Duration of treatment	Cyclic (>30 days)
Main expected effect	Improvement of erectile dysfunction, libido and sexual performance
Secundary positive effects	Improvement of anxiety, cognitive decline, glaucoma, peripheral vascular disease, premenstrual syndrome, dyskinesia, vertigo, schizophrenia, attention deficit-hyperactivity disorder (preliminary data)
Possible side effects (for suggested dosages)	Stomach upset, headache, dizziness, constipation, forceful heartbeat, allergic skin reactions
Relative controindication	Pregnancy and lactation, infants and children, seizures, bleeding conditions, diabetes, infertility
Possible pharmacokinetic interactions of clinical interest	Ibuprofen, anticoagulant/antiplatelet drugs (increased risk of bleeding), alprazolam, efavirenz (ginkgo might decrease the effect of these drugs), buspirone, efavirenz, fluoxetine, medications substrate of CYP450 1A2 (as clozapine, cyclobenzaprine, fluvoxamine, haloperidol, imipramine, mexiletine, olanzapine, pentazocine, propranolol, theophylline, zileuton, zolmitriptan), CYP450 2C19 (as amitriptyline, carisoprodol, citalopram, diazepam, lansoprazole, omeprazole, phenytoin, warfarin), CYP450 2C9 (as amitriptyline, diazepam, zileuton, celecoxib, diclofenac, fluvastatin, glipizide, ibuprofen, irbesartan, losartan, phenytoin, piroxicam, tamoxifen, tolbutamide, torasemide, warfarin), CYP450 2D6 (as amitriptyline, clozapine, codeine, desipramine, donepezil, fentanyl, flecainide, fluoxetine, meperidine, methadone, metoprolol, olanzapine, ondansetron, tramadol, trazodone) and CYP450 3A4 (as lovastatin, clarithromycin, cyclosporine, diltiazem, estrogens, indinavir, triazolam), antidiabetes drugs
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Yao DF, Mills JN. Asian J Androl. 2016;18(3):410–8. Corazza O, et al. Biomed Res Int. 2014;2014:841798.

	Ginseng
Main source	*Panax ginseng meyer*, *Panax quinquefolus*
Main indication	Idiopathic infertility
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant, adaptogen

	Ginseng
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1000–2000 mg/day The title and the standardization of ginsenosides could be important to recognize the most effective extracts
Duration of treatment	Cyclic (>30 days)
Main expected effect	Improvement of erectile dysfunction, sperm motility, premature ejaculation and sexual arousal, reduction of production of reactive oxygen species, creatine phosphokinase, and interleukin-6 levels
Secundary positive effects	Improvement of exercise performance, VO2 max, muscular strength, nitric oxide production, mental performance in cognitive decline, chronic obstructive pulmonary disease, flu
Possible side effects (for suggested dosages)	Insomnia, menstrual problems, breast pain, increased heart rate, high or low blood pressure, headache, loss of appetite, diarrhea, itching, rash, dizziness, mood changes, vaginal bleeding, Stevens-Johnson syndrome (rare), liver damage (rare) and severe allergic reactions (rare)
Relative controindication	Pregnancy and lactation, infants and children, auto-immune diseases, insomnia, hormone-sensitive conditions as endometriosis, or uterine fibroids, schizophrenia, bleeding conditions and heart diseases
Possible pharmacokinetic interactions of clinical interest	Alcohol, caffeine, antidiabetic drugs, MAOIs and stimulant drugs (Ginseng might increase the side effects of these drugs), furosemide (Ginseng might decrease the effects of furosemide), medications substrates of CYP 2D6 [amitriptyline, clozapine, codeine, desipramine, donepezil, fentanyl, flecainide, fluoxetine, meperidine, methadone, metoprolol, olanzapine, ondansetron, tramadol, trazodone (alterations of pharmacokinetic profiles), immunosuppressant (Ginseng increases the immune system), anticoagulant/antiplatelet drugs (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Vitamin C
Suggested recent bibliography	Park HJ, et al. Chin J Integr Med. 2016;22(7):490–5. Yao DF, Mills JN. Asian J Androl. 2016;18(3):410–8.

	Green tea
Main source	*Camellia sinensis*
Main indication	Prevention of prostate cancer
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of cell growth, induction of apoptosis, reduction of angiogenesis and expression of matrix metalloproteases
Level of support	Randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	250 to 1200 mg/day of green tea extract / 170 to 850 mg/day of epigallocatechin-3-gallate (EGCG)
Duration of treatment	Chronic
Main expected effect	Prevention of prostate cancer (data to be confirmed)

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	Green tea
Secundary positive effects	Improvement of arterial stiffnees [Flow Mediated Dilation (FMD), Pulse Wave Velocity (PWV)], glycemia, cholesterolemia and reduction of blood pressure
Possible side effects (for suggested dosages)	Mild grastrointestinal discomfort. High doses of green tea can cause a deficiency of iron and folate due to its capacity to bind and reduce their intestinal absorption
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Warfarin, Pentobarbital, Dipyridamole (decrease their effectiveness), Theophylline, Adenosine (synergistic actions with caffeine), Riluzole, Phenylpropanolamine, MAO inhibitors, Clozapine (green tea increase the effects and side effects of these drugs)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Lee PMY et al. Prostate Cancer Prostatic Dis. 2017;20(3):318–22. Saverio B et al. Cancer Res 2006;66(15):1234.

	L-carnitine
Main source	Dietary supplements
Main indication	Erectile dysfunction (ED), idiopathic infertility
Oral bioavailability	14–18%
Supposed main mechanism of action	Key role in beta-oxidation of fatty acids
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–2000 mg/day Deficiencies of vitamin C impair carnitine biosynthesis thus causing the need for higher dosages
Duration of treatment	Cyclic (>30 days)
Main expected effect	Improvement of sperm quality and motility, erectile function
Secundary positive effects	Improvement of heart failure left ventricular ejection fraction (LVEF) stroke volume (SV), cardiac output (CO)], athletic performance, power output, anaerobic running capacity and lean mass, symptoms of intermittent claudication, symptoms of fibromyalgia, plasma nitrate, exercise induced oxidation, fat mass and insulin sensitivity (preliminary data), fatigue, cognitive function, attention, reduction of lipid peroxidation, peripheral neuropathic pain and muscle damage
Possible side effects (for suggested dosages)	Mild nausea, stomach upset, heartburn, diarrhea
Relative controindication	Pregnancy and lactation, hypothyroidism

	L-carnitine
Possible pharmacokinetic interactions of clinical interest	Acenocoumarol and warfarin (increased risk of bleeding), thyroid hormone (L-carnitine seems to decrease the effectiveness of the thyroid hormone)
Possible additive or synergistic nutraceuticals	Garlic, Vitamin C
Suggested recent bibliography	Mongioi L, et al. Andrology. 2016 Sep;4(5):800–7. Yao DF, Mills JN. Asian J Androl. 2016;18(3):410–8.

	Lepidium
Main source	*Lepidium meyenii*
Main indication	Erectile dysfunction (ED), idiopathic infertility
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Unclear
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	200–2000 mg/day The title and the standardization of macaine could be important to recognize the most effective extracts
Duration of treatment	Cyclic (>30 days)
Main expected effect	Improvement of motility, functionality and sperm count
Secundary positive effects	Ergogenic effect
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation, breast cancer, uterine cancer, ovarian cancer, endometriosis, uterine fibroids
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been confirmed
Possible additive or synergistic nutraceuticals	*Pfaffia paniculata*
Suggested recent bibliography	Lee MS, et al. Maturitas. 2016;92:64–69. Yao DF, Mills JN. Asian J Androl. 2016;18(3):410–8.

	Lycopene
Main source	Dietary supplement
Main indication	Benign prostatic hypertrophy (BPH)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant, free radical scavenger
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	20–40 mg/day
Duration of treatment	Long-term

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	Lycopene
Main expected effect	Reduction of the incidence or progression of prostate cancer, improvement of BPH symptoms
Secundary positive effects	Reduction of blood pressure, 1–10 mmHg (systolic) and 1–3 mmHg (diastolic) and cholesterolemia
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects (diarrhea and stomach cramps)
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been confirmed.
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Capurso C, et al. Front Nutr. 2017;4:38. Rowles JR, et al. Prostate Cancer Prostatic Dis. 2017 Apr 25. doi: https://doi.org/10.1038/pcan.2017.25.

	Pfaffia
Main source	*Pfaffia paniculata*
Main indication	Erectile dysfunction (ED), idiopathic infertility
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Stimulation of catecholaminergic centers of the central nervous system and mediated nitric oxide vasodilation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	150–200 mg/day
Duration of treatment	Cyclic (>30 days)
Main expected effect	Improvement of motility, functionality and sperm count
Secundary positive effects	Improvement of anemia
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been confirmed.
Possible additive or synergistic nutraceuticals	*Lepidium meyenii*
Suggested recent bibliography	Lee MS, et al. Maturitas. 2016;92:64–69. Yao DF, Mills JN. Asian J Androl. 2016;18(3):410–8.

	Plant sterols (Beta-sytosterol)
Main source	Vegetable oils, nuts, seeds, legumes and some fat spreads Dietary supplements
Main indication	Mild-to-moderate hypercholesterolemia, Benign prostatic hypertrophy (BPH)

	Plant sterols (Beta-sytosterol)
Oral bioavailability	<2%
Supposed main mechanism of action	Inhibition of 5-alpha reductase
Level of support	Meta-analyses of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–3000 mg
Treatment duration	Long-term
Main expected effect	8–12% LDL, improvement of BPH symptoms
Secundary positive effects	Mild decrease in TG and increase in HDL-C, reduction of biomarkers of vascular inflammation as hsCRP
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Patients with sitosterolemia
Possible pharmacokinetic interactions of clinical interest	Ezetimibe (it might decrease the effectiveness of beta-sitosterol)
Possible additive or synergistic nutraceuticals	Alpha-lipoic acid, L-carnitine
Suggested recent bibliography	Chen L et al. Phytother Res. 2016;30(6):1016–20. Pagano E et al. Phytother Res. 2014;28(7):949–55.

	Pygeum
Main source	*Pygeum africanum (Prunus africana)*
Main indication	Benign prostatic hypertrophy (BPH)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined (inhibition of leukotrienes)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–800 mg/day of dry extract (4–7% of phytosterols)
Duration of treatment	Cyclic (>30 days)
Main expected effect	Improvement of LUTS (Lower Urinary Tract Symptoms)
Secundary positive effects	Improvement of cholesterolemia (preliminary data)
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been confirmed
Possible additive or synergistic nutraceuticals	*Serenoa repens, Urtica dioica*, selenium, zink, lycopene
Suggested recent bibliography	Jena AK, et al. J Ethnopharmacol. 2016;190:33–45. Pagano E, et al. Phytother Res. 2014;28(7):949–55.

	Selenium
Main source	Dietary supplement
Main indication	Benign prostatic hypertrophy (BPH)
Oral bioavailability	50–65%
Supposed main mechanism of action	Element for the function of numerous enzymes, including glutathione-peroxidase, essential to remove free radicals and protect tissues from oxidative damage
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	80–500 mcg/day
Duration of treatment	Long-term
Main expected effect	Improvement of selenium deficiency, LUTS (Lower Urinary Tract Symptoms), quality of life and BPH symptomatology [international prostate function score (IPSS), brief sexual function inventory (bSFI)]
Secundary positive effects	Improvement of prostate swelling and chronic pelvic pain syndrome, Hashimoto's thyroiditis, alcohol-related liver disease inflammatory bowel disease (preliminary data)
Possible side effects (for suggested dosages)	Mild nausea, nail changes, loss of energy, and irritability. At high dosages (>400 mcg/day in chronic): hair loss, white horizontal streaking on fingernails, nail inflammation, garlic breath odor, metallic taste, muscle tenderness, tremor, lightheadedness, facial flushing, blood clotting problems, liver and kidney problems
Relative controindication	Pregnancy and lactation (>400 mcg/day), autoimmune diseases, hemodialysis, fertility problems in men, hypothyroidism and skin cancer
Possible pharmacokinetic interactions of clinical interest	Niacin, warfarin, antiplatelet/anticoagulant drugs (increased risk of bleeding), contraceptive drugs
Possible additive or synergistic nutraceuticals	*Serenoa repens. Prunus africanum, Urtica dioica,* lycopene
Suggested recent bibliography	Cui Z, et al. Medicine . 2017;96(5):e5944 Cai X, et al. Sci Rep. 2016;6:19,213.

	Serenoa
Main source	*Serenoa repens*
Main indication	Benign prostatic hypertrophy (BPH)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of 5 alpha-reductase I and II, phospholipase A2, epidermal growth factor (EGF)
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	300–1200 mg/day The title and the standardization of short chain fatty acid (myristic and oleic acid) could be important to recognize the most effective extracts

	Serenoa
Duration of treatment	Long-term
Main expected effect	Improvement of LUTS (Lower Urinary Tract Symptoms), quality of life and BPH symptomatology [international prostate function score (IPSS), brief sexual function inventory (bSFI)]
Secundary positive effects	Improvement of prostate swelling and chronic pelvic pain syndrome
Possible side effects (for suggested dosages)	Dizziness, headache, nausea, constipation, diarrhea.
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Contraceptive drugs, estrogens, anticoagulant/antiplatelet drugs
Possible additive or synergistic nutraceuticals	Lycopene, selenium, *Prunus africanum, Urtica dioica*
Suggested recent bibliography	Ooi SL, et al. J Altern Complement Med. 2017;23(8):599–606. Russo A, et al. Expert Opin Drug Saf. 2016;15(12):1661–1670.

	Urtica dioica
Main source	*Urtica dioica*
Main indication	Benign prostatic hypertrophy (BPH)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined (urtica might increase the caspase 3 and 9 mRNA expression, and decrease Bcl-2)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–300 mg/day of aqueous extract
Duration of treatment	Cyclic (>30 days)
Main expected effect	Improvement of LUTS (Lower Urinary Tract Symptoms), quality of life and BPH symptomatology [international prostate function score (IPSS)]
Secundary positive effects	Improvement of prostate swelling and chronic pelvic pain syndrome, osteoarthritis (preliminary data)
Possible side effects (for suggested dosages)	Stomach complaints and sweating
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Lithium, warfarin
Possible additive or synergistic nutraceuticals	*Serenoa repens, Prunus africanum,* Lycopene
Suggested recent bibliography	Pagano E, et al. Phytother Res. 2014;28(7):949–55. Mohammadi A, et al. Cell Mol Biol. 2016;62(3):78–83.

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Main source	Dietary supplements
Main indication	Prevention of prostate cancer
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Downregulation of phosphoinositide 3-kinase pathway, NF-kB modulation and reduction of prostate androgen hormone levels
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	<400 IU/day
Duration of treatment	Chronic
Main expected effect	Prevention of prostate cancer in smoking subjects
Secundary positive effects	Improvement of arterial stiffness and endothelial function (reduction of the serum levels of hsCRP, advanced glycation end products, metalloproteinases and cell adhesion molecules)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects; Chronically assumed dosages >400 IU/day might increase the total mortality risk
Relative controindication	Pregnancy and lactation, bleeding disorders, head and neck cancer, prostate cancer, heart attack, stroke, angioplasty and diabetes
Possible pharmacokinetic interactions of clinical interest	Warfarin (risk of bleeding), Cyclosporine (Vitamin E might enhance the bioavailability of this drug), Medications substrate of CYP450 (Vitamin E might enhance the hepatic clearance)
Possible additive or synergistic nutraceuticals	Vitamin C, selenium, lycopene
Suggested recent bibliography	Lance P, et al. Cancer Prev Res (Phila). 2017;10(1):45–54. Oh B, et al. Prostate Int. 2016;4(3):71–87.

	Zinc
Main source	Dietary supplement Other Main sources*: fish, red meat, grains, legumes, nuts and seeds, oysters, yeast, milk, mushrooms, cocoa and egg yolk (to achieve the indicated effects the integration in the form of dietary supplement is needed: standard daily food intake do not warrant sufficient quantities)
Main indication	Idiopathic infertility
Oral bioavailability	20/40% as single component. Some substances (phytate, iron and cadmium), drugs (diuretics, corticosteroids, MAO inhibitors), alcoholic beverages or pathologies (rheumatoid arthritis, malabsorption syndromes) could reduce its bioavailability
Supposed main mechanism of action	Superoxide-dismutase cofactor, anti-oxidant, anti-mutagenic and DNA repair activity
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	25 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of prostate swelling and male infertility

	Zinc
Secundary positive effects	Improvement and treatment of eczema, psoriasis, acne vulgaris, degenerative retinal lesions, common cold and respiratory infections, attention deficit-hyperactivity disorder (ADHD), depressive symptoms [Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], cognitive decline, Wilson's disease, diarrhea, dyspepsia, muscle cramps, anorexia (preliminary data), inflammatory bowel diseases (preliminary data), diabetes (preliminary data), dental plaque formation and gingivitis
Possible side effects (for suggested dosages)	Mild nausea, mouth irritation, dysgeusia, mouth sores, diarrhea. An increase in prostate cancer and genitourinary symptoms has been related to high dosages of chronic zinc supplementation (data to be confirmed)
Relative controindication	None identified for standard dosages Pregnancy: few available data but little concern
Possible pharmacokinetic interactions of clinical interest	Zinc may decrease the plasma concentrations of certain drugs (eg. ciprofloxacin, cisplatin, penicillamine, amiloride or tetracycline) and micronutrients (calcium, iron, copper and vitamin A)
Possible additive or synergistic nutraceuticals	*Serenoa repens, Prunus africanum*
Suggested recent bibliography	Mahmoud AM et al. PLoS One. 2016;11(11):e0165956. Yao DF, Mills JN. Asian J Androl. 2016;18(3):410–8.

Nutraceuticals Active on Women Disorders

	Alpha-lipoic acid
Main source	Dietary supplement
Main indication	Polycistic Ovary Syndrome (PCOS), peripheral neuropathies, hyperglycemia
Oral bioavailability	Approximately 30%
Supposed main mechanism of action	Antioxidant, improvement of vascularization of the nerve and promoter of axonal sprouting, insulin sensitizers
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–1800 mg/day
Duration of treatment	Subacute/Long-term (depending on the disease)
Main expected effect	Improvement of neuropathic symptoms [visual analogue scale (VAS), Total Symptom Score (TSS) and present pain intensity], paresthesia, strength, paresthesia, tendon reflexes, PCOS
Secundary positive effects	Improvement of Fasting Plasma Glucose (FPG) Post-prandial glycemia (PPG), HbA1c and insulinemia, cholesterolemia, oxidative stress, reactive oxygen species (ROS), nerve conduction velocity and positive neuropathic symptoms, glucose and ascorbate handling, levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) and endothelial nitric oxide synthase (eNOS) activity, activation of Phase II detoxification via the transcription factor Nrf2, and lower expression of matrix metallopeptidase 9 (MMP-9) and vascular cell adhesion protein 1 (VCAM-1) through repression of NF-kappa-B, reduction of malondialdehyde (MDA), hsCRP (high sensible C reactive protein) and body weight
Possible side effects (for suggested dosages)	Mild to moderate rash, stomach burn
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Chemotherapy (the antioxidant properties of alpha-lipoic acid may reduce chemotherapeutic efficacy) thyroid disease (taking alpha-lipoic acid might interfere with treatments for under-active or over-active thyroid), excessive consumption of alcohol/thiamine deficiency

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https://doi.org/10.1007/978-3-319-73642-6_12

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	Alpha-lipoic acid
Possible additive or synergistic nutraceuticals	Other neuroprotective nutraceuticals
Suggested recent bibliography	De Cicco S et al. Gynecol Endocrinol. 2017;33(9):698–701. Cakici N et al. Diabet Med. 2016;33(11):1466–1476.

	Calcium
Main source	Milk, yogurt and fortified foods, dietary supplement
Main indication	Hypocalcemia, Menopausal syndrome
Oral bioavailability	Bioavailability is variable (5–50%). Among supplements, the best-absorbed forms of calcium are salts like carbonate (in fed state) or phosphate (in fed/fasted state). Calcium gluconate and calcium lactate are absorbed well by pregnant women also in fasted state. Hypochlorhydria decreases calcium bioavailability. Vitamin D, sugars (in particular lactose), some amino acids (lysine, arginine) and an increase of the intraluminal pH may increase calcium bioavailability.
Supposed main mechanism of action	Calcium plays a key role in physiology and biochemistry of the cell, particularly in signal transduction pathways
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–3000 mg/day
Duration of treatment	Cyclic/Long-term
Main expected effect	Improvement of calcemia
Secundary positive effects	Improvement of blood pressure, pre-eclampsia, hyperkalemia, osteoporosis, cholesterolemia, symptoms of premenstrual syndrome (PMS), hyperparathyroidism, fluoride poisoning, reduction of the risk of stroke
Possible side effects (for suggested dosages)	Mild stomach upset, bloating, nausea, diarrhea
Relative controindication	Hyperphosphatemia or hypophosphatemia, hypothyroidism, poor kidney function, hypercalcemia
Possible pharmacokinetic interactions of clinical interest	Ceftriaxone (increased risk of lungs and kidneys damage), quinolone and tetracycline antibiotics, bisphosphonates, levothyroxine, sotalol, calcium channel blockers (reduction of the effectiveness of these drugs), calcipotriene, estrogens and thiazide diuretics (increased risk of hypercalcemia), digoxin (calcium could increase the pharmacological effectiveness)
Possible additive or synergistic nutraceuticals	Vitamin D
Suggested recent bibliography	Purdue-Smithe AC et al. Am J Clin Nutr. 2017;105(6):1493–1501. Chung M et al. Ann Intern Med. 2016;165(12):856–866.

	Cimicifuga
Main source	*Cimicifuga racemosa*
Main indication	Menopausal syndrome
Oral bioavailability	Definitive data not available in humans in humans
Supposed main mechanism of action	Unclear: possible an action as selective estrogen receptor modulator (SERM)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	20–40 mg/day of dry extract The title and the standardization of cyclo-artenols and triterpenes could be important to recognize the most effective extracts
Duration of treatment	Middle term
Main expected effect	Improvement of mood and sleep disorders (latency, quality and duration of sleep), paraesthesia, hot flashes, dizziness, weakness, myalgia, headache, palpitations, tingling associated to menopause
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Medications substrate of CYP 3A4 and 2D6
Possible additive or synergistic nutraceuticals	Calcium, Vitamin D
Suggested recent bibliography	Van Breemen RB et al. Clin Pharmacol Ther. 2010; 87(2): 219–25. Schmidt M et al. J Menopause. 2005; 12(1):27–32.

	Folic acid (5′-methyltetrahydrofolate)
Main source	Dietary supplements
Main indication	Pregnancy, hyperhomocysteinemia
Oral bioavailability	30–98% (folate from foods > bioavailable of folate supplements > bioavailable of folic acid)
Supposed main mechanism of action	Precursor of tetrahydrofolic acid and methyltetrahydrofolate (essential for the maintenance of normal erythropoiesis and cofactors for the synthesis of purine and thymidylate nucleic acids), cofactor in serveral enzymatic reactions (eg. interconversion of amino acids as histidine and glutamic acid or methione and homocysteine)
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	250–5000 mcg/day It is advisable to reduce folate dosage to less than 1 mg/day (and probably even less) addying Vit. B12, in case of reduced Vit. B12 plasma level.
Treatment duration	Cyclic/Long-term (depending on the condition)
Main expected effect	Prevention of birth defects

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	Folic acid (5′-methyltetrahydrofolate)
Secundary positive effects	Improvement of depressive symptoms [Edinburgh Postnatal Depression Scale (EPDS), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], folate deficiency and hyperhomocysteinemia, prevention of anemia, age-related macular degeneration
Possible side effects (for suggested dosages)	Mild diarrhea, abdominal cramps, irritability, stomach upset, nausea, rash, sleep disorders, confusion
Relative controindication	Cancer (preliminary data)
Possible pharmacokinetic interactions of clinical interest	Fosphenytoin, methotrexate, phenoarbital, phenytoin, primidone, pyrimethamine (drecreased effectiveness of drugs)
Possible additive or synergistic nutraceuticals	Group B vitamins (especially B12)
Suggested recent bibliography	Haider BA et al. Cochrane Database Syst Rev. 2017;4:CD004905. Wolf HT et al. Am J Obstet Gynecol. 2017;217(4):404.e1–404.e30.

	Hop
Main source	*Humulus lupulus*
Main indication	Mild-to-moderae anxiety, insomnia
Oral bioavailability	Definitive data not available in humans in humans
Supposed main mechanism of action	Not determined: possible a GABA-A agonism effect The 2-methyl-3-buten-2-ol it seems to be the metabolite with major sedative action
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	80–460 mg/day of dry extract (rutin titration 0.3–0.5%) The title and the standardization of flavonoids (as rutin) and terpenoids (as farnesene) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of anxiety sypmtoms and sleep disorders (latency, quality and duration of sleep) associated to menopause
Secundary positive effects	Improvement of depressive symptoms (preliminary data)
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (no information available), hormone sensitive cancers conditions (some chemicals in hops act like estrogen)
Possible pharmacokinetic interactions of clinical interest	Sedative medications as benzodiazepines, zolpidem or barbiturates (sleepiness and drowsiness), alcohol (sleepiness and drowsiness)

	Hop
Possible additive or synergistic nutraceuticals	Valerian, passionflower
Suggested recent bibliography	Koetter U et al. Phytother Res. 2007; 21:847–51. Maroo N et al. Indian J Pharmacol. 2013; 45(1):34–9.

	Magnesium
Main source	Dietary supplement
Main indication	Menopausal syndrome, dysmenorrhoea, premenstrual syndrome
Oral bioavailability	20–50% variable, depending on the complex Calcium, iron, copper, manganese, phosphorous and alcohol migh decrease its bioavailability Magnesium aspartate, citrate, chloride and lactate is most bioavailable than magnesium hydroxide, oxide, and sulfate
Supposed main mechanism of action	Antagonist of NMDA (N-methyl-D-aspartate) receptor and modulation of HPA (hypothalamic–pituitary–adrenal) axis Cofactor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis, responsible of several processes including hormone receptor binding, gating of calcium channels, muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability, neurotransmitter release, calcium antagonist
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults
Dose ranges	150–2500 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of anxiety and perceived stress, reduction of hot flashes
Secundary positive effects	Improvement of depressive symptoms, attention deficit-hyperactivity disorder (ADHD), bipolar disorder (preliminary data), chronic fatigue syndrome (CFS), premenstrual syndrome (PMS), myalgia, headache, fibromyalgia, hearing loss, osteoporosis, high blood pressure
Possible side effects (for suggested dosages)	Mild diarrhea, stomach upset, nausea, heartbeat
Relative controindication	Pregnancy (>350 mg/day: few data available), kidney failure, heart block
Possible pharmacokinetic interactions of clinical interest	Aminoglycoside antibiotics (muscle side effects), quinolone and tetracycline antibiotics and bisphosphonates (drecreased effectiveness of drugs), calcium channel blockers (increased effect of drus), muscle relaxants [(eg. Orphenadrine, pancuronium, cyclobenzapirine, succinylcholine) increased risk of side effects], potassium sparing diuretics (risk of hypermagnesemia)
Possible additive or synergistic nutraceuticals	Multivitamin-Multimineral supplements
Suggested recent bibliography	Park H et al. Menopause. 2015; 22(6): 627–632. López-González B et al. Nutr Hosp. 2014;29(3):658–64.

	Myoinositol
Main source	Dietary supplements
Main indication	Polycystic ovaric syndrome (PCOS)
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Increasing insulin sensitivity, which helps to improve ovarian function and reduce hyperandrogenism
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults
Dose ranges	1200–18,000 mg/day
Duration of treatment	Cyclic
Main expected effect	Improvement PCOS and reduction of metabolic disease
Secundary positive effects	Improvement of panic disorder, obsessive-compulsive disorder (OCD), psoriasis and acute respiratory distress syndrome
Possible side effects (for suggested dosages)	Mild nausea, tiredness, headache and dizziness
Relative controindication	Pregnancy and lactation, bipolar disorders
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Alpha-lipoic acid
Suggested recent bibliography	Orrù B, et al. Eur Rev. Med Pharmacol Sci. 2017;21(2 Suppl):83–88. De Cicco S, et al. Gynecol Endocrinol. 2017;33(9):698–701.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*)
Main indication	Dysmenorrhoea, cardiovascular prevention, hypertriglyceridemia
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Reduction of the release and synthesis of inflammatory cytokines. Activation of endothelial NO synthase (eNOS), prostaglandins synthesis balance toward vasodilating ones, insulin-resistance reduction, vascular tone regulation by parasympathetic nervous system stimulation, and suppression of the renin–angiotensin–aldosterone system
Level of support	Randomized clinical trials
Population tested	Adults, adolescent females
Dose ranges	1–6 g/day of eicosapentanoic and/or docosahexaenoic acid
Duration of treatment	Chronic/ Cyclic (dymenorrhoea)
Main expected effect	Improvement of dysmenorrhoea symptomatology (reduction of both pain duration and pain severity)
Secundary positive effects	Reduction of blood pressure (1–5 mmHg, both systolic and diastolic), inflammatory markers and *delayed onset muscle soreness (DOMS),* improvement of arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)], anti-proarrhytmic and antinflammatory effects, macula protection, brain protection, mood stabilization

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Possible side effects (for suggested dosages)	Mild aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Warfarin (Dose-related increase in bleeding time)
Possible additive or synergistic nutraceuticals	Vitamin E, zinc
Suggested recent bibliography	Prego-Dominguez J, et al. Pain Physician. 2016;19(8):521–535. Hansen SO, et al. Eur J Obstet Gynecol Reprod Biol. 2013;169(2):162–71.

	Phytoestrogens
Main source	Dietary supplements *Glycine max, Trifolium pratense*
Main indication	Menopause, pre-menopause
Oral bioavailability	55–90%
Supposed main mechanism of action	Partial agonists of beta-estrogen receptors (ERs), inhibition of epidermal growth factor (EGF)
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults
Dose ranges	40–80 mg/day of isoflavones The title and the standardization of isoflavones (daidzein and genistein) could be important to recognize the most effective extracts
Duration of treatment	Long-term (some years around menopause)
Main expected effect	Improvement anxiety sypmtoms and sleep disorders, paraesthesia, hot flashes, night sweats, nervousness, melancholy, dizziness, weakness, myalgia, headache, palpitations, tingling associated to menopause
Secundary positive effects	Reduction of risk of osteoporosis, cardiovascular disease and estrogen-dependent tumors
Possible side effects (for suggested dosages)	Constipation, bloating, nausea, allergic reactions (rash, itching)
Relative controindication	Pregnancy and lactation, children, cystic fibrosis, kidney failure, kidney stones, urinary bladder cancer, hypothyroidism, asthma
Possible pharmacokinetic interactions of clinical interest	Estrogens (taking isoflavones along with estrogen pills might decrease the effects of estrogen pills), tamoxifen, warfarin
Possible additive or synergistic nutraceuticals	Probiotics
Suggested recent bibliography	Myers SP et al. Phytomed. 2017;24:141–147. Lethaby A et al. Cochrane Database Syst Rev. 2013;12:CD001395.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplement
Main indication	Vitamin D deficiency, menopausal syndrome, osteopenia
Oral bioavailability	Ergocalciferol (vit. D2) is apparently absorbed with similar efficiency to cholecalciferol (vit. D3), however 25-hydroxyvitamin D (25OHD) is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol. The amount of fat with which vit. D is ingested does not seem to significantly modify the bioavailability of vit. D3. Hypochlorhydria and achlorhydria decrease vitamin D bioavailability
Supposed main mechanism of action	Agonist VDR receptors, regulation of over 200 genes related to cell proliferation, angiogenesis and cell differentiation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–50000 IU of cholecalciferol /day (400 IU = 10 mcg)
Duration of treatment	Cyclic (usually 30–120 days)
Main expected effect	Reduced risk of early menopause, traumatic and stress fractures, painful bone and muscular symptoms, muscular injuries, inflammatory modulation and athletic performance (VO2 max, muscular strength and endurance)
Secundary positive effects	Improvement of depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], vitamin C deficiency, age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache, kidney stones
Relative controindication	Pregnancy and lactation (>1.8–2 g/day)
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (increased effects), diltiazem, verapamil (decreased efficacy), thiazide diuretics (elevated serum calcium), proton pump inhibitors, sucrose polyesters and tetrahydrolipstatin (diminish vit. D absorption)
Possible additive or synergistic nutraceuticals	Phytoestrogens
Suggested recent bibliography	Purdue-Smithe AC et al. Am J Clin Nutr. 2017;105(6): 1493–1501. Palacios S, Coronado PJ. Minerva Ginecol. 2017;69(2):160–170.

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Main source	Dietary supplements
Main indication	Dysmenorrhoea
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Anti-oxidant, NF-kB modulation
Level of support	Randomized clinical trials
Population tested	Adults, adolescent females

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Dose ranges	400 IU/day
Duration of treatment	Long-term
Main expected effect	Improvement of dysmenorrhoea symptomatology (reduction of both pain duration and pain severity)
Secundary positive effects	Improvement of arterial stiffness and endothelial function (reduction of the serum levels of hsCRP, advanced glycation end products, metalloproteinases and cell adhesion molecules) Prevention of prostate cancer in smoking subjects
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects; chronically assumed dosages >400 IU/day might increase the total mortality risk
Relative controindication	Pregnancy and lactation, bleeding disorders, head and neck cancer, prostate cancer, heart attack, stroke, angioplasty and diabetes
Possible pharmacokinetic interactions of clinical interest	Warfarin (risk of bleeding), Cyclosporine (Vitamin E might enhance the bioavailability of this drug), Medications substrate of CYP450 (Vitamin E might enhance the hepatic clearance)
Possible additive or synergistic nutraceuticals	Zinc
Suggested recent bibliography	Kashanian M et al. J Reprod Med. 2013;58(1–2):34–8. Pattanittum P et al. Cochrane Database Syst Rev. 2016;3:CD002124.

	Zinc
Main source	Dietary supplements Other main sources: fish, red meat, grains, legumes, nuts and seeds, oysters, yeast, milk, mushrooms, cocoa and egg yolk (in order to achieve the expected positive effects on human health, the integration in the form of dietary supplements is needed since usual portions of foods or beverages do not contain sufficient amount of this nutraceutical)
Main indication	Idiopathic infertility, dysmenorrhoea
Oral bioavailability	20/40% as single component. Some substances (phytate, iron and cadmium), drugs (diuretics, corticosteroids, MAO inhibitors), alcoholic beverages or pathologies (rheumatoid arthritis, malabsorption syndromes) could reduce its bioavailability
Supposed main mechanism of action	Superoxide-dismutase cofactor, anti-oxidant, anti-mutagenic and DNA repair activity
Level of support	Randomized clinical trials
Population tested	Adults, adolescent females
Dose ranges	25–50 mg/day
Duration of treatment	Cyclic (usually 30–60 days)
Main expected effect	Improvement of dysmenorrhoea symptomatology (reduction of both pain duration and pain severity)
Secundary positive effects	Improvement and treatment of eczema, psoriasis, acne vulgaris, degenerative retinal lesions, common cold and respiratory infections, attention deficit-hyperactivity disorder (ADHD), depressive symptoms, cognitive decline, prostate swelling and male infertility, Wilson's disease, dyspepsia, diarrhea, inflammatory bowel diseases (preliminary data), anorexia (preliminary data), muscle cramps, diabetes (preliminary data), dental plaque formation and gingivitis

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	Zinc
Possible side effects (for suggested dosages)	Mild nausea, mouth irritation, dysgeusia, mouth sores, diarrhea. An increase in prostate cancer and genitourinary symptoms has been related to high dosages of chronic zinc supplementation (data to be confirmed)
Relative controindication	None identified for standard dosages Pregnancy: few available data but little concern
Possible pharmacokinetic interactions of clinical interest	Zinc may decrease the plasma concentrations of certain drugs (eg. Ciprofloxacin, cisplatin, penicillamine, amiloride or tetracycline) and micronutrients (calcium, iron, copper and vitamin A)
Possible additive or synergistic nutraceuticals	Omega-3, Vitamin E
Suggested recent bibliography	Zekavat OR et al. Aust N Z J Obstet Gynaecol. 2015;55(4):369–73. Pattanittum P et al. Cochrane Database Syst Rev. 2016;3:CD002124.

Nutraceuticals Active on Immune System

	Andrographis
Main source	*Andrographis paniculata*
Main indication	Upper respiratory tract infections
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Non-specific immunostimulation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–1800 mg/day The title and the standardization of andrographolide (5–6%) could be important to recognize the most effective extracts
Duration of treatment	Seasonal cycles (60–90 days)
Main expected effect	Improvement of cough, expectoration, nasal discharge, headache, fever, sore throat, earache, malaise/fatigue and sleep disturbance
Secundary positive effects	Improvement of inflammatory bowel disease [IBD (Simple Clinical Colitis Activity Index and histological scores)] common cold, reduction of the fever and sore throat due to tonsillitis
Possible side effects (for suggested dosages)	Abdominal cramps, hematochezia, hematuria, rash
Relative controindication	Pregnancy and lactation, auto-immune diseases, diseases associated to increased bleeding time
Possible pharmacokinetic interactions of clinical interest	Immunosuppressants (andrographis might reduce their efficacy) and anticoagulant or antiplatelet drugs (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Saxena RC, et al. Phytomed. 2010;17(3–4):178–85. Poolsup N, et al. J Clin Pharm Ther. 2004; 29(1):37–45.

A.F.G. Cicero, A. Colletti, *Handbook of Nutraceuticals for Clinical Use*,
https://doi.org/10.1007/978-3-319-73642-6_13

	Astragalus
Main source	*Astragalus glycyphyllos, Astragalus lentiginosus, Astragalus trichopodus, Astragalus canadensis, Astragalus lemmonii, Astragalus didymocarpus, Astragalus miguelensis, Astragalus pachypus, Astragalus nuttallii Astragalus pulsiferae, Astragalus purshii, Astragalus nevinii, Astragalus agrestis, Astragalus tener*
Main indication	Immunodeficiencies
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Increase in activity of macrophages, natural killer cells (NK), release of T and B lymphocytes, IgM, IgE and interleukin-2, stimulation of adrenergic and cholinergic system
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	400–8000 mg/day of dry extract
Duration of treatment	Seasonal cycles (60–90 days)
Main expected effect	Specific and unspecified immunity stimulation
Secundary positive effects	Improvement of sperm motility
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (at high dosages not enough data available), auto-immune diseases
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Li L, et al. Fundam Clin Pharmacol. 2017;31(1):17–36. Piao YL, et al. Chin J Int Med. 2014; 20(10):787–91.

	Bioactive peptides (from bovine milk, soy, rice, oysters, cod and salmon)
Main source	Dietary supplement
Main indication	Immunodeficiencies
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Increase in activity of macrophages, natural killer cells (NK), release of T and B lymphocytes, modulation of cytokines release
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	10–100 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of immune system functionality
Secundary positive effects	Reduction of blood pressure, 1–6 mmHg (systolic) and 1–5 mmHg (diastolic), improvement of arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)]

	Bioactive peptides (from bovine milk, soy, rice, oysters, cod and salmon)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects (diarrhea and stomach cramps)
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Cicero AF, et al. Br J Pharmacol. 2017;174(11):1378–1394. Bouglé D, Bouhallab S. Crit Rev Food Sci Nutr. 2017;57(2):335–343.

	Colostrum and lactoferrin
Main source	Dietary supplements, human or bovin colostrum
Main indication	Immune stress conditions
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Intestinal eubyotic action, antioxidant, modulation of release of proinflammatory cytokines and Treg cells, alteration of the lipopolysaccharide layer (LPS) of the Gram negative membrane
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, children, infants
Dose ranges	20–100 mg/day of lactoferrin 1.5- 20 g/day of bovine colostrum
Duration of treatment	Seasonal cycles (60–90 days)
Main expected effect	Reduction of the incidence of late sepsis in infants, fungal infections, and adjuvant in post-surgical therapies
Secundary positive effects	Improvement of the intestinal microbiome and microbiota and immune dysfunction from physical activity
Possible side effects (for suggested dosages)	In usually it's well tolerated
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Jones AW, et al. Scand J Med Sci Sports. 2015; 25(6):788–96. Akin IM, et al. Am J Perinatol. 2014; 31(12):1111–20.

	Goji
Main source	*Lycium barbarum*
Main indication	Immune stress conditions
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Adaptogen

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	Goji
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	100 g/day
Duration of treatment	Seasonal cycles (60–90 days)
Main expected effect	Improvement of immune stress conditions
Secundary positive effects	Improvement in sense of weakness, stress, mental acuity and concentration, sleep disturbances, fatigue, depression
Possible side effects (for suggested dosages)	Mild nausea
Relative controindication	Pregnancy and lactation
Possible pharmacokinetic interactions of clinical interest	Medications CYP2C9 substrates, warfarin
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Cheng J, et al. Drug Des Devel Ther. 2014;9:33–78. Paul HC, et al. J Med Food. 2012;15(11):1006–14.

	Curcumin
Main source	*Curcuma longa*
Main indication	Immunodeficiencies, inflammation related pain
Oral bioavailability	Very low (< 1%) Biopharmaceutical interventions (eg. Nanoemulsion, micelles) are important to improve the curcumin intestinal absorption and its clinical efficacy
Supposed main mechanism of action	Inhibition of inflammatory markers production (COX, vascular endothelial grow factor (VEGF), tumor necrosis factor-alpha (TNF-alpha), interleukins (IL-23,-17,-1β,-4), improvement of glutathione plasma concentrations and NrF-2
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	Curcumin: >1 g/day (usually 1.5 g/day) Curcumin in specific pharmaceutical forms improving the curcumin bioavailability (for instance micelles or nanoemulsions): >400/500 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of immune system dysfunction
Secundary positive effects	Improvement of depressive symptoms [Hamilton Depression Rating Scale (HAM-D)] and reduction of serum and salivary stress markers such as cortisol and interleuchins; improvement of cardiovascular disease risk factors [Reduction of inflammatory markers, plasma glutathione concentrations, insulin-resistance], prevention and/or treatment of any inflammation related disease
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps and/or upset, diarrhea, dizziness

	Curcumin
Relative controindication	Pregnancy and lactation (only as Dietary supplement), Gilbert's disease or gallbladder problems, infertility, iron deficiency, bleeding problems, hormone-sensitive conditions (breast cancer, uterine cancer, ovarian cancer, uterine fibroids or endometriosis)
Possible pharmacokinetic interactions of clinical interest	Inhibition of CYP450 (in particular CYP2C9) Possible interactions with anticoagulant and antiplatelet drugs (aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin), diclofenac, ibuprofen, naproxen and other NSAIDs

Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Zuccotti GV, et al. J Biol Regul Homeost Agents. 2009; 23(2):119–23. Ranjan D, et al. J Surg Res; 2004. 121(2):171–7.

	Echinacea
Main source	*Echinacea purpurea L., Echinacea angustifolia, Echinacea pallida*
Main indication	Immunodeficiencies, common cold, flu, upper respiratory tract diseases
Oral bioavailability	Activation of phagocytosis, stimulation of fibroblasts and enhancement of respiratory activity
Supposed main mechanism of action	Agonist of cannabinoid receptor2 (CB2), amplification of cAMP signal, JNK, NF-kB, p38/MAPK pathways and inhibition of (tumor necrosis factor-alpha) TNF-α, cyclooxygenases (COX-1 and COX-2) and 5-LO (5-lypoxigenase) in monocytes as well as in macrophages, stimulation of interferon gamma production and inhibition of viral ialuronidases
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	500–3000 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Reduction of recurrent respiratory infections, recurrent virological infections
Secundary positive effects	Reduction of the incidence of common cold and upper respiratory infections, duration of cold, improvement of exercise performance (preliminary data)
Possible side effects (for suggested dosages)	Fever, nausea, aftertaste, stomach pain, diarrhea, xerostomia, headache, dizziness, insomnia, disorientation, joint and muscle aches.
Relative controindication	Pregnancy and lactation, auto-immune disorders
Possible pharmacokinetic interactions of clinical interest	Caffein, medications CYP1A2 and CYP3A4 substrates, immunosoppressants

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Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Manayi A, et al. Pharmacogn Rev. 2015; 9(17):63–72. Shah SA, et al. Lancet Infect Dis. 2007; 7(7):473–480.

	Garlic
Main source	*Allium sativum*
Main indication	Immunodeficiencies, common cold, influence
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Increase in activity of macrophages, natural killer cells (NK), release of T and B lymphocytes
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	180–900 mg/day The title and the standardization of S-allylcysteine and ajoene (0.4–1%) could be important to recognize the most effective extracts
Duration of treatment	Symptomatic/Cyclic
Main expected effect	Reduction in the incidence of common colds, flu and enhancement of the immune response
Secundary positive effects	Reduction of blood pressure 10–15 mmHg (systolic) and 8–10 mmHg (diastolic), improvement of lipid profile (−5/−10% LDL), improvement of sexual dysfunction, arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)], Peripheral Obstructive Artery Disease (POAD), reduction of platelet aggregation
Possible side effects (for suggested dosages)	Halitosis, aftertaste, heartburn, nausea, smelly transpiration, diarrhea, bloating, mildly increased bleeding time
Relative controindication	Pregnancy and lactation (at high dosages not enough data available), bleeding disorder, stomach or digestion problems, low blood pressure
Possible pharmacokinetic interactions of clinical interest	Isoniazid (garlic could reduce its absorption), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), birth control pills, cyclosporine and saquinavir (garlic might decrease their effectiveness), medications CYP2E1 substrates as acetaminophen, chlorzoxazone, theophylline (garlic is an inhibitor of CYP2E1), medications CYP3A4 substrates as lovastatin, ketoconazole, itraconazole, fexofenadine, triazolam (garlic is an inducer of CYP3A4), anticoagulant/antiplatelet drugs as aspirin, clopidogrel, diclofenac, ibuprofen, naproxen, dalteparin, enoxaparin, heparin, warfarin (garlic might increase the effectiveness of these drugs)
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Ried K, et al. J Nutr. 2016; 146(2):389S–396S. Percival SS. J Nutr. 2016;46(2):433S:436S.

	Ginseng
Main source	*Panax ginseng meyer*, *Panax quinquefolus*
Main indication	Immunodeficiencies, common cold, influence
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Adaptogen
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1000–2000 mg/day The title and the standardization of ginsenosides could be important to recognize the most effective extracts
Duration of treatment	Cyclic (>30 days)
Main expected effect	Reduction in the incidence of common cold, flu and enhancement of the immune response
Secundary positive effects	Improvement of exercise performance, VO2 max, muscular strength, nitric oxide production, reduction of reactive oxygen species, and interleukin 6 levels, mental performance (in Alzheimer's disease as well), obstructive pulmonary disease, erectile dysfunction, premature ejaculation and sexual arousal
Possible side effects (for suggested dosages)	Insomnia, headache, mood changes, menstrual problems, breast pain, increased heart rate, high or low blood pressure, loss of appetite, diarrhea, itching, rash, dizziness, vaginal bleeding, and allergic reactions (rare)
Relative controindication	Pregnancy and lactation, infants and children, "Auto-immune diseases" as multiple sclerosis (MS), lupus (systemic lupus erythematosus, SLE) and rheumatoid arthritis (RA), insomnia, hormone-sensitive conditions as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids, schizophrenia, bleeding conditions and heart diseases
Possible pharmacokinetic interactions of clinical interest	Alcohol, caffeine, antidiabetic drugs, MAOIs and stimulant drugs (ginseng might increase their side effects), furosemide (ginseng might decrease its effects), medications substrates of CYP 2D6 (amitriptyline, clozapine, codeine, desipramine, donepezil, fentanyl, flecainide, fluoxetine, meperidine, methadone, metoprolol, olanzapine, ondansetron, tramadol, trazodone), immunosuppressants (ginseng stimulates the immune system), anticoagulant/antiplatelet drugs (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins (in particular Vitamin C), Selenium, Zinc
Suggested recent bibliography	Block KI et al. Integr Cancer Ther. 2003; 2(3):247–67. Kim H et al. J Pharm Pharmacol. 2016;68(3):406–20.

	Magnesium
Main source	Dietary supplement
Main indication	Immune disorders associated with magnesium deficiencies

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	Magnesium
Oral bioavailability	20–50% Calcium, iron, copper, manganese, phosphorous and alcohol migh decrease its bioavailability Magnesium aspartate, citrate, chloride and lactate are most bioavailable than magnesium hydroxide, oxide, and sulfate
Supposed main mechanism of action	Cofactor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis, responsible of several processes including hormone receptor binding, muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability, neurotransmitter release and immune system regulation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–1500 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of immune disorders associated with magnesium deficiencies
Secundary positive effects	Reduction of blood pressure, 3–6 mmHg (systolic), 2–5 mmHg (diastolic), improvement of anxiety, perceived stress, depressive symptoms, attention deficit-hyperactivity disorder (ADHD), bipolar disorder (preliminary data), chronic fatigue syndrome (CFS), premenstrual syndrome (PMS), myalgia, headache, fibromyalgia, hearing loss, osteoporosis, kidney stones
Possible side effects (for suggested dosages)	Mild diarrhea, stomach upset, nausea, heartbeat
Relative controindication	Pregnancy (>350 mg/day: few data available), kidney failure, atrio-ventricular heart blocks
Possible pharmacokinetic interactions of clinical interest	Aminoglycoside antibiotics (muscle side effects), quinolone and tetracycline antibiotics and bisphosphonates (drecreased effectiveness of drugs), calcium channel blockers (increased effect of drus), muscle relaxants [(eg. Carisoprodol, gallamine, orphenadrine, pancuronium, cyclobenzapirine, succinylcholine) increased risk of side effects], potassium sparing diuretics (risk of hypermagnesemia)
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Tarleton EK, et al. PLoS One. 2017;12(6):e0180067. Tam M, et al. Eur J Clin Nutr. 2003;57,1193–1197.

	Medicinal mushrooms
Main source	Dietary supplements *Cordyceps sinensis, Ganoderma lucidum, Grifola frondosa, Agaricus blasei, Polyporus umbellatus, Lentinus edodes, Muril kyowa, Pleurotus ostreatus*
Main indication	Immunodeficiencies

	Medicinal mushrooms
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Increase in activity of macrophages, natural killer cells (NK), release and modulation of T and B lymphocytes
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–1000 mg/day The title and the standardization of beta-glucans (beta-1,3-D-glucans and beta-1,6-D-glucans) could be important to recognize the most effective extracts
Duration of treatment	Long-term/Cyclic
Main expected effect	Improvement of plasma levels of interleukin-2, −6, interferon gamma (IFN-gamma), CD3+, CD56+, CD4+, CD8+, natural killer (NK) and immunoglobulin A secretory (sIgA), reduction of interleukin-1, tumor necrosis factor alpha (TNF-alpha), C-reactive protein
Secundary positive effects	Improvement of exercise performance (preliminary data), VO2 max, testosterone/cortisol ratio (overtraining), antioxidant and ergogenic muscle capacity
Possible side effects (for suggested dosages)	Mild (gastrointestinal nature)
Relative controindication	Pregnancy and lactation (not enough information available)
Possible pharmacokinetic interactions of clinical interest	Rare and mild with standard suggested dosages
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Jin X, et al. Cochrane Database Syst Rev. 2016; 4:CD007731. Dai X, et al. J Am Coll Nutr. 2015; 34(6):478:87.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*)
Main indication	Immune disorders associated with inflammatory components
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Inhibition of trans-endothelial migration of polymorphonucleate infiltration (PMN) and interleukin-6 and 1beta release
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, Elderly
Dose ranges	2–6 g/day of eicosapentanoic and/or docosahexaenoic acid
Duration of treatment	Long-term
Main expected effect	Reduction of acne, incidence of atopic dermatitis, protection against UVR-induced genotoxicity

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	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Secundary positive effects	Cardiovascular prevention (reduction of triglyceridemia), anti-proarrhytmic and antinflammatory effects, macula protection, brain protection, mood stabilization, melanoma prevention
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Relative controindication	Rare and mild with standard suggested dosages
Possible pharmacokinetic interactions of clinical interest	Warfarin (dose-dependent increase in bleeding time)
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Calder PC, et al. Proc Nutr Soc. 2013; 72:326–336. Spite M, et al. Nature. 2009; 461:1287–1291.

	Papaya
Main source	*Carica papaya*
Main indication	Immune disorders associated with inflammatory components
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Not definitively determined (Antioxidant)
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	3–4.5 gr/day
Duration of treatment	Cyclic
Main expected effect	Improvement of immune stress disorder
Secundary positive effects	Reduction of hospitalization days in patients with dengue fever
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects, allergic reactions
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Muszyńska B et al. Psychiatr Pol. 2015;49(3):435–53. Sarala N et al. Ann Med Health Sci Res. 2014; 4(3):320–324.

	Resveratrol
Main source	Dietary supplement
Main indication	Immune disorders associated with inflammatory components
Oral bioavailability	Less than 1% (extensive first pass liver metabolism)
Supposed main mechanism of action	Antioxidant, improvement of plasma levels of interferon gamma (IFN-gamma) and natural killer (NK) cells
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>150 mg/day
Duration of treatment	Cyclic
Main expected effect	Protection from inflammaging
Secundary positive effects	Reduction of vascular inflammation and blood pressure 1–10 mmHg (systolic), 1–5 mmHg (diastolic), improvement of athletic performance (preliminary data), protection against UVR-induced genotoxicity and photoaging
Possible side effects (for suggested dosages)	Minors (mostly of gastrointestinal nature)
Relative controindication	Pregnancy and lactation (few data available), bleeding disorders, hormone-sensitive condition such as breast cancer, uterine cancer, ovarian cancer, uterine fibroids, endometriosis (resveratrol might act like estrogen)
Possible pharmacokinetic interactions of clinical interest	Medications substrate of cytochrome P450 3A4 as lovastatin, ketoconazole, itraconazole, fexofenadine, triazolam (resveratrol is an inhibitor of CYP3A4), anticoagulant/antiplatelet (resveratrol might slow blood clotting) as aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Patel S. Biomed Pharmacother. 2017;91:767–775. Magrone T et al. Curr Pharm Design. 2014; 20:1011–10,119.

	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Main source	Dietary supplements Dairy products and derivatives
Main indication	Intestinal dysbiosis
Oral bioavailability	*Lactobacilli* and *Bifidobacteria* colonize the intestinal lumen *Saccharomyces* it's a fermenter yeast, but doesn't colonize the intestinal lumen The administration of probiotic strains, to obtain the maximum effectiveness, should be taken before the main meal with a lipid vehicle (eg. Yogurt or milk)
Supposed main mechanism of action	Interaction with Toll receptors and modulation the levels of interleukins, tumor necrosis factor-alpha (TNF-alpha) and transforming growth factor-beta (TGF-beta)
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	>3.5 UFC (live)/day

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	Probiotics (*Lactobacilli, Bifidobacteria, Saccharomyces*)
Duration of treatment	Cyclic (>30 days)
Main expected effect	Protection from inflammaging conditions and functionality of immune system
Secundary positive effects	Improvement of bowel health, blood pressure 1–10 mmHg (systolic), 1–5 mmHg (diastolic), regulation of cholesterolemia, inflammatory markers, prevention of urinary infections and improvement of its symptoms (eg. Burning, pain), regulation of mood, depressive symptoms and anxiety [Improvement of Leiden Index of Depression Sensitivity (LEIDS-r), Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D)]
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Not determined: it is possible that probiotics interfere with the molecules subject to intestinal enzymatic metabolism (eg. Polyphenols, berberine)
Possible additive or synergistic nutraceuticals	Multivitamins, Selenium, Zinc
Suggested recent bibliography	Garcia G et al. Benef Microbes. 2016; 7(5):659–668. Magrone T et al. Immun Ageing. 2013;10–31.

	Rhodiola
Main source	*Rhodiola rosea, Rodiola algida, Rodiola kirilowii*
Main indication	Immune system dysfunction
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Non-specific immunostimulation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	340–680 mg/day of dry extract The title and the standardization of salidroside, rhodioloside, rosavin and tyrosol could be important to recognize the most effective extracts
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of immunity mediated by T cells and macrophage response
Secundary positive effects	Improvement of mood memory, cognition and depressive symptoms [Hamilton Depression Rating Scale (HAM-D), Mini Mental State Examination (MMSE), Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)], reduction of physical and mental fatigue, anxiety

	Rhodiola
Possible side effects (for suggested dosages)	Gastrointestinal symptoms, insomnia, nervousness
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Rhodiola is an inhibitor of CYP3A4 and CYP2C19 (*in vitro*) even if it does not interfere with the warfarin metabolism (CYP2C9)
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Khanna K et al. Biomed Pharmacother. 2017;87:496–502. Xu X et al. PlosOne. 2013; 8(10):e77401.

	Schizandra
Main source	*Schisandra chinensis*
Main indication	Immune system dysfunction, common cold, flu
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Adjustment of "immune homeostasis" (adaptogen)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1–20 mg/day of schizandrine
Duration of treatment	Cyclic (usually 30–120 days)
Main expected effect	Stimulation of T helper lymphocytes, cytotoxic T and natural killer cells (NK), macrophage phagocytosis, modulation of cytokines release
Secundary positive effects	Reduction of the incidence of flu, common cold and duration of the days of upper respiratory tract diseases
Possible side effects (for suggested dosages)	Heartburn, dyspepsia, decreased appetite, skin rash, and itching
Relative controindication	Pregnancy and lactation (not enough data available in humans), epilepsy (schizandra could stimulate the central nervous system), gastroesophageal reflex disease (GERD) or peptic ulcers, high intracranial pressure
Possible pharmacokinetic interactions of clinical interest	Medications substrate of CYP3A4 and CYP2C19, warfarin, tacrolimus (alteration of pharmakinetic profile)
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium, Zinc
Suggested recent bibliography	Lin RD et al. Molecules. 2011; 16(6):4836–49. Panossian A et al. J Ethnopharmacol. 2008; 118(2):183–212.

	Selenium
Main source	Dietary supplement
Main indication	Immune system dysfunction
Oral bioavailability	50–65%

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	Selenium
Supposed main mechanism of action	Adjustment of "immune homeostasis" (element for the function of numerous enzymes, including glutathione-peroxidase, essential to remove free radicals and protect tissues from oxidative damage)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	80–500 mcg/day
Duration of treatment	Cyclic (usually 30–120 days)
Main expected effect	Stimulation of T helper lymphocytes, cytotoxic T and natural killer cells (NK), macrophage phagocytosis
Secundary positive effects	Improvement of selenium deficiency, LUTS (Lower Urinary Tract Symptoms), quality of life and BPH symptomatology [international prostate function score (IPSS), brief sexual function inventory (bSFI)], prostate swelling and Long-term pelvic pain syndrome, Hashimoto's thyroiditis, alcohol-related liver disease, inflammatory bowel disease (preliminary data)
Possible side effects (for suggested dosages)	Mild nausea, nail changes, loss of energy, and irritability. At high dosages (>400 mcg/day in Long-term): hair loss, white horizontal streaking on fingernails, nail inflammation, garlic breath odor, metallic taste, muscle tenderness, tremor, lightheadedness, facial flushing, blood clotting problems, liver and kidney problems
Relative controindication	Pregnancy and lactation (>400 mcg/day), autoimmune diseases, hemodialysis, fertility problems in men, hypothyroidism and skin cancer
Possible pharmacokinetic interactions of clinical interest	Niacin, warfarin, antiplatelet/anticoagulant drugs (increased risk of bleeding), contraceptive drugs
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Zinc
Suggested recent bibliography	Steinbrenner H, et al. Adv Nutr. 2015;6(1):73–82. Maggini S, et al. Br J Nutr. 2007; 98 Suppl 1: S29-S35.

	Vitamin B1, B6, B12 (in combination)
Main source	Dietary supplements
Main indication	Group B vitamin deficiencies
Oral bioavailability	Variable: B1: 3–7% B6: 50% B12: highly variable depending on the presence of intrinsic factor of stomach, dosage administered and Main source of extraction
Supposed main mechanism of action	Vitamin B1 influences the potential of mitochondrial membrane, apoptotic proteins, protein kinases (p38-MAPK), suppresses oxidative stress induced by NF-kB and has anti-inflammatory properties. Vitamin B6 influences humoral and cellular immunity. Vitamin B6 deficiency alters lymphocyte differentiation and maturation, reduces delayed hypersensitivity responses, and antibody synthesis can be indirectly altered. Vitamin B12 modifies the immune system facilitating the synthesis of T lymphocytes, restoring the CD4/CD8 ratio and maintaining the count of subgroups of lymphocytes within the normal range

	Vitamin B1, B6, B12 (in combination)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	250–750 mg B1, 90–750 mg B6, 30–75 mcg/die B12
Treatment duration	Cyclic (at least 1 month)
Main expected effect	Improvement of vitamin deficiencies and modulation of the immune system
Secundary positive effects	Improvement of neuropathic symptoms [visual analogue scale (VAS) and present pain intensity], paresthesia, strength, paresthesia, tendon reflexes and neurological objectivity, prevention of cognitive decline and cardiovascular disease
Possible side effects (for suggested dosages)	Restlessness, nausea and insomnia
Relative controindication	Pregnancy and lactation (high dosages of vitamins B1 and B6)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Probiotics, Selenium, Zinc
Suggested recent bibliography	Huang SC, et al. Eur J Clin Nutr. 2010; 64(9):1007–13. Spinas E, et al. J Biol Regul Homeost Agents;2015. 29(2):293–8.

	Vitamin C
Main source	Dietary supplement
Main indication	Immunodepression induced by exercise, common cold, flu
Oral bioavailability	50–90% (above 1 g may be less than 50%)
Supposed main mechanism of action	Antioxidant (protection cells against the oxidants released by phagocytes)
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	250–1000 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of common cold, flu and functionality of immune system, reduction of severity of infections
Secundary positive effects	Improvement of vitamin C deficiency, depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption, tyrosinemia
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Hemochromatosis, previous kidney stones

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	Vitamin C
Possible pharmacokinetic interactions of clinical interest	Aluminium, iron, estrogens (vitamin C could increase the effects), fluphenazine, warfarin, protease inhibitors (vitamin C could decrease the effects) and chemotherapy (preliminary data)
Possible additive or synergistic nutraceuticals	Probiotics, Selenium, Zinc
Suggested recent bibliography	Hemilä H. Nutrients. 2017;9(4). pii: E339. Hemila H et al. Cochrane Database Syst Rev. 2013;(1):CD000980.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplement
Main indication	Immune disorders associated with vitamin D deficiencies, osteopenia, osteoporosis
Oral bioavailability	Ergocalciferol (vitamin D2) is apparently absorbed with similar efficiency to cholecalciferol (vitamin D3) 25-hydroxyvitamin D (25OHD) is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol Hypochlorhydria decreases vitamin D bioavailability
Supposed main mechanism of action	Modulation of B cell proliferation and differentiation, immunoglobulin secretion, lymphocytes T proliferation and maturation
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	400–3000 IU of cholecalciferol /day (400 IU = 10 mcg)
Duration of treatment	Cyclic (usually 30–120 days)
Main expected effect	Reduction of the incidence of upper respiratory tract infections and influenza
Secundary positive effects	Reduced risk of traumatic and stress fractures, painful bone and muscular symptoms, muscular injuries, inflammatory inflammation modulation and athletic performance (VO2 max, muscular strength and endurance), improvement of depressive symptoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], vitamin C deficiency, age-related vision loss, albuminuria, osteoarthritis, physical performance, iron absorption, tyrosinemia, heart failure symptoms, cognitive decline (preliminary data)
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Previous kidney stones, previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (vitamin D could increase the effects), diltiazem, verapamil, (vitamin D could decrease the effects) thiazide diuretics (elevated serum calcium), proton pump inhibitors (PPIs), sucrose polyesters and tetrahydrolipstatin (probably diminish vitamin D absorption)

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Possible additive or synergistic nutraceuticals	Probiotics, Selenium, Zinc
Suggested recent bibliography	Del Pinto R et al. Infalmm Bowel Dis. 2015; 21(11):2708–17. Aranow C. J Investig Med. 2011; 59(6):881–6.
	Zinc
Main source	Dietary supplement Other Main sources: fish, red meat, grains, legumes, nuts and seeds, oysters, yeast, milk, mushrooms, cocoa and egg yolk (standard daily portions does not contain sufficient Zinc amount to get the desired effects)
Main indication	Alterations of immune system associated to zinc deficiencies
Oral bioavailability	20/40% as single component. Some substances (phytate, iron and cadmium), drugs (diuretics, corticosteroids, MAO inhibitors), alcoholic beverages or pathologies (rheumatoid arthritis, malabsorption syndromes) could reduce its bioavailability
Supposed main mechanism of action	Zinc is crucial for normal development and function of cells mediating nonspecific immunity as neutrophils and natural killer cells
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	25 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of humoral immune response
Secundary positive effects	Improvement and treatment of eczema, psoriasis, acne vulgaris, degenerative retinal lesions, common cold and respiratory infections, male infertility, attention deficit-hyperactivity disorder (ADHD), Wilson's disease, diarrhea, muscle cramps, prostate swelling, depressive symptoms [Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], anorexia (preliminary data), insulin-resistance, cognitive impairment, peptic ulcers (preliminary data), inflammatory bowel disease (preliminary data), dental plaque formation and gingivitis
Possible side effects (for suggested dosages)	Mild nausea, mouth irritation, dysgeusia, mouth sores, diarrhea. An increase in prostate cancer and genitourinary symptoms has been related to high dosages of chronic zinc supplementation (data to be confirmed)
Relative controindication	None identified for standard dosages Pregnancy: few available data but little concern
Possible pharmacokinetic interactions of clinical interest	Zinc may decrease the plasma concentrations of certain drugs (eg. Ciprofloxacin, cisplatin, penicillamine, amiloride or tetracycline) and micronutrients (calcium, iron, copper and vitamin A)
Possible additive or synergistic nutraceuticals	Probiotics, Multivitamins, Selenium
Suggested recent bibliography	Gammoh NZ, Rink L. Nutrients. 2017;9(6). pii: E624. Barnett JB, et al. Am J Clin Nutr. 2016;103(3):942–51.

Nutraceuticals Active on Bones and Joints

	Boswellia
Main source	*Boswellia serrata*
Main indication	Arthritis, chronic colitis
Oral bioavailability	Compared to the fasted state, the administration of boswellic acids concomitantly with a high-fat meal led to several-fold increased areas under the plasma concentration-time curves as well as peak concentrations of boswellic acids
Supposed main mechanism of action	Interaction on 5-LOX, leukocyte elastase, topoisomerase 1 and 2, and IkappaB kinases
Level of support	Randomized clinical trials
Population tested	Osteoarthritis
Dose ranges	>100 mg/day (>500 GDU)
Duration of treatment	>90 days
Main expected effect	Patients with arthritis: reduction of pain, reduction of cartilage degradation, improvement of physical activity
Secundary positive effects	Benefits on ulcerative colitis, Crohn's disease, bronchial asthma and peritumoral cerebral edema.
Possible side effects (for suggested dosages)	Rare and mild with standard suggested dosages
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Increase of the anticoagulant effect of drugs
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Sengupta K et al. Int J Med Sci. 2010;7(6):366–77. Gupta I et al. Planta Med 2001;67:391–395.

	Bromelain
Main source	*Ananas comosus*
Main indication	Joint inflammation with edema
Oral bioavailability	Definitive data not available in humans

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A.F.G. Cicero, A. Colletti, *Handbook of Nutraceuticals for Clinical Use*,
https://doi.org/10.1007/978-3-319-73642-6_14

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	Bromelain
Supposed main mechanism of action	Increase in serum fibrinolytic activity, reduction of plasma fibrinogen and bradykinin levels. Reduction of prostaglandin E2 and thrombasane A2 levels and modulation of surface adhesion molecules of certain types of immune cells
Level of support	Randomized clinical trials
Population tested	People with acute knee pain
Dose ranges	200–400 mg/day (>500 GDU)
Duration of treatment	1 month (at least)
Main expected effect	Reduction of pain and stiffness, draining effect
Secundary positive effects	Improvement of physical functions and psychological well-being. Antithrombotic, fibrinolytic, anticancer and immunomodulatory activities
Possible side effects (for suggested dosages)	Good safety profile
Relative controindication	Pregnancy and lactation. People with a bleeding disorder, asthma, heart problems, liver or kidney disease, or stomach ulcers.
Possible pharmacokinetic interactions of clinical interest	Enhanced absorption of drugs, particularly of antibiotics
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Muhammad ZA, et al. J Pak Med Assoc. 2017;67(1):121–125. Walker AF, et al. Phytomedicine. 2002; 9:681–686.

	Calcium
Main source	Dietary supplements Milk, yogurt, and fortified foods
Main indication	Hypocalcemia with or without mild hypertension, pre-eclampsia, osteoporosis, osteopenia
Oral bioavailability	5–50% Bioavailability is variable, depending on the kind of fortified foods and not only by the content of calcium per unit [eg. Spinach (115 mg Ca/125 ml) 5% vs bok choy (79 mg Ca/125 ml) 50/55% vs cheddar cheese (300 mg Ca/40 g) 32%] The best-absorbed form of calcium are salts like carbonate (in fed state) or phosphate (in fed/fasted state). Calcium gluconate and calcium lactate are absorbed well by pregnant women also in fasted state. Hypochlorhydria decreases calcium bioavailability. Vitamin D, sugars (in particular lactose), some amino acids (lysine, arginine) and increase of the intraluminal pH may increase calcium bioavailability
Supposed main mechanism of action	Calcium plays a key role in physiology and biochemistry of the cell, particularly in signal transduction pathways

	Calcium
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–3000 mg/day
Treatment duration	Long-term
Main expected effect	Improvement of calcemia, blood pressure and osteopenia
Secundary positive effects	Improvement of hyperkalemia, premenstrual syndrome, hyperparathyroidism
Possible side effects (for suggested dosages)	Mild nausea, stomach upset, belching or bloating, diarrhea
Relative controindication	Pregnancy and lactation (not enough information available with high dosages), hyperphosphatemia or hypophosphatemia, hypothyroidism, poor kidney function, hypercalcemia
Possible pharmacokinetic interactions of clinical interest	Ceftriaxone (increased toxicity), quinolone and tetracycline antibiotics, bisphosphonates, L-thyroxine, sotalol, calcium channel blockers (reduced effectiveness), calcipotriene, estrogens and thiazide diuretics (increased risk of hypercalcemia), digoxin (reduced therapeutic range)
Possible additive or synergistic nutraceuticals	Vitamin D
Suggested recent bibliography	An LB et al. Int J Nurs Pract. 2015;21 Suppl 2:19–31. Hofmeyr GJ et al. Cochrane Database Syst Rev. 2014;6:CD001059.

	Capsaicin
Main source	Plants of genus *Capsicum*
Main indication	Osteoarthritis, rheumatoid arthritis
Oral bioavailability	Unclear
Supposed main mechanism of action	Activation of transient receptor potential vanilloid 1 receptor (TRPV1)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	50–300 mg/day
Duration of treatment	Cyclic (usually 10–15 days)/Symptomatic
Main expected effect	Improvement of pain
Secundary positive effects	Weight reduction (preliminary data)
Possible side effects (for suggested dosages)	Stomach irritation and upset, sweating, flushing, and runny nose
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data)
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Engler A et al. Biochem Biophys Res Comm. 2007;359:884–888. Cavin C et al. Biochem Biophys Res Commun 2005;327:742–49.

	Chicory
Main source	*Cichorium intybus*
Main indication	Osteoarthritis and joint pain
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of cyclooxygenase (COX)-2, interleukin (IL)-1β expression, tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB)
Level of support	Open label clinical trials
Population tested	Adults, elderly
Dose ranges	1 g/kg/day
Duration of treatment	Cyclic (at least 30 days)
Main expected effect	Improvement of osteoarthritis
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps
Relative controindication	Pregnancy and lactation (not enough data available in humans), gallstones, chicory allergy
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Schmidt BM et al. Food Chem Toxicol. 2007; 45:1131:1139. Cavin C et al. Biochem Biophys Res Commun 2005;327:742–49.

	Chondroitin sulfate
Main source	Dietary supplement
Main indication	Osteoarthritis and joint and knee pain
Oral bioavailability	15–25%
Supposed main mechanism of action	Inhibition of matrix metalloproteinases (MMPs), Interleukin-1 (IL-1) and induction of cyclooxygenase (COX)-2 a and stimulation of proteoglycan synthesis
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>1200 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation
Secundary positive effects	Reduction of workout related pain in athletes and circulating CTX-II (biomarker for collagen degradation), protection from cataracts
Possible side effects (for suggested dosages)	Mild nausea, heartburn, water retention, stomach cramps and diarrhea. Uncommon side effects are drowsiness, skin reactions, and headache
Relative controindication	Pregnancy and lactation (not enough data available in humans)

	Chondroitin sulfate
Possible pharmacokinetic interactions of clinical interest	Warfarin (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Glucosamine sulfate, methylsulfonylmethane (MSN), quercetin, fish oil, D-pintol, *Boswellia serrata*, hydrolyzed collagen, hyaluronic acid
Suggested recent bibliography	Lee YH et al. Rheumatol Int. 2010;30(3):357–63. Singh JA et al. Cochrane Database Syst Rev. 2015 28;1:CD005614.

	Curcumin
Main source	*Curcuma longa*
Main indication	Osteoarthritis, joint pain and inflammation
Oral bioavailability	Very low (<1%)
Supposed main mechanism of action	Inhibition of arachidonic acid metabolism, inhibition of COX-2, lipoxygenase, interleukins, TNF-α and NF-kB
Level of support	Meta-analysis of RCTs
Population tested	Adults, elderly
Dose ranges	500 mg/day Due to the very low bioavailability, for clinical efficacy they're important biopharmaceutical intervention (eg. Nanoemulsion, micelles) to improve the intestinal absorption of this molecule
Duration of treatment	Cyclic (8 weeks)
Main expected effect	Improvement of the "Disease Activity Score" and of the "American College of Rheumatology criteria" for reduction in stiffness and swelling of joints
Secundary positive effects	Improvement of cardiovascular disease risk factors, prevention and/or treatment of headaches, stomach pain, ulcerative colitis, diarrhea, irritable bowel syndrome, fibromyalgia, immune system dysfunction, bladder inflammation, cognitive impairment, Crohn's disease (preliminary data) Improvement of depressive symptoms [Hamilton Depression Rating Scale (HAM-D)] and reduction of serum and salivary stress markers such as cortisol and interleuchins
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps and/or upset, diarrhea, dizziness
Relative controindication	Pregnancy and lactation (only as Dietary supplement), Gilbert's disease or gallbladder problems, infertility, iron deficiency, bleeding problems, hormone-sensitive conditions (breast cancer, uterine cancer, ovarian cancer, uterine fibroids or endometriosis)
Possible pharmacokinetic interactions of clinical interest	Inhibition of CYP450 (in particular CYP2C9) Possible interactions with anticoagulant and antiplatelet drugs (aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin), diclofenac, ibuprofen, naproxen and other NSAIDs
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Arshad L et al. Future Med Chem. 2017;9(6):605–626. Chandran B, Goel A. Phytother Res. 2012; 26(11):1719–25.

	Devil's Claw
Main source	*Harpagophytum procumbens*
Main indication	Treatment of acute and subacute inflammation
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of the release of TNF-α, IL-6, IL-1β and PG-E2 Inhibition of the expression of pro-inflammatory genes (TNF-α and COX-2)
Level of support	Meta-analyses of RCTs
Population tested	Adults, elderly
Dose ranges	50 mg/day
Duration of treatment	Symptomatic/Short term
Main expected effect	Reduction of pain and inflammation
Secundary positive effects	Antimicrobial and antioxidant effects, improvement of cardiovascular and neuromuscular health
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Pregnancy and lactation (not enough data available in humans), cardiovascular diseases (it can affect heart rate, heartbeat, and blood pressure; it might increase the production of stomach acids)
Possible pharmacokinetic interactions of clinical interest	Interaction with CYP2C19 (increased effect of omeprazole, lansoprazole and pantoprazole; diazepam; carisoprodol; nelfinavir), CYP2C9 (increased effect of diclofenac, ibuprofen, meloxicam and piroxicam; celecoxib; amitriptyline; warfarin; glipizide; losartan), CYP450 3A4 (increased effect of lovastatin, ketoconazole, itraconazole, fexofenadine, triazolam).
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Warnock M et al. Phytother Res 2007; 21:1228–1233. Chrubasik S et al. Phytomedicine. 2007; 14(6):371–6.

	Ginger
Main source	*Zingiber officinale*
Main indication	Osteoarthritis, joint pain and inflammation
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of cyclooxygenase (COX)-2, interleukin (IL)-1β expression, tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and matrix metalloproteinases (MMP), neutralization of free radicals and oxidative stress
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	200–2500 mg/day of dry extract The title and the standardization of gingerols + shogaols (1–4%) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (usually 30–90 days)/Symptomatic
Main expected effect	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation

	Ginger
Secundary positive effects	Reduction of nausea and vomiting (especially in association with chemotherapy, antiretroviral drugs and after surgical treatments), dyspepsia, painful menstrual periods, morning sickness and dizziness, improvement of headache (preliminary data), irritable bowel syndrome (inconcolusive data), alcohol hangover (preliminary data), chronic obstructive pulmonary disease (COPD) (preliminary data), muscle pain after exercise (preliminary data)
Possible side effects (for suggested dosages)	Mild heartburn, diarrhea, stomach discomfort and extra menstrual bleeding
Relative controindication	Bleeding disorders, heart conditions
Possible pharmacokinetic interactions of clinical interest	Warfarin, aspirin, clopidogrel, dalteparin, heparin, phenprocoumon, and others anticoagulant and antiplatelet drugs (Ginger might slow blood clotting)
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Barteis EM et al. Osteoarthritis Cartilage. 2015;23(1):13–21. Altman RD et al. Arthritis Rheum. 2001;44:2531–38.

	Glucosamine sulfate
Main source	Dietary supplement
Main indication	Osteoarthritis
Oral bioavailability	25–30%
Supposed main mechanism of action	Inhibition of matrix metalloproteinases (MMPs), Interleukin-1 (IL-1) and induction of cyclooxygenase (COX)-2 a and stimulation of proteoglycan synthesis
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>1200 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation
Secundary positive effects	Reduction of workout related pain in athletes and circulating CTX-II (biomarker for collagen degradation)
Possible side effects (for suggested dosages)	Mild nausea, vomiting, heartburn, water retention, stomach cramps and diarrhea. Uncommon side effects are drowsiness, skin reactions, and headache
Relative controindication	Pregnancy and lactation (not enough data available in humans), asthma (there is one report linking an asthma attack with taking glucosamine), shellfish allergy (some glucosamine sulfate products are made from the shells of shrimp, lobsters or crabs)
Possible pharmacokinetic interactions of clinical interest	Warfarin (increased risk of bleeding)

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	Glucosamine sulfate
Possible additive or synergistic nutraceuticals	Chondroitin sulfate, methylsulfonylmethane (MSN), quercetin, fish oil, D-pintol, *Boswellia serrata*, hydrolyzed collagen, hyaluronic acid
Suggested recent bibliography	Wu D et al. Int J Clin Pract. 2013;67(6):585–94. Wandel S et al. BMJ. 2010;341:c4675.

	Hydrolised Collagen
Main source	Dietary supplement
Main indication	Osteoarthritis, rheumatoid arthritis
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Formation of new collagen type II and stimulation of proteoglycan synthesis
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	Largely variable depending on the collagen formulation and the prevalent type
Duration of treatment	Long-term
Main expected effect	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation
Secundary positive effects	Not clinically relevant
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps and diarrhea. Uncommon side effects are drowsiness, skin reactions, and headache
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Deal CL et al. Rheum Dis Clin North Am. 1999;25(2):379–95. Figueres CT et al. Nutr Hosp. 2015;32 Suppl 1:62–6.

	Grape
Main source	*Vitis vinifera*
Main indication	Inflammation in patients with cardiovascular diseases
Oral bioavailability	Resveratrol: very low
Supposed main mechanism of action	Grape polyphenols inhibit the synthesis and release of pro-inflammatory mediators, inhibit COX-1 and COX-2, and some transcription factors such as NF-kB or activator protein (AP)-1. Resveratrol acts as a COX inhibitor and receptor activator activated by peroxisome proliferators (PPARs)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	8–16 mg of resveratrol

	Grape
Duration of treatment	12 months
Main expected effect	Decreased expression of the major inflammatory cytokines in hypertensive patients with diabetes mellitus
Secundary positive effects	Prevention of diseases of the heart and blood vessels, varicose veins, hemorrhoids, atherosclerosis, high blood pressure, swelling after injury or surgery, heart attack, and stroke. Mild laxative for constipation. Detoxification. Used for diabetes complications such as nerve and eye problems, improving wound healing, preventing tooth decay, preventing cancer, an eye disease called age-related macular degeneration, poor night vision, liver disorders, and hay fever. Dried grapes, raisins, or sultanas (white raisins) are used for cough. Grape leaf is also used for attention deficit-hyperactivity disorder, chronic fatigue syndrome, heavy menstrual bleeding, uterine bleeding, and tumour sores
Possible side effects (for suggested dosages)	Diarrhea, stomach upset, indigestion, nausea, cough, xerostomia, sore throat, infections, headache, and muscular problems
Relative controindication	Pregnancy and lactation (not enough is known about the use of grape in medicinal amounts). Bleeding conditions (rare)
Possible pharmacokinetic interactions of clinical interest	Reduction of the effects of phenacetin and increase of the activity of warfarin. Interaction with medications changed by the liver CYP1A2: clozapine, cyclobenzaprine, fluvoxamine, haloperidol, imipramine, mexiletine, olanzapine, pentazocine, propranolol, tacrine, theophylline, zileuton, zolmitriptan
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Tomé-Carneiro J et al. Pharmacol Res. 2013; 72:69–82. Tomé-Carneiro J et al. Am J Cardiol. 2012; 110(3):356–63.

	Hyaluronic acid
Main source	Dietary supplement
Main indication	Osteoarthritis and joint and knee pain
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Joint lubrication, anti-inflammatory effects [inhibition of interleukin (IL)-1β and IL-17 expression, tumor necrosis factor-alpha (TNF-α) and matrix metalloproteinase (MMP) -1, 2, 3, 9], proteoglycan synthesis and cartilage matrix alterations
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>150 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation
Secundary positive effects	Protection from cataracts
Possible side effects (for suggested dosages)	Rare allergies reactions

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	Hyaluronic acid
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Glucosamine sulfate, chondroitin sulfate and keratin matrix
Suggested recent bibliography	Lambova S et al. Curr Rheumatol Rev. 2017; doi: https://doi.org/10.2174/1573397113666170829155149 Galluccio F et al. Eur J Rheumatol. 2015;2(3):106–108.

	Methylsulfonylmethane (MSN)
Main source	Dietary supplement
Main indication	Osteoarthritis
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Block peripheral nerve conductance, antioxidant activity, increased cartilage formation, cell membrane stabilization, slowed down cell loss and neutralization of free radicals that trigger inflammation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1500–6000 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation] and joint inflammation
Secundary positive effects	Reduction of exercise induced oxidation, oxidative biomarkers, exercise-induced lipid peroxidation, biomarkers of muscle damage (creatinine and bilirubin), muscle soreness, upper respiratory symptoms and pollen-induced allergies
Possible side effects (for suggested dosages)	Mild nausea, gastroesophageal reflux, heartburn, stomach cramps, bloating, diarrhea, headache
Relative controindication	Pregnancy and lactation (not enough data available in humans), chronic venous insufficiency (MSN can increase pain and swelling in people with varicose veins and other circulatory problems) Antinflammatory and/or condroprotective nutraceuticals
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Chondroitin sulfate, glucosamine sulfate, hyaluronic acid
Suggested recent bibliography	Withee ED et al. J Int Soc Sports Nutr. 2017;14:24. Brien S et al. Evid Based Complement Alternat Med. 2011;2011:528,403.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*)
Main indication	Rheumatoid arthritis or secondary articular pain in intestinal inflammatory bowel disease and dysmenorrhoea
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Inhibiting the activation of NF-kB and the release of IL-1β and TNF-α
Level of support	Meta-analyses of RCTs
Population tested	Adults, elderly
Dose ranges	2–6 g/day of eicosapentanoic and/or docosahexaenoic acid
Duration of treatment	3–4 months
Main expected effect	Reduction of articular pain, morning stiffness and of the number of joint pain
Secundary positive effects	Cardiovascular prevention and anti-proarrhytmic effects, macula protection, brain protection, mood stabilization
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Warfarin (mild dose-related increase in bleeding time)
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Lee YH et al. Arch Med Res. 2012;43(5):356–62. Goldberg RJ, Katz J. Pain. 2007;129(1–2):210–23.

	Unsaponifiable fraction of avocado and soy
Main source	Dietary supplement
Main indication	Osteoarthritis, rheumatoid arthritis
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of cyclooxygenase (COX)-2, interleukin (IL)-1β expression, tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS) and matrix metalloproteinases (MMP)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	300–800 mg/day of unsaponifiable fraction
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation
Secundary positive effects	Improvement of cholesterolemia
Possible side effects (for suggested dosages)	None, beyond individual intolerance to the product

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	Unsaponifiable fraction of avocado and soy
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data)
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Boileau et al. Arthritis Res Ther. 2009;11:R41. Au RY et al. Osteoarthritis Cartilage. 2007;15:1249–55.

	Vitamin C (Ascorbic acid)
Main source	Dietary supplement
Main indication	Chondroprotection
Oral bioavailability	50–90% (above 1 g may be less than 50%)
Supposed main mechanism of action	Vitamin C decrease in apoptosis and in the expression of pro-inflammatory cytokines and matrix metalloproteinases (MMPs) in addition to the well-known antioxidation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	250–1000 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of osteoarthritis and joint inflammation
Secundary positive effects	Improvement of vitamin C deficiency, depressive symptoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], age-related vision loss, albuminuria, common cold and infections, physical performance, iron absorption, tyrosinemia
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Haemocromatosis, previous kidney stones
Possible pharmacokinetic interactions of clinical interest	Aluminium, iron, estrogens (vitamin C could increase the effects), fluphenazine, warfarin, protease inhibitors (vitamin C could decrease the effects)
Possible additive or synergistic nutraceuticals	Antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Pu-Rong C et al. Int J Mol Sci. 2017; 18(1):38. Huang TL et al. J Biomed Mater Res B Appl Biomater. 2017; doi: https://doi.org/10.1002/jbm.b.33988.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplements
Main indication	Osteopenia, osteoporosis
Oral bioavailability	Ergocalciferol (vit. D2) is apparently absorbed with similar efficiency to cholecalciferol (vit. D3), however 25-hydroxyvitamin D (25OHD) is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol. The amount of fat with which vit. D is ingested does not seem to significantly modify the bioavailability of vit. D3. Hypochlorhydria and achlorhydria decrease vitamin D bioavailability
Supposed main mechanism of action	Agonist of vitamin D receptor (VDR)
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	400–3000 IU of cholecalciferol /day (400 IU = 10 mcg)
Treatment duration	Long-term
Main expected effect	Improvement of osteoarthritis, osteopenia and osteoporosis
Secundary positive effects	Improvement of depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], vit. C deficiency, age-related vision loss, albuminuria, common cold and infections, physical performance, iron absorption, tyrosinemia, heart failure symptoms, cognitive decline (preliminary data)
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache, kidney stones
Relative controindication	Pregnancy and lactation (>1.8–2 g/day)
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (increased effects), diltiazem, verapamil (decreased efficacy), thiazide diuretics (elevated serum calcium), proton pump inhibitors, sucrose polyesters and tetrahydrolipstatin (diminish vit. D absorption)
Possible additive or synergistic nutraceuticals	Multivitamins, antinflammatory and/or condroprotective nutraceuticals
Suggested recent bibliography	Annweiler C. Ann N Y Acad Sci. 2016;1367(1):57–63. Bikle D. Chem Biol. 2014; 21(3): 319–329.

Nutraceuticals Active on Skin

	Alpha-lipoic acid
Main source	Dietary supplements
Main indication	Smoking induced skin damage, skin aging, photoprotection
Oral bioavailability	Approximately 30%
Supposed main mechanism of action	Antioxidant (improvement the plasma concentrations of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), endothelial nitric oxide synthase (eNOS) activity, activation of Phase II detoxification via the transcription factor Nrf2, and lower expression of matrix metallopeptidase 9 (MMP-9) and vascular cell adhesion protein 1 (VCAM-1) through repression of NF-kappa-B, reduction of malondialdehyde (MDA) and hsCRP (high sensible C reactive protein)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–1800 mg/day
Duration of treatment	Long-term
Main expected effect	Slowing of skin aging
Secundary positive effects	Improvement of neuropathic symptoms [visual analogue scale (VAS), Total Symptom Score (TSS) and present pain intensity], paresthesia, strength, palesthesia, osteotendhens reflexes and neurological objectivity, Fasting Plasma Glucose (FPG) Post-prandial glycemia (PPG), HbA1c and insulinemia, cholesterolemia, oxidative stress, reactive oxygen species (ROS), nerve conduction velocity and positive neuropathic symptoms, glucose and ascorbate handling, levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) and endothelial nitric oxide synthase (eNOS) activity, activation of Phase II detoxification via the transcription factor Nrf2, and lower expression of matrix metallopeptidase 9 (MMP-9) and vascular cell adhesion protein 1 (VCAM-1) through repression of NF-kappa-B, reduction of malondialdehyde (MDA), hsCRP (high sensible C reactive protein) and body weight
Possible side effects (for suggested dosages)	Mild to moderate rash
Relative controindication	Pregnancy and lactation (not enough data available in humans)

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https://doi.org/10.1007/978-3-319-73642-6_15

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	Alpha-lipoic acid
Possible pharmacokinetic interactions of clinical interest	Chemotherapy (the antioxidant properties of alpha-lipoic acid may reduce chemotherapeutic efficacy) thyroid disease (taking alpha-lipoic acid might interfere with treatments for under-active or over-active thyroid), excessive consumption of alcohol/thiamine deficiency
Possible additive or synergistic nutraceuticals	Coenzyme Q10, vitamin E, vitamin A, epigallocatechin gallate
Suggested recent bibliography	El-Komy L et al. J Cosmet Dermatol. 2017;16(3):358–363. Pegoraro NS et al. Colloids Surf B Biointerfaces. 2017;150:32–40.

	Cocoa flavanols
Main source	*Theobroma cacao L.*
Main indication	Photoprotection
Oral bioavailability	The bioavailability of polyphenols is widely variable: cold roasted cocoa > hot roasted cocoa and cold chocolate cold worked > dark chocolate hot worked Other aspects as dietary fat intake, form and the dose ingested, gut transit time, fecal degration rate and intestinal eubiosis could also influence the bioavailability of cocoa-polyphenols
Supposed main mechanism of action	Improvement of nitric oxide (NO) endothelial concentrations, reduction of oxidative stress
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	250–1000 mg/day of dry extract total polyphenols The title and the standardization of total flavonoids could be important to recognize the most effective extracts
Duration of treatment	Long-term
Main expected effect	Improvement in blood flow of cutaneous and subcutaneous tissues, skin density and skin hydration, skin thickness, reduction of transepidermal water loss, acne improvement
Secundary positive effects	Improvement of cognitive function and mood, blood pressure, insulin-resistance, arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)]
Possible side effects (for suggested dosages)	Mild-gastrointestinal side effects
Relative controindication	Gastroesophageal reflux disease (GERD), migraine
Possible pharmacokinetic interactions of clinical interest	Adenosine (antagonism effect), clozapine, phenylpropanolamine, theophylline, MAO inhibitors (improvement of the effects), ergotamine (improvement of caffeine-cocoa availability), estrogens (reduction of caffeine-cocoa availability), lithium (improvement of bioavailability)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Scapagnini G et al. Nutrients. 2014;6(8):3202–13. doi: https://doi.org/10.3390/nu6083202. Heinrich U et al. J Nutr. 2006;136(6):1565–9.

	Coenzyme Q10
Main source	Dietary supplement
Main indication	Skin aging
Oral bioavailability	Highly variable and not completely determined but in general: Bioavailability ubiquinol > ubiquinone Bioavailability of powder < suspension < emulsion Bioavailability of particles (mm) < particles (μm) < particles (nm) Bioavailability in fasted state < fed state
Supposed main mechanism of action	Antioxidant activity
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>200 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of seasonal deterioration of viscoelasticity, skin smoothness, reduction some visible signs of ageing (wrinkles and microrelief lines)
Secundary positive effects	Improvement of of left ventricular ejection fraction (LVEF) and left atrial diameter, reduction of Major Adverse Cardiovascular Events (MACE) and mortality migraine, myalgia, fibromyalgia, post-training recovery
Possible side effects (for suggested dosages)	Mild nausea, stomach upset, loss of appetite, diarrhea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data), chemotherapy (preliminary data)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Žmitek K et al. Biofactors. 2017;43(1):132–140. Knott A et al. Biofactors. 2015 Nov-Dec;41(6):383–90.

	Hyaluronic acid
Main source	Dietary supplement
Main indication	Skin aging
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Anti-inflammatory effects [inhibition of interleukin (IL)-1β and IL-17 expression, tumor necrosis factor-alpha (TNF-α) and matrix metalloproteinase (MMP) -1, 2, 3, 9], proteoglycan synthesis and cartilage matrix alterations
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>150 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of seasonal deterioration of viscoelasticity, skin smoothness, reduction some visible signs of ageing (wrinkles and microrelief lines)

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	Hyaluronic acid
Secundary positive effects	Improvement of osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation
Possible side effects (for suggested dosages)	Rare allergies reactions
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Glucosamine sulfate, chondroitin sulfate and keratin matrix
Suggested recent bibliography	Oe M et al. Clin Cosmet Investig Dermatol. 2017;10:267–273. Galluccio F et al. Eur J Rheumatol. 2015;2(3):106–108.

	Green tea
Main source	*Camellia sinensis*
Main indication	Anti-aging
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant, radical scavenger
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	250–1200 mg/day of green tea extract / 170–850 mg/day of epigallocatechin-3-gallate (EGCG)
Duration of treatment	Long-term
Main expected effect	Improvement in the radical scavenging activity of the skin (reduction of cutaneous oxidative stress), reduction of sebum production, acne improvement
Secundary positive effects	Improvement of arterial stiffnees [Flow Mediated Dilation (FMD), Pulse Wave Velocity (PWV)], cholesterolemia, glycemia and reduction of blood pressure
Possible side effects (for suggested dosages)	Mild gastrointestinal disorders
Relative controindication	Pregnancy and lactation (High doses of green tea can cause a deficiency of iron and folate due to its capacity to bind and reduce their intestinal absorption)
Possible pharmacokinetic interactions of clinical interest	Warfarin, Pentobarbital, Dipyridamole (decrease their effectiveness), Theophylline, Adenosine (synergistic actions with caffeine), Riluzole, Phenylpropanolamine, MAO inhibitors, Clozapine (green tea increase the effects and side effects of these drugs)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Megow I et al. Skin Pharmacol Physiol. 2017;30(5):225–233. Saric S et al. Antioxidants. 2016;6(1). pii: E2.

	Lycopene
Main source	Dietary supplement
Main indication	Photoprotection
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant, free radical scavenger [reduction of the expression of UVA, modulation of radiation-inducible genes HO1 (hemeoxygenase-1), inhibition of Intercellular Adhesion Molecule 1 (ICAM1) and matrix-metalloproteinase 1 (MMP1)]
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	10–40 mg/day
Duration of treatment	Cyclic (at least 30 days)
Main expected effect	Protection against solar radiation-induced health damage
Secundary positive effects	Reduction of blood pressure, 1–10 mmHg (systolic) and 1–3 mmHg (diastolic), improvement of cholesterolemia
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects (diarrhea and stomach cramps)
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Lutein
Suggested recent bibliography	Grether-Beck S et al. Br J Dermatol. 2017;176(5):1231–1240. Cooperstone JL et al. Sci Rep. 2017;7(1):5106.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*)
Main indication	Anti-aging, photoprotection, skin, inflammation, atopic dermatitis
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Modification of sebum composition and omega-3/omega-6 ratio [reduction of IGF-1 (insulin-like growth factor) activity and therefore reduction of lipogenesis and proliferation of sebocytes], reduction of arachidonic acid synthesis
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	2–6 g/day of eicosapentanoic and/or docosahexaenoic acid
Duration of treatment	Long-term
Main expected effect	Reduction of acne, incidence of atopic dermatitis, protection against UVR-induced genotoxicity
Secundary positive effects	Cardiovascular prevention (reduction of triglyceridemia), anti-proarrhytmic and antinflammatory effects, macula protection, brain protection, mood stabilization, melanoma prevention

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	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Possible side effects (for suggested dosages)	Aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Warfarin (dose-dependent increase in bleeding time)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Distante F et al. Int J Cosmet Sci. 2002; 24(2):81–7. Black HS et al. J Clin Med. 2016;5(2). pii: E23.

	Phytoestrogens
Main source	Dietary supplements *Glycine max, Trifolium pratense*
Main indication	Anti-aging, hyperpigmentation of skin
Oral bioavailability	55–90%
Supposed main mechanism of action	Soy contains serine protease inhibitors (inhibiting protease-activated receptor-2-mediated phagocytosis of melanosomes by keratinocytes). Inhibitory effects on UV-induced MMP-1 expression and the subsequent collagen degradation
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults
Dose ranges	40–80 mg/day of isoflavones The title and the standardization of isoflavones (daidzein and genistein) could be important to recognize the most effective extracts
Duration of treatment	Long-term
Main expected effect	Reduction of skin aging and skin hyperpigmentation
Secundary positive effects	Improvement anxiety symptoms and sleep disorders, paraesthesia, hot flashes, night sweats, nervousness, melancholy, dizziness, weakness, myalgia, headache, palpitations, tingling associated to menopause, reduction of risk of osteoporosis, cardiovascular disease and estrogen-dependent tumors
Possible side effects (for suggested dosages)	Constipation, bloating, nausea, allergic reactions (rash, itching)
Relative controindication	Pregnancy and lactation, children, cystic fibrosis, breast cancer, endometrial cancer, kidney failure, kidney stones, urinary bladder cancer, hypothyroidism, asthma
Possible pharmacokinetic interactions of clinical interest	Estrogens (taking isoflavones along with estrogen pills might decrease the effects of estrogen pills), tamoxifen, warfarin
Possible additive or synergistic nutraceuticals	Probiotics

	Phytoestrogens
Suggested recent bibliography	Del Gaudio P et al. Carbohydr Polym. 2017;165:22–29. Lephart ED. Ageing Res Rev. 2016;31:36–54.

	Resveratrol
Main source	Dietary supplement
Main indication	Photoaging
Oral bioavailability	Less than 1% (extensive first pass liver metabolism)
Supposed main mechanism of action	Anti-oxidant, stimulation of cell proliferation, collagen synthesis, endothelial production of nitric oxide (NO), inhibition of vascular inflammation, keratinocyte synthesis and formation of comedons
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	>150 mg/day
Duration of treatment	Long-term
Main expected effect	Protection against UVR-induced genotoxicity and photoaging
Secundary positive effects	Reduction of vascular inflammation and blood pressure 1–10 mmHg (systolic), 1–5 mmHg (diastolic), improvement of athletic performance (preliminary data)
Possible side effects (for suggested dosages)	Minors (mostly of gastrointestinal nature)
Relative controindication	Pregnancy and lactation (few data available), bleeding disorders, hormone-sensitive condition such as breast cancer, uterine cancer, ovarian cancer, uterine fibroids, endometriosis (resveratrol might act like estrogen)
Possible pharmacokinetic interactions of clinical interest	Medications substrate of cytochrome P450 3A4 as lovastatin, ketoconazole, itraconazole, fexofenadine, triazolam (resveratrol is an inhibitor of CYP3A4), anticoagulant/antiplatelet (resveratrol might slow blood clotting) as aspirin, clopidogrel, enoxaparin, dalteparin, heparins, warfarin
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Subedi L et al. Oxid Med Cell Longev. 2017;2017:8,379,539. Chedea VS et al. Food Funct. 2017 Oct 16. doi: https://doi.org/10.1039/c7fo01086a.

	Selenium
Main source	Dietary supplement
Main indication	Acne
Oral bioavailability	50–65%
Supposed main mechanism of action	Element for the function of numerous enzymes, including glutathione-peroxidase, essential to remove free radicals and protect tissues from oxidative damage
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	80–500 mcg/day
Duration of treatment	Cyclic (usually 30–120 days)

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	Selenium
Main expected effect	Prevention of ultraviolet (UV) B-induced lipid peroxidation and edema, epidermal protection from oxidative stress, reduction of acne onset
Secundary positive effects	Improvement of selenium deficiency, LUTS (Lower Urinary Tract Symptoms), quality of life and BPH symptomatology [international prostate function score (IPSS), brief sexual function inventory (bSFI)], prostate swelling and chronic pelvic pain syndrome, Hashimoto's thyroiditis, alcohol-related liver disease, inflammatory bowel disease (preliminary data)
Possible side effects (for suggested dosages)	Mild nausea, nail modification, loss of energy, and irritability. At high dosages (>400 mcg/day in Long-term): hair loss, white horizontal streaking on fingernails, nail inflammation, garlic breath odor, metallic taste, muscle tenderness, tremor, lightheadedness, facial flushing, blood clotting problems, liver and kidney problems
Relative controindication	Pregnancy and lactation (>400 mcg/day), autoimmune diseases, hemodialysis, fertility problems in men, hypothyroidism and skin cancer
Possible pharmacokinetic interactions of clinical interest	Niacin, warfarin, antiplatelet/anticoagulant drugs (increased risk of bleeding), contraceptive drugs
Possible additive or synergistic nutraceuticals	Lycopene
Suggested recent bibliography	Jablonska E et al. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2015;33(3):328–68. Wacewicz M et al. J Trace Elem Med Biol. 2017;44:109–114.

	Vitamin A and Beta-carotene
Main source	Dietary supplements
Main indication	Photoprotection, acne vulgaris, psoriasis, ittiosis and other keratinization disorders
Oral bioavailability	10–70%
Supposed main mechanism of action	Unclear
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	200,000 IU/day Iron and zinc deficiencies may alter the absorption and metabolism of vitamin A
Treatment duration	Cyclic (at least 30 days)
Main expected effect	Prevention of ultraviolet (UV) B-induced lipid peroxidation and edema, epidermal protection from oxidative stress, reduction of acne onset

	Vitamin A and Beta-carotene
Secundary positive effects	Reduction of the incidence of urinary tract infections Improvement of vitamin a deficiency, malaria symptoms, cataracts, diarrhea related to HIV, measles complications, oral leukoplakia, complications after and during pregnancy in malnourished women, retinitis pigmentosa
Possible side effects (for suggested dosages)	Fatigue, irritability, mental changes, anorexia, stomach discomfort, nausea, mild fever, excessive sweating, increased risk of osteoporosis (inconclusive data)
Relative controindication	Pregnancy and lactation (<10,000 units per day), Type V hyperlipoproteinemia, excessive use of alcohol and liver disease
Possible pharmacokinetic interactions of clinical interest	Tetracycline antibiotics (icreased risk of intracranial hypertension) and warfarin (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Not investigated
Suggested recent bibliography	Sies H et al. Photochem Photbiol Sci. 2004;3(8):749–52. Uray IP et al. Semin Oncol. 2016;43(1):49–64.

	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Main source	Dietary supplements
Main indication	Photoaging, skin ulcers
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	400–800 IU/day
Duration of treatment	Long-term
Main expected effect	Prevention of sunburn cell formation, ultraviolet (UV) B-induced lipid peroxidation and edema, epidermal protection from oxidative stress, role in photoadduct formation and immunosuppression
Secundary positive effects	Improvement of cholesterolemia, arterial stiffness and endothelial function (reduction of the serum levels of hsCRP, advanced glycation end products, metalloproteinases and cell adhesion molecules), atopic dermatitis (preliminary data), psoriasis (preliminary data), epidermolysis bullosa (preliminary data), cutaneous ulcers (preliminary data), acne vulgaris (preliminary data), melasma (preliminary data), wound healing (preliminary data), sclerodermia (preliminary data) Despite development of new formulations for use in cosmetics and skin care products, there is a lack of controlled clinical trials providing a rationale for well-defined dosages and clinical indications for oral and topical vitamin E

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	Vitamin E (α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol)
Possible side effects (for suggested dosages)	Mild gastrointestinal side effects
Relative controindication	Preganncy and lactation, bleeding disorders, head and neck cancer, prostate cancer, heart attack, stroke, angioplasty and diabetes
Possible pharmacokinetic interactions of clinical interest	Warfarin (risk of bleeding), Cyclosporine (Vitamin E might enhance the bioavailability of this drug), Medications substrate of CYP450 (Vitamin E might enhance the hepatic clearance)
Possible additive or synergistic nutraceuticals	Vitamin C, green tea extract, selenium
Suggested recent bibliography	Keen MA et al. Indian Dermatol J. 2016;7(4):311–5. Kosari P et al. Dermatitis. 2010;21(3):148–53.

	Vitamin C
Main source	Dietary supplement
Main indication	Photoprotection, skin aging slowing
Oral bioavailability	50–90% (above 1 g may be less than 50%)
Supposed main mechanism of action	Antioxidant, cofactor in collagen synthesis, inhibition of tyrosinase and matrix metalloproteinases (MMP)
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	2000 mg/day
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of skin hydratation, reduction of hyperchromia, protection against UVR-induced genotoxicity, prevention of skin aging
Secundary positive effects	Improvement of vitamin C deficiency, depressive sypmtoms [Children's Depression Rating Scale (CDRS) and Children's Depression Inventory (CDI), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI)], age-related vision loss, albuminuria, common cold and infections, osteoarthritis, physical performance, iron absorption, tyrosinemia
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Hemochromatosis, previous kidney stones

	Vitamin C
Possible pharmacokinetic interactions of clinical interest	Aluminium, iron, estrogens (vitamin C could increase the effects), fluphenazine, warfarin, protease inhibitors (vitamin C could decrease the effects) and chemotherapy (preliminary data)
Possible additive or synergistic nutraceuticals	Vitamin E
Suggested recent bibliography	Pullar JM et al. Nutrients. 2017;9(8). pii: E866. Lee JH, et al. Ann Dermatol. 2017;29(5):548–558.

Nutraceuticals for Physical Activity Support

	Beetroot and organic nitrates
Main source	Dietary supplement *Beta vulgaris*
Main indication	Support to physical activity
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Nitric oxide (NO) donor
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	10–13 mmol of NO_3^- The title and the extract standardization are important requirements for the effectiveness of this nutraceutical
Duration of treatment	Acute/Subacute
Main expected effect	Improvement of exercise performance
Secundary positive effects	Reduction of blood pressure and heart failure symptoms, improvement of arterial stiffness
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps, diarrhea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	NO donor drugs (eg. nitroglycerin and isosorbide), antuhypertensive drugs
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Wilie LJ et al. Nitric Oxide. 2016;57:30–9 Wilie LJ et al. Appl Physiol. 2013;115:325–36.

	Beta-alanin
Main source	Dietary supplement
Main indication	Support to physical activity
Oral bioavailability	Definitive data not available in humans. L-carnosine is absorbed in the intestine by a peptide transporter (PEPT): increasing the dosages and saturated the transporters, bioavailability decreases
Supposed main mechanism of action	Buffer agent and regulator of muscle pH, improvement of functionality and dynamism of muscle cells, antioxidant activity, reduction of glication and cross-linking between muscle proteins

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A.F.G. Cicero, A. Colletti, *Handbook of Nutraceuticals for Clinical Use*,
https://doi.org/10.1007/978-3-319-73642-6_16

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	Beta-alanin
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–6000 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of functional capacity, left ventricular ejection fraction (LVEF) and quality of life (EQ-5D test and VAS score)
Secundary positive effects	Improvement of exercise performance, muscle contractility and reduction of fatigue
Possible side effects (for suggested dosages)	Mild gastrointestinal sude effects
Relative controindication	Pregnancy and lactation (not enough information available)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Trexler ET et al. J Int Soc Sports Nutr. 2015; 12–30. Quesnele JJ et al. Int J Sport Nutr Exerc Metab. 2014; 24(1):14–27.

	Betaine
Main source	Dietary supplement *Beta vulgaris*
Main indication	Support to physical activity
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Modulation of IGF-1 (insulin-like growth factor), lipolysis and lipogenesis
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–9000 mg/day
Duration of treatment	Cyclic
Main expected effect	Improvement of exercise performance, muscular strength, lean mass
Secundary positive effects	Reduction of homocysteine, fat mass and improvement of VO2 max
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps, diarrhea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Support to physical activity
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Apicella JM, et al. Eur J App Physiol. 2012. Lee EC, et al. Int J Sports Nutr. 2010;7–27.

	Caffeine
Main source	Dietary supplement
Main indication	Body weight modulation, improvement of the athletic performance
Oral bioavailability	>95%
Supposed main mechanism of action	Enhancement of cyclic AMP (adenosine 5′-cyclic monophosphate) pathway, cAMP synthesis and reduction of cAMP degradation
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	100–400 mg/day
Duration of treatment	Cyclic
Main expected effect	Improvement of muscle contractility and athletic performance
Secundary positive effects	Antiemicranic and analgesic action (reduction of release of adenosine-mediated pain mediators and activation of noradrenergic routes), positive inotropic and chronotropic effect, temporary increase of blood pressure, improvement of acid secretion at gastric level (action on H2 receptors), mobilization of abdominal fat reserves, reduction of weight 1–5 kg in 60 days of treatment (if associated to a correct lifestyle)
Possible side effects (for suggested dosages)	Mild insomnia, nervousness and restlessness, stomach irritation, nausea, increased heart rate and blood pressure, rapid breathing, tremors, increased diuresis. Large guarana doses might cause headache, anxiety, agitation, tinnitus, and irregular heartbeats
Relative controindication	Preganncy and lactation, children under the age of 12, diarrhea, irritable bowel syndrome (IBS), anxiety
Possible pharmacokinetic interactions of clinical interest	Cocaine, ephedrine, amphetamines, quinolone antibiotics, verapamil, cimetidine, disulfiram, estrogens, fluvoxamine, MAOIs, theophylline, nicotine (increase in side effects of caffeine), riluzole, lithium, phenylpropanolamine, clozapine (increase in side effects of these drugs)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Meeusen R et al. Nestle Nutr Inst Workshop Ser. 2013;76:1–12. Souza DB et al. Eur J Nutr. 2017;56(1):13–27.

	Coenzyme Q10
Main source	Dietary supplement
Main indication	Heart failure NYHA-I/IV, muscular weakness, recovery phase after physical activity
Oral bioavailability	Highly variable and not completely determined but in general: Bioavailability ubiquinol > ubiquinone Bioavailability of powder < suspension < emulsion Bioavailability of particles (mm) < particles (μm) < particles (nm) Bioavailability in fasted state < fed state
Supposed main mechanism of action	Improvement of functionality and dynamism of cardiac-muscle cells, antioxidant activity, sensitizing of Ca^{++} channels, inductor of the synthesis of ATP, reduction of oxidative stress and lipid peroxidation
Level of support	Meta-analysis of randomized clinical trials

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	Coenzyme Q10
Population tested	Adults, elderly
Dose ranges	>200 mg/day
Duration of treatment	Chronic
Main expected effect	Improvement of left ventricular ejection fraction (LVEF) and left atrial diameter, peak power production in trained athetes, prevention of accumulation of lactic acid developing during exercise perfomance, reduction of Major Adverse Cardiovascular Events (MACE) and mortality
Secundary positive effects	Improvement of blood pressure (in hypertensive patients), migraine, myalgia, fibromyalgia, post-training recovery
Possible side effects (for suggested dosages)	Mild stomach upset, loss of appetite, nausea, and diarrhea
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Warfarin (preliminary data)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Mortensen SA et al. JACC Heart Fail. 2014;2(6):641–9. Dietmar A et al. J Int Soc Sports Nutr. 2013; 10: 24.

	Curcumin
Main source	*Curcuma longa*
Main indication	Recovery phase after physical activity
Oral bioavailability	Very low (< 1%)
Supposed main mechanism of action	Inhibition of inflammatory markers production (COX, vascular endothelial grow factor (VEGF), tumor necrosis factor-alpha (TNF-alpha), interleuchins (IL-23,-17,-1β,-4), improvement of glutathione plasma concentrations and NrF-2
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	Curcumin in specific pharmaceutical forms (with biopharmaceutical strategies as micelles or nanoemulsions): >400/500 mg/day Curcumin single: >1 g/day (usually 1.5 g/day)
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of the recovery phase after physical activity, delayed onset muscle soreness *(*DOMS*)* and muscle atrophy

	Curcumin
Secundary positive effects	Improvement of depressive symptoms [Hamilton Depression Rating Scale (HAM-D)] and reduction of serum and salivary stress markers such as cortisol and interleuchins. Improvement of cardiovascular disease risk factors [Reduction of inflammatory markers, improvement of glutathione plasma concentrations and NrF-2, regulation of glycemia and cholesterolemia], prevention and/or treatment of headaches, arthritis, joint pain, stomach pain, diarrhea, irritable bowel syndrome, inflammatory bowel diseases, fibromyalgia, immune system dysfunction, bladder inflammation, cognitive decline
Possible side effects (for suggested dosages)	Mild nausea, stomach cramps and/or upset, diarrhea, dizziness
Relative controindication	Pregnancy and lactation (only as Dietary supplement), Gilbert's disease or gallbladder problems, infertility, iron deficiency, bleeding problems, hormone-sensitive conditions (breast, uterus and ovarian cancer, uterus fibroids or endometriosis)
Possible pharmacokinetic interactions of clinical interest	Inhibition of CYP450 (in particular CYP2C9) Possible interactions with anticoagulant and antiplatelet drugs (increasing bleeding time)

Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Meamarbashi A. Avicenna J Phytomed. 2017;7(1):16–26. Kawanishi N et al. Biochem Biophys Res Commun. 2013;441(3):573–8.

	Creatine
Main source	Dietary supplements
Main indication	Physical activity, muscular asthenia
Oral bioavailability	Creatine hydrochloride > Creatine monohydrate (<30%) The bioavailability of creatine might be increased by using micronized forms (micronized creatine) with the addition of simple sugars
Supposed main mechanism of action	Energy reserve involved in ATP synthesis, modulation of IGF-1 (insulin-like growth factor)
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	3–20 gr/day
Duration of treatment	Cyclic
Main expected effect	Improvement of performance and quality of high-speed and intermittent training, increased lean mass, muscular strength and neurological function (in young and old)
Secundary positive effects	Improvement of VO2 max, deposits of muscle glycogen and reduction of oxygen consumption in sub maximal effort
Possible side effects (for suggested dosages)	Mild stomach pain, nausea, diarrhea, and muscle cramping
Relative controindication	Pregnancy and lactation, kidney diseases, bipolar disorders

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	Creatine
Possible pharmacokinetic interactions of clinical interest	Cyclosporine, aminoglycosides, nonsteroidal anti-inflammatory drugs and other nephrotoxic drugs (creatine may worsen drug-induced nephrotoxicity)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Harry F et al. Sports Nutr. 2016; 1:1. Naderi A et al. J Exerc Nutr Biochem. 2016; 20(4):1–12.

	Ginger
Main source	*Zingiber officinale*
Main indication	Nausea and vomiting (especially in association with chemotherapy, antiretroviral drugs and after surgical treatments), recovery phase after physical activity
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Inhibition of cyclooxygenase (COX)-2, interleukin (IL)-1β expression, tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and matrix metalloproteinases (MMP), neutralization of free radicals and oxidative stress
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	200–2500 mg/day of dry extract The title and the standardization of gingerols + shogaols (1–4%) could be important to recognize the most effective extracts
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Improvement of the recovery phase after physical activity, delayed onset muscle soreness *(*DOMS*)* and muscle atrophy, Reduction of nausea and vomiting (especially when secondary to drugs or surgical treatments)
Secundary positive effects	Reduction of abdominal pain, improvement of irritable bowel syndrome (preliminary data), dyspepsia, osteoarthritis [visual analogue scale (VAS), Lequesne index, WOMAC ratings of pain, stiffness, and function] and joint inflammation, reduction of painful menstrual periods, morning sickness and dizziness, improvement of headache/migraine (preliminary data), alcohol hangover (preliminary data), chronic obstructive pulmonary disease (preliminary data)
Possible side effects (for suggested dosages)	Mild heartburn, diarrhea, general stomach discomfort and extra menstrual bleeding
Relative controindication	Bleeding disorders, heart conditions
Possible pharmacokinetic interactions of clinical interest	Anticoagulant and antiplatelet drugs (Ginger might slow blood clotting)

	Ginger
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Nayebifar S et al. J Res Med Sci. 2016;21:116. Mohd Yusof YA. Adv Exp Med Biol. 2016;929:177–207.

	Ginseng
Main source	*Panax ginseng meyer*, *Panax quinquefolus*
Main indication	Physical activity, muscular asthenia
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Antioxidant, adaptogen
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	1000–2000 mg/day The title and the standardization of ginsenosides could be important to recognize the most effective extracts
Duration of treatment	Acute/Cyclic (>30 days)
Main expected effect	Improvement of exercise performance, VO2 max, muscular strength, nitric oxide production, reduction of reactive oxygen species (ROS), creatine phosphokinase (CPK), and interleukin (IL)-6 levels
Secundary positive effects	Improvement of mental performance in Alzheimer's disease, chronic obstructive pulmonary disease (COPD), mental function, erectile dysfunction, flu, premature ejaculation and sexual arousal
Possible side effects (for suggested dosages)	Insomnia, menstrual disorders, breast pain, increased heart rate, high or low blood pressure, headache, loss of appetite, diarrhea, itching, rash, dizziness, mood changes
Relative controindication	Pregnancy and lactation, infants and children, auto-immune diseases, insomnia, hormone-sensitive conditions as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids, schizophrenia, bleeding conditions and heart diseases
Possible pharmacokinetic interactions of clinical interest	Alcohol, caffeine, antidiabetic drugs, MAOIs and stimulant drugs (ginseng might increase their side effects), furosemide (ginseng might decrease its effects), medications substrates of CYP 2D6 (amitriptyline, clozapine, codeine, desipramine, donepezil, fentanyl, flecainide, fluoxetine, meperidine, methadone, metoprolol, olanzapine, ondansetron, tramadol, trazodone), immunosuppressants (ginseng stimulates the immune system), anticoagulant/antiplatelet drugs (increased risk of bleeding)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Hou CW et al. PlosOne. 2015;10(1):e0118367. Shergis JL et al. Phytother Res 2013; 27(7):949–65.

	L-carnitine
Main source	Dietary supplements
Main indication	Physical activity, muscular asthenia
Oral bioavailability	14–18%
Supposed main mechanism of action	Key role in beta-oxidation of fatty acids
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–2000 mg/day Deficiencies of vitamin C impair carnitine biosynthesis, requiring higher dosages
Duration of treatment	Cyclic
Main expected effect	Improvement of athletic performance, power output, anaerobic running capacity and lean mass, acceleration of muscle recovery after damages
Secundary positive effects	Improvement of heart failure [left ventricular ejection fraction (LVEF) stroke volume (SV), cardiac output (CO)], sperm quality and motility, symptoms of intermittent claudication, symptoms of fibromyalgia, plasma nitrate, exercise induced oxidation, fat mass (preliminary data), fatigue, blood glucose and insulin sensitivity (preliminary data), cognitive function, attention, reduction of lipid peroxidation, Lipoprotein (a) plasma level, peripheral neuropathic pain
Possible side effects (for suggested dosages)	Nausea, stomach upset, heartburn, diarrhea, seizures
Relative controindication	Pregnancy and lactation, kidney failure, hypothyroidism
Possible pharmacokinetic interactions of clinical interest	Acenocoumarol and warfarin (increased risk of bleeding), thyroid hormone (L-carnitine seems to decrease the effectiveness of the thyroid hormone)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Song X et al. Biomed Res Int. 2017;2017:6,274,854. Brass EP et al. Vasc Med. 2013;18(1):3–12.

	L-carnosine
Main source	Dietary supplement
Main indication	Heart failure NYHA-I/IV, physical activity
Oral bioavailability	Definitive data not available in humans. L-carnosine is absorbed in the intestine by a peptide transporter (PEPT): increasing the dosages and saturated the transporters, bioavailability decreases
Supposed main mechanism of action	Improvement of functionality and dynamism of cardiac-muscle cells, antioxidant activity, sensitizing of Ca^{++} channels, Na/K-ATPase activation and prevention of membrane depolarization, reduction of oxidative stress, plasma levels of proinflammatory cytokines and synthesis of fibronectin and type IV collagen
Level of support	Randomized clinical trials

	L-carnosine
Population tested	Adults, elderly
Dose ranges	500–1000 mg/day
Duration of treatment	Long-term
Main expected effect	Improvement of functional capacity, left ventricular ejection fraction (LVEF) and èerceived quality of life (EQ-5D test and VAS score)
Secundary positive effects	Improvement of exercise performance, muscle contractility and reduction of fatigue
Possible side effects (for suggested dosages)	Mild gastrointestinal discomfort
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed.
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Invernizzi PL et al. In J Sports Physiol Perform. 2016;11(3):344–9. Lombardi C et al. Nutrition 2015;31(1):72–8.

	Medicinal mushrooms
Main source	Dietary supplements *Ophiocordyceps sinensis, Ganoderma lucidum, Grifola frondosa, Agaricus blasei, Polyporus umbellatus*
Main indication	Physical activity, immunodeficiency
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Activation of glucose transporter-4 (GLUT-4) and antioxidant activity
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	500–1000 mg/day The title and the standardization of beta-glucans could be important to recognize the most effective extracts
Duration of treatment	Chronic
Main expected effect	Improvement of exercise performance, VO2 max, testosterone/cortisol ratio (overtraining), antioxidant and ergogenic muscle capacity
Secundary positive effects	Stimulation of immune system
Possible side effects (for suggested dosages)	Mild gastrointestinal discomfort
Relative controindication	Pregnancy and lactation (not enough information available)
Possible pharmacokinetic interactions of clinical interest	No clinically relevant interaction has been yet confirmed
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Hirsch KR et al. J Int Soc Sports Nutr. 2015; 12:P45. Rossi P et al. Evid Based Comp Alt Med. 2014; 979,613.

	Ω-3 Polyunsaturated Fatty Acids (EPA/DHA)
Main source	Caught fish, Krill, vegetal seeds and oils, algae (*Schizochytrium*)
Main indication	Cardiovascular prevention, inflammation induced by exercise, hypertriglyceridemia
Oral bioavailability	Bioavailability may differ between the commonly used types of ω-3 preparations: krill oil > Re-esterified triglycerides > Free fatty acids > Ethyl esters
Supposed main mechanism of action	Reduction of the release and synthesis of inflammatory cytokines. Activation of endothelial NO synthase (eNOS), prostaglandins synthesis balance toward vasodilating ones, insulin-resistance reduction, vascular tone regulation by parasympathetic nervous system stimulation, and suppression of the renin–angiotensin–aldosterone system
Level of support	Meta-analysis of randomized clinical trials
Population tested	Adults, elderly
Dose ranges	2–6 g/day of eicosapentanoic and/or docosahexaenoic acid
Duration of treatment	Chronic (cardiovascular prevention)/ Cyclic
Main expected effect	Reduction of inflammatory markers and delayed onset muscle soreness *(*DOMS*)*
Secundary positive effects	Reduction of blood pressure (1–5 mmHg, both systolic and diastolic), improvement of arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)], anti-proarrhytmic and antinflammatory effects, macula protection, brain protection, mood stabilization
Possible side effects (for suggested dosages)	Mild aftertaste, nausea, gastroesophageal reflux, bloating, dyspepsia, increased bleeding time The process of extraction and conservation of w-3, along with the pharmaceutical form, is important to reduce the risk of toxic contaminants and the oxidation of these molecules
Relative controindication	None identified for standard dosages
Possible pharmacokinetic interactions of clinical interest	Warfarin (dose-related increase in bleeding time)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Di Lorenzo FM et al. J Strenght Cond Res. 2014;28(10):2768–74. Capò X et al. J Int Soc Sports Nutr. 2016;13:16.

	Pomegranate
Main source	*Punica granatum L.*
Main indication	Physical activity, inflammation induced by exercise
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Reduction of the release and synthesis of inflammatory cytokines, activation of endothelial NO synthase (eNOS), prostaglandins synthesis balance toward vasodilating ones, antioxidant
Level of support	Randomized clinical trials

	Pomegranate
Population tested	Adults, elderly
Dose ranges	>200 ml/day
Duration of treatment	Cyclic
Main expected effect	Reduction of inflammatory markers (high sensible C reactive protein and advanced glycation andproducts), creatine phosphokinase (CPK) and delayed onset muscle soreness (DOMS)
Secundary positive effects	Reduction of blood pressure, aspartate aminotransferase (AST), alanine aminotransferase (ALT), improvement of arterial stiffness [flow-mediated dilation (FMD), augmentation index (AI), pulse wave velocity (PWV)], insulin resistance
Possible side effects (for suggested dosages)	Rare allergic reactions
Relative controindication	Pregnancy and lactation (not enough data available in humans)
Possible pharmacokinetic interactions of clinical interest	Medications CYP2D6 substrates [eg. Amitriptyline, codeine, desipramine, flecainide, fluoxetine, ondansetron and tramadol (Pomegranate might decrease how quickly the liver breaks down these medications)]
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Ammar A et al. PlosOne. 2017;9(8):pii E819. Koncic MZ. Tomczyk M. Curr Drug Targets 2013:14(9):1079–92.

	Rhodiola
Main source	*Rhodiola rosea*
Main indication	Psyhcophysical stress
Oral bioavailability	Definitive data not available in humans
Supposed main mechanism of action	Adaptogen: the exact Supposed main mechanism of action is not yet determined
Level of support	Randomized clinical trials
Population tested	Adults, elderly
Dose ranges	340–680 mg/day of dry extract The title and the standardization of salidroside, rhodioloside, rosavin and tyrosol could be important to recognize the most effective extracts
Duration of treatment	Cyclic (usually 30–90 days)
Main expected effect	Reduction of physical and mental fatigue
Secundary positive effects	Improvement of mood memory, cognition and depressive symptoms [Hamilton Depression Rating Scale (HAM-D), Mini Mental State Examination (MMSE), Perceived Stress Questionnaire Index (PSQI), Self Rating Depression Scale (SRDS)], anxiety and modulation of immune system
Possible side effects (for suggested dosages)	Mild gastrointestinal symptoms, insomnia, nervousness
Relative controindication	Pregnancy and lactation (not enough data available in humans)

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	Rhodiola
Possible pharmacokinetic interactions of clinical interest	Rhodiola is an inhibitor of CYP3A4 and CYP2C19 (*in vitro*) even if it does not interfere with the warfarin metabolism (CYP2C9)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Koncic MZ. Tomczyk M. Curr Drug Targets 2013:14(9):1079–92. Sana I et al. BMC Comp and Alter Med. 2012;12:70.

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Main source	Dietary supplement
Main indication	Physical activity, osteopenia
Oral bioavailability	Ergocalciferol (vitamin D2) is apparently absorbed with similar efficiency to cholecalciferol (vitamin D3) 25-hydroxyvitamin D (25OHD) is better absorbed than the nonhydroxy vitamin D forms cholecalciferol and ergocalciferol Hypochlorhydria decreases vitamin D bioavailability
Supposed main mechanism of action	Agonist VDR receptors, regulation of over 200 genes related to cell proliferation, angiogenesis and cell differentiation
Level of support	Randomized clinical trials
Population tested	Adults, elderly, children
Dose ranges	400–100000 IU of cholecalciferol /day (400 IU = 10 mcg)
Duration of treatment	Cyclic (usually 30–120 days)
Main expected effect	Reduced risk of traumatic and stress fractures, painful bone and muscular symptoms, muscular injuries, inflammatory inflammation modulation and athletic performance (VO2 max, muscular strength and endurance)
Secundary positive effects	Improvement of depressive sypmtoms [Children's Depression Rating Scale and Children's Depression Inventory, Hamilton Depression Rating Scale, Beck Depression Inventory], vitamin C deficiency, age-related vision loss, albuminuria, common cold and infections, osteoarthritis, iron absorption, tyrosinemia, heart failure symptoms, cognitive decline (preliminary data)
Possible side effects (for suggested dosages)	Mild nausea, heartburn, stomach cramps, diarrhea, headache
Relative controindication	Pregnancy and lactation (>1.8–2 g/day) Hemochromatosis, previous kidney stones

	Vitamin D [cholecalciferol (vit. D3), ergocalciferol (vit. D2)]
Possible pharmacokinetic interactions of clinical interest	Aluminium, calcipotriene, digoxin (vitamin D could increase the effects), diltiazem, verapamil, (vitamin D could decrease the effects) thiazide diuretics (elevated serum calcium), proton pump inhibitors, sucrose polyesters and tetrahydrolipstatin (probably diminish vitamin D absorption)
Possible additive or synergistic nutraceuticals	Other nutraceuticals acting as physical performance enhancers
Suggested recent bibliography	Dylan T et al. J Int Soc Sports Nutr. 2015. Angelini F et al. J Int Soc Sports Nutr. 2011;8:P35.