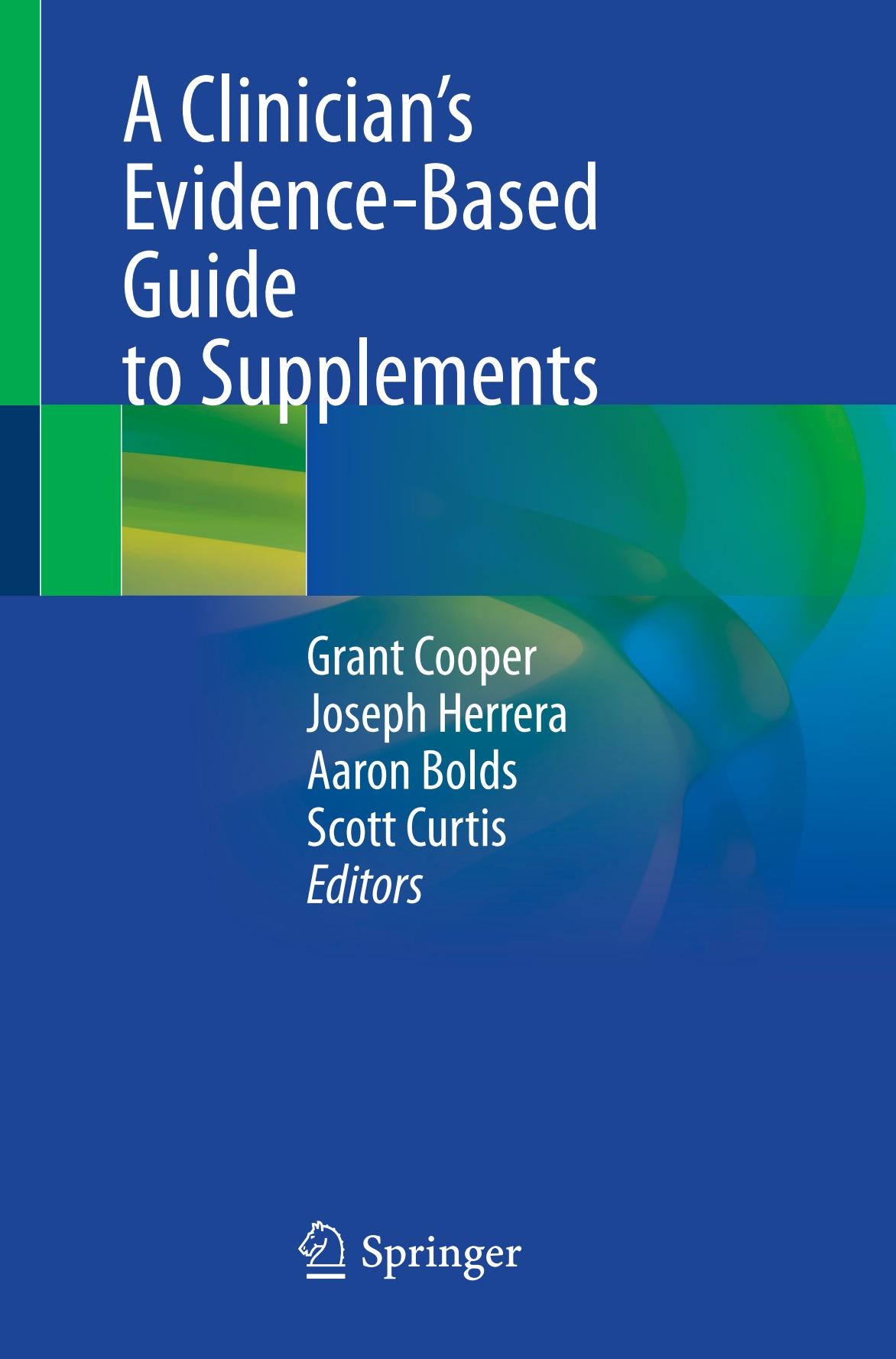


A Clinician's Evidence-Based Guide to Supplements



Grant Cooper
Joseph Herrera
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Editors



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Preface

The book you hold in your hand (or see on your screen as the case may be) came to be out of a growing necessity. As physicians who see patients on a daily basis, we are constantly inundated with questions about different supplements. *I heard X is good for Y. My uncle said I should take Turmeric, is he right?* It would be wrong to say that doctors receive inadequate training on supplements, including how they work, why they work or don't work, how we should evaluate them, which ones might be dangerous, how do you select the best brand and so forth. The truth is, we receive basically no training on these subjects. It is barely touched on in medical school, residency, or fellowship.

Fortunately, as doctors, we do receive plenty of training in critical thinking, an ability to soberly scrutinize literature, and of course we are equipped with an up-to-date understanding of the human body, including its physiology and pathophysiology, as science has progressed. Armed with these tools and understandings, we set out to analyze the current state of our science and evidence-based understanding of supplements.

The results of our work are the pages in front of you. We wrote these pages for ourselves as much as for you. As care providers answering our patients' pressing questions, and as humans and patients ourselves, we all are interested in healthy living and are all curious about which supplements are actually worth taking for different circumstances. This book provides the most current and responsibly informed answers to those important questions.

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Introduction

In today's dynamic and evolving medical landscape, physicians understand that many—perhaps most—of their patients are taking at least one supplement. Many patients are taking whole handfuls of supplements. Patients come into doctors' offices with questions about a wide array of supplements. They heard about a supplement online or from a friend and they want to know what the supplement is and is it safe and effective. Should they take it? Will the supplement interact with their medications? How does the supplement work to help solve their specific problems? Patients have many questions about supplements, but are physicians and other healthcare professionals in a position to answer them? Where do doctors get their information? Are doctors seeking information about supplements in the same way that their patients are? Is everyone relying on a handful of websites to get it right?

This book offers an authoritative, evidence-based reference book that healthcare professionals can turn to in order to educate themselves and their patients with accurate information about various kinds of supplements. This book answers the following critical questions—What is the supplement? What is it used for? How does the supplement work? What dosage works best and for which people? What are the safety concerns and how does the supplement interact with other medications and/or other supplements? And, finally, but equally importantly, what is the scientific evidence, if any, for all of these answers? With *A Clinician's Evidence-Based Guide to Supplements*, physicians and other healthcare providers finally have a trustworthy reference they can turn to in order to answer these pressing questions.

Contents

1	Acarbose–Creatine	1
	Carley Trentman, Laurenie Louissaint, and Ovie Enaohwo	
2	Green Tea	43
	German Valdez, Abid Haque, Craig Silverberg, Morgen Owens, Daniel Weng, and Farrah Asaad	
3	Hawthorn–Lysine	69
	Esha Jain, Chibuike Ezeibe, and Glenn Adesoji	
4	Maca–Pyridoxine (Vitamin B6)	111
	Alana Weisstuch	
5	Quercetin–Syrian Rue	153
	Michelle Gorbonosov and Lawrence Markel	
6	Tamarind–<i>Vitex agnus-castus</i>	171
	David Shukhman and Paul Bernstein	
7	Wallflower–Zinc	199
	Caroline Varlotta and Gaurav Majmudar	
Index		211

Chapter 1

Acarbose–Creatine



Carley Trentman, Laurenie Louissaint, and Ovie Enaohwo

Acarbose

- **What is it and how does it work in the body?**
 - Acarbose is an alpha-glucosidase inhibitor. It competitively binds to α-glucosidase, which acts on the absorption of carbohydrates in the small intestine. It causes optimal inhibition of postprandial increases in glucose, insulin, and triglycerides.
- **What is it used for and at what dosage?**
 - Although most commonly known for its use in type 2 diabetes, other studies have its cardioprotective effects as well as helping patient with metabolic syndrome.
 - Acarbose is typically dispensed in 25, 50, and 100 mg tablets its maximum dose is 50 mg q8hr for individuals weighing less than 60 kg and 100 mg for those weighing greater than 100 mg q8hr. With its most commonly prescribed to treat type 2 DM.
- **Evidence for or against its different uses:**
 - The STOP-NIDDM randomized trial showed evidence that acarbose significantly increased reversion of impaired glucose tolerance to normal glucose tolerance [1].

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- Acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of type 2 diabetes in patients with impaired glucose tolerance. Acarbose monotherapy was also shown to be beneficial in reducing triglyceride levels in obese or overweight patients and did not result in hypoglycemia during medication [2]. Participants with metabolic syndrome treated with acarbose experienced a decrease in weight and abdominal obesity as well as the inflammatory and cardiovascular markers, including flow-mediated dilation (FMD), intima media thickness (IMT), epicardial fat thickness (EFT), and C-reactive protein (CRP) levels [3].

- **Safety concerns, side effects, and precautions:**

- No serious side effects have been reported during treatment with acarbose although it is associated with a high incidence of troublesome gastrointestinal symptoms such as flatulence, abdominal distension, and diarrhea. The incidence of these reactions usually decreases with time.

- **Interactions with medications:**

- Acarbose administered during excessive alcohol consumption has shown to affect glycemic control and produce a disulfiram-like reaction. Digoxin absorption can be lowered by approximately 57–62% when coadministered with Acarbose, regardless of its dosing [4]. Multiple dose of acarbose impacts the peak concentration of metformin and lowers the value 30% and extent of absorption by over 35% [5, 6].

3-Acetyl-7-Oxo-Dehydroepiandrosterone

- **What is it and how does it work in the body?**

- 3-Acetyl-7-oxo-dehydroepiandrosterone (7-oxo-DHEA) is a dietary supplement that is a naturally occurring metabolite of the adrenal steroid DHEA. 7-oxo-DHEA differs from DHEA in that it has no androgenic activity, nor it is converted into estrogens.

- **What is it used for/what dosage?**

- Studies have discussed 7-oxo-DHEA use in bodyweight and body fat reduction and increase lean body mass. It is well tolerated at dosing ranging from 200 to 400 mg daily.

- **Evidence for or against its different uses (broken down by evidence for each use):**

- In a randomized controlled trial 7-oxo-DHEA combined with moderate exercise and a reduced-calorie diet significantly reduces body weight and body fat compared with exercise and a reduced-calorie diet alone. It was also found to

have a thermogenic effect by significantly elevate T3 levels although it did not affect TSH or T4 levels. Hence not adversely affecting thyroid function in the short term [7].

- It was also found to increase lean body mass (WMD: 0.45 kg, 95% CI: 0.15–0.75, $p = 0.004$) [8]. We could reasonably expect to see at least 69% of the 7-oxo-DHEA group achieving a meaningful $\rightarrow 5\%$ weight loss at 6 months.

- **Safety concerns, side effects, and precautions:**

- Unlike DHEA, 7-oxo-DHEA does not cause alterations of sex hormone levels seen in the transformation of DHEA to testosterone and estrogen.

- **Interactions with medications:**

- No drug interactions were noted in the observed studies [9].

ATP

- **What is it and how does it work in the body?**

- Adenosine triphosphate (ATP) is an important biological molecule in all living organisms. It is made up of three subunits, namely an adenine base, a 5-carbon ribose sugar, and a triphosphate. In living organisms, ATP is typically produced in a series of reactions in the presence of enzymes, mainly in the mitochondria and chloroplasts of living cells. The main function of ATP is usage as a major form of energy currency in living organisms [10].

- **What is it used for and at what dosage?**

- It has been used to increase strength and power, improve body composition, maintain muscle health during stress, increase recovery, and reduce pain.
 - Additionally, other literature indicates a role for ATP in improving cardiovascular health. Studies performed show safe dosing ranging from 100 to 400 mg daily.

- **Evidence for or against its different uses (broken down by evidence for each use):**

- In an experimental study by Jordan et al., three groups of nine healthy men received ATP (150 or 225 mg) or placebo for 14 days. Participants' physical performance and muscular strength and strength endurance (1RM), repetitions to fatigue during set 1 of posttesting, and total lifting volume at post (22%; $p < 0.003$) were positively affected [11].
 - Rathmacher et al. further supported ATP's performance enhancing abilities in their three sets of 50 maximal knee extensions to induce fatigue after supplementing with ATP (two doses of 200 mg/day) or placebo using a randomized,

double-blind, placebo-controlled, crossover design seem to enhance resistance to the accumulation of fatigue that inevitably results from maximal muscular contractions [12].

- In a randomized, double-blind, placebo-controlled trial, 21 resistance-trained males were supplemented with either 400 mg/day of ATP or placebo in conjunction with a 12-week heavy resistance training program resulted in lean mass gains in both groups, but changes were found to be significantly greater in the ATP.

- **Safety concerns, side effects, and precautions:**

- Although not reported in any formal studies, with uric acid as a metabolite of ATP, it is worth considering hyperuricemia as a risk factor for gout and its association with hypertension [13].

- **Interactions with medications:**

- No known interactions with medication were reported.

Alpha Lipoic Acid

- **What is it and how does it work in the body?**

- Alpha Lipoic acid (ALA), also known as thioctic acid, is a natural short-chain fatty acid. It is an essential cofactor of dehydrogenase enzymes and involved in mitochondrial macronutrient metabolism. It has largely been used worldwide as a dietary supplement. ALA has antioxidant characteristics that unlike most other antioxidants, is both water- and fat-soluble; thus, it can reach easily into tissues composed of fat, such as the nervous system as well as those mainly of water such as the cardiovascular system.

- **What is it used for and at what dosage?**

- As described above, ALA acts within the nervous system in diabetic neuropathy, Alzheimer's disease, as an analgesic and even improving behavior.
 - Effective dosing in studies ranged from 6000 mg daily up to 1800 mg daily (600 mg three times daily).

- **Evidence for or against its different uses:**

- The Alpha Lipoic Acid in Diabetic Neuropathy (ALADIN) trials (I-III) were successful multicenter studies that supported the efficacy of ALA in alleviating diabetic neuropathic pain and safe dosing. Although ineffective in glucose control (Hgb A1c unchanged) the ALADIN trial showed ALA's benefits in symptomatic relief (total symptom score, neuropathy impairment score, etc.) and improvements in electrophysiological nerve measurements [14].

- Postoperative administration of ALA was associated with a reduced incidence of postoperative pillar pain (frequent symptom following carpal tunnel release) compared with placebo. The difference was statistically significant although groups were slightly underpowered [15].
- Dayong's animal study showed a potential benefit of ALA in traumatic brain injury simulated by a weight drop injury model in rats. ALA was administered via intraperitoneal injection after TBI-induced neuron cell apoptosis and improved neurobehavioral function [16].
- ALA was also found to have cardioprotective properties. Supplementation with 1200 mg ALA after 8 weeks resulted in a substantial reduction in the risk of CVD in type 2 diabetic patient via a decrease in biomarkers such as ox-LDL and Lp-PLA2 mass and improvement in Lp-PLA2 distribution between HDL and apoB-containing lipoproteins [17].
- ALA treatment coincided with a 1.27 kg (confidence interval = 0.25–2.29) greater mean weight loss compared with the placebo group and an overall mean BMI difference of -0.43 kg/m^2 (confidence interval = -0.82 to -0.03) was found between the ALA and placebo groups [18].
- On the contrary, some concerns have been recently raised regarding ALA, after some reports suggesting a direct causal link between its use and insulin autoimmune syndrome (IAS, Hirata's disease) due to its sulfhydryl group. About 50% IAS development cases are associated with drugs or dietary supplements containing a sulfur or sulfhydryl group [19].

- **Safety concerns, side effects, and precautions:**

- ALADIN trials reported side effects such as gastrointestinal distress, headaches, skin irritation, and possible hypoglycemia associated with 1200 mg/day of parenteral ALA. It may also cause mineral shortages, and iron level should be periodically monitored [14].
- **Interactions with medications:**
 - Co-administering ALA with Valproic Acid (VA) exhibited significant inhibition on the β -oxidation of VA, particularly on the formation of VA-CoA. Separate dosing at least 2 h apart from any medication that chelate such as antiacids [20].

Alpha-Tocopherol (Vitamin E)

- **What is it and how does it work in the body?**

- Vitamin E is a fat-soluble vitamin which forms a group (i.e., chroman-6-ols), collectively termed tocochromanols (divided into tocopherols and tocotrienols). Alpha- and gamma-tocopherols are the two major forms of the vitamin. Vitamin E acts as a potent chain-breaking antioxidant that inhibits the

production of reactive oxygen species molecules when fat undergoes oxidation and during the propagation of free radical reactions. A build-up of reactive oxygen species in cells may cause damage to DNA, RNA, and proteins and may cause cell death at the microscopic level that leads to pathology in the human body [21].

- **What is it used for and at what dosage?**

- As an antioxidant Vitamin E works in preventing the oxidative process linked to numerous possible conditions and diseases including cancer, aging, arthritis, and cataracts. It also helps prevent or delay the chronic diseases associated with reactive oxygen species molecules [21].
- Vitamin E is found in various foods and oils. Nuts, seeds, and vegetable oils contain high amounts of alpha-tocopherol, and significant amounts are also available in green leafy vegetables and fortified cereals. When obtained from food sources alone, Vitamin E has no documented evidence of toxicity. Studies have shown tolerated dosing ranging from 400 to 2000 IU/day [21].

- **Evidence for or against its different uses (broken down by evidence for each use):**

- The trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD) trial showed that with 2000 IU/day of alpha-tocopherol (Vitamin E) patient with significantly delayed clinical progression in ADLs with mild-to-moderate AD who were taking an AChEI. This effect was not seen in the memantine and the memantine plus alpha-tocopherol groups. A delay in the annual rate of clinical progression in the alpha-tocopherol group of 19% or approximately 6.2 months was seen over the follow-up period [22].
- In 2007, reports from the Women's Health Study (WHS) demonstrated that Vitamin E supplements decrease the risk of mortality from thromboembolism and that alpha-tocopherol decreases the tendency for clotting in normal healthy women [23].
- The SELECT trial showed the negative effects of Vitamin E supplementation. Healthy men with average risk of prostate cancer subjected to contemporary community standards of screening and biopsy who took a common dose and formulation of Vitamin E (400 IU/day) had an observed 17% increase in prostate cancer incidence compared to patients treated with a placebo [24].
- Poston's VIP trial revealed an increase in low birthweight and no benefit with respect to risk of pre-eclampsia suggests a contraindication of the studied doses of Vitamin C and Vitamin E in pregnancy [25].

- **Safety concerns, side effects, and precautions:**

- Concomitant supplementation with Vitamin C and Vitamin E increase the rate of babies born with a low birthweight and an increased risk for prostate cancer [26].

- **Interactions with medications:**

- Vitamin E is heavily dependent on Vitamin C, Vitamin B3, selenium, and glutathione [21].

Arginine-Alpha-Ketoglutarate

- **How it works?**

- Arginine-alpha-ketoglutarate (AAKG) has the main role in acting as an ergogenic aid to increase nitric oxide in the bloodstream resulting in vasodilation. This occurs by supplying the precursor for nitric oxide synthase (NOS), L-arginine. L-Arginine is then metabolized into L-citrulline, producing nitric oxide in the process. This nitric oxide production would then in turn cause vasodilation which would increase oxygen and nutrient delivery to muscles resulting in muscle hypertrophy [27, 28].

- **What is it used for/dosage?**

- AAKG is used for muscle hypertrophy [27].

- **Evidence for or against its use:**

- There is much less published data on AAKG compared to L-arginine, and from the data examined, the efficacy is unclear.
 - A double-blind placebo trial examined the biomarker effect on a 7-day AAKG supplementation (NO_2 Platinum) on various biomarkers. This included 24 active males who were prescribed 12 g/day or a placebo for 7 days resistance training. Three samples were collected at intervals of prior to initiation of exercise, immediately post-exercise, and 30 min after exercise. The results suggest that AAKG increased plasma L-arginine levels, but the increase in nitric oxide after exercise were not statistically significant between the supplementation group and placebo group, suggesting AAKG did not have any influence on nitric oxide levels [27].

- **Safety concerns, side effects, and precautions:**

- So far, there have been four adverse events published while taking AAKG supplementation. In a case series published by Prosser and colleagues, there were three patients with adverse events after ingesting AAKG. The first was a 22-year-old male who ingested three “ NO_2 Platinum” tablets who subsequently developed palpitations, dizziness, generalized numbness, and persistent vomiting. He was admitted overnight for observation and was discharged the next day. The second patient was a 21-year-old male who ingested one tablet of a “nitric oxide” tablet who developed palpitations and near syncope while lifting weights. He was admitted and required IV fluids with resolution of his symptoms the following day. The third was a 24-year-old male who had

palpitations and a headache 45 min after AAKG ingestion. He was treated with acetaminophen and sent home [28].

- The only other adverse occurring after AAKG supplementation recorded was a patient who underwent laser *in situ* keratomileusis procedure. Postoperatively, the patient developed subconjunctival hemorrhages, dilated circumcorneal vessels, and corneal infiltrates—the authors hypothesize that the vasodilatory and antithrombotic effects lead to these complications [29].

- **Interactions with other medications:**

- There have been no documented interactions of AAKG with other medications [30].

Ascorbic Acid

- **How it works?**

- Ascorbic acid (AA), or Vitamin C, acts as a biological antioxidant. This works as a substance that prevents the oxidation of important biomolecules such as fatty acids, DNA, or proteins from a reactive oxygen species. It is found in fruits and vegetables, especially strawberries, citrus, kiwi, brussels sprouts, and cauliflower [31].

- **What is it used for/dosage?**

- Ascorbic acid is utilized for the prevention and treatment of scurvy, macular degeneration, respiratory infections, and idiopathic methemoglobinemia [32–34]. This literature review will examine the efficacy of ascorbic acid as a supplementation.
 - The recommended dietary allowance for men greater than 19 years of age is 90 mg daily and for women greater than 19 years of age is 75 mg daily [35].

- **Evidence for or against its use:**

- There are mixed studies that support the efficacy of ascorbic acid supplementation in improving glycemic outcomes. A recent study assessed 31 individuals with type 2 diabetes and its effect on postprandial glucose responses under free-living conditions demonstrated improved postprandial and 24-h hyperglycemia and decreased blood pressure after 4 months of supplementation compared to placebo [36].

- **Safety concerns, side effects, and precautions:**

- If the supplement is paired with sodium (sodium ascorbate), this contains approximately 5 mEq of sodium and must be taken with caution in sodium-restricted diet patients.

- Renal calculi have also been reported in patients with renal disease taking large doses of ascorbic acid; however, no kidney stone formation was observed in healthy individuals even with excess AA intake. There are also some AA injections that contain aluminum, therefore premature neonates with immature kidneys or individuals with renal disease must be treated with caution [37].

- **Interactions with other medications:**

- Ascorbic acid interacts with aspirin by increased urinary excretion of ascorbic acid and decreased excretion of aspirin with concomitant administration. In addition, taking fluphenazine with AA can decrease fluphenazine concentrations. It can increase GI absorption of iron. Finally, there is a possibility that it can decrease the anticoagulant effect although not all investigators observed this effect [32].

Biotin (Also Known as Vitamin B7 or Vitamin H)

- **How it works?**

- There are biotin-dependent carboxylases that biotin acts as a coenzyme for. These carboxylases act in essential processes such as gluconeogenesis, amino acid metabolism, ATP production, regulation of oxidative stress, regulation of immunologic and inflammatory function, and fatty acid synthesis [38].

- **What is it used for?**

- A major claim biotin supplementation can help with is to have longer and healthier nails and hair. This supplementation can range up to 500–1000 µg in dosage daily. The Food and Nutrition Board of the Institute of Medicine recommends a daily dietary intake of 30 mcg/day to maintain health. The average dietary intake of biotin in the western population is 35–70 mcg/day.
- Foods rich in biotin include egg yolk, liver, cereals containing wheat and oats, spinach, mushrooms, rice, breast milk, and dairy items contain biotin.
- Typically, patients can obtain biotin through diet alone, but if deficiency is present, oral supplementation has high bioavailability and is given starting at 5 mg/day.

- **Evidence for or against its use:**

- A recent study in 2017 reviewed 18 reported cases of use of biotin for hair and nail changes. The overall results show that 10 of the 18 cases had patients with inherited enzyme deficiencies that utilize biotin as a cofactor. All patients reported some underlying pathology for poor hair and poor nail growth. All cases reported clinical improvement of hair and nail growth after receiving biotin. However, none of the studies included any information regarding effi-

cacy of hair and nail growth in healthy individuals. The author's conclusion was that there is no evidence for biotin supplementation outside of known biotin deficiencies [39].

- There has not been any reported injuries from taking too much biotin [40].

- **Safety concerns, side effects, and precautions:**

- Per the FDA in 2017, there was a potential complication of biotin interference to cause inaccurate laboratory results, including falsely low troponin that could result in missed or delayed myocardial infarction diagnosis [41].
- Another study investigated the prevalence of biotin supplementation use in the general population (surveying the outpatient population) and corresponded these results with quantifying biotin in plasma samples collected from patients presenting to the emergency department. These results revealed that among completed surveys, 7.7% indicated biotin use (of 1944 patients surveyed). Of the samples collected in the ED ($n = 1442$), 7.4% had concentrations of biotin at or above the biotin level in plasma that would qualify for biotin interference in immunoassay tests. This finding was concerning as this identifies a population at risk for potential harm such as falsely low troponins as mentioned above [42].

- **Interactions with other medications:**

- Taking anticonvulsants such as carbamazepine or phenobarbital can increase requirements for biotin due to inhibiting uptake of biotin into brush borders of membrane vesicles.
- Smoking and pregnancy can also metabolize biotin quickly, therefore biotin supplementation may be indicated; however, this is controversial with conflicting studies.
- Biotin can interfere with hormone assays such as thyroid functions, gonadotrophins, and Vitamin D [43].

Bitter Orange

- **How it works?**

- Bitter orange is known by a few different names. The scientific name for the small citrus tree is *Citrus aurantium*. It is also known by Zhi Shi, Seville orange, and sour orange. These names refer to the small citrus tree, the peel, and the fruit. The active ingredients are synephrine and octopamine which are structurally similar to epinephrine and norepinephrine. These structures are believed to affect alpha and beta-3 receptors, but affect beta-1 and beta-2 receptors less actively, theorized to have fewer CNS side effects. However, there are conflicting studies on the mechanism of action of synephrine specifically. Some studies [44] report the beta-3 activity stimulate the heart and act

in systemic vasodilation, but [45, 46] primarily stimulate alpha-1 adrenergic receptors due to structural similarity to phenylephrine which would result in vasoconstriction and increase of blood pressure.

- **What is it used for/dosage?**

- Weight loss supplement by increasing energy—expenditure.
- There has been evidence of effective weight loss at a synephrine dose of 32 mg daily, and doses up to 80 mg/day have been used for the treatment of obesity [47].

- **Evidence for or against its use:**

- All the current studies investigate bitter orange in combination with other supplements, such as caffeine, guarana, white willow bark, ginger root extract, and ma huang. There were no studies found of investigating bitter orange as a supplement alone.
- In a study investigating which isomers were present in a weight loss supplement containing bitter orange, the label reported it only contained one isomer (*m*-synephrine), but the authors' analysis proved that it contained two types (*m*-synephrine and *p*-synephrine). *p*-Synephrine is known to cause more CNS stimulation [48].
- One of the first clinical studies was a 6-week, double-blind, placebo-controlled randomized study involving 23 subjects. This study investigated bitter orange on weight loss examined a mixture of bitter orange, St. John's wort, and caffeine compared to a control group, placebo group, and an active group. The results did show that after 6 weeks, there was a statistically significant loss in body fat and percent fat in the active group compared to control/placebo, however, no significant differences between groups for body weight, basal metabolic rate, blood pressure, heart rate, or EKG (loss of -2.9% compared to 0.8%). These results per the authors suggest that bitter orange in combination with St. John's wort and caffeine was safe and effective for weight loss in combination with diet and exercise. However, this study should be interpreted with caution due to the confounding factors of other supplements involved, as well as the statistical analysis being performed within the group, it was not performed between groups [49].
- Another trial examined the cardiovascular effects involving 15 subjects of a single dose of bitter orange (6% synephrine). Heart rate and systolic and diastolic heart rate were measured at baseline and every hour for 6 h after administration.
- Increase or changes in systolic and diastolic blood pressure and heart rate were observed for 5 h following administration of bitter orange [50].
- However, another randomized, open-label, placebo-controlled crossover design study examined blood pressure and heart rate with synephrine or water placebo, measuring blood pressure hourly for 5 h, and there was no effect of blood pressure or pulse [46].

- Finally, a double-blind, placebo-controlled safety study was conducted in 67 moderately overweight adults (mean BMI of 30.8) and were assigned one of three treatments, *p*-synephrine, a combination of *p*-synephrine with naringin and hesperidin, or placebo for 60 days twice a day. There were no differences among the three groups for lipid profiles, liver enzymes, electrolytes, or CBC, and no differences in systolic or diastolic blood pressures were observed. However, the placebo group experienced a significant reduction in heart rate from baseline compared to the other active treatment groups. There was no data noted on body weight changes [51].

- **Safety concerns, side effects, and precautions:**

- Patients with premorbid conditions such as cardiac arrhythmias, hyperthyroidism, and narrow angle glaucoma due to the vasoconstriction effect of synephrine.
- There has been documentation of a 38-year-old man who suffered an ischemic stroke after taking a dietary supplement containing bitter orange for 1 week. No other etiology could be identified as the individual did not suffer from an atherosclerotic history or have any other comorbidities [52].
- Another case involves a 52-year-old woman with hypothyroidism (on thyroxine) who had been consuming bitter orange daily (containing 30 mg/daily) who had developed unremitting tachycardia [53].
- A 22-year-old male developed rhabdomyolysis after consuming a bitter orange weight loss formula. He developed fatigue, dehydration, and myalgias while exercising [54].
- There has not been enough evidence regarding safety and efficacy to safely administer to any patient who is pregnant or lactating.

- **Interactions with other medications:**

- Bitter orange interacts intestinal CYP3A4 and therefore should be avoided in drugs such as amiodarone, anxiolytics, antidepressants, antiviral medications, calcium channel blockers, dextromethorphan, prokinetic agents to aide in digestion, vasoconstricting medications, and other weight loss formula pharmaceuticals [47].

Blue-Green Algae

- **How it works?**

- Blue-green algae (cyanobacteria) are Gram-negative oxygenic photosynthetic autotrophs that have been used as food in both ancient and present-day civilizations in various continents including Asia, Africa, and South America [55].

- **What is it used for and what dosage?**

- Blue-green algae (most commonly *Chlorella*, *Scenedesmus*, *Spirulina*, and *Dunaliella*) are mainly marketed as having high nutritive value [55]. *Spirulina* is marketed for protein, γ -linolenic acid (GLA), and phycocyanin content [56].
- Researchers and manufacturers also report numerous claims of being a “super food for super health” with claims of having antiviral, anticancer, antidiabetic, antibiotic, immune boosting, hypocholesterolemic and weight loss effects [55].
- They are also a rich source of vitamins. *S. platensis* has a higher content of Vitamin B12 and *Spirulina* is rich in provitamin A, Vitamin E, thiamine, cobalamine, biotin, and inositol [57].
- The FDA regulates algal products. The status GRAS (generally regarded as safe) was given to *Spirulina* and *Schizochytrium*. The microcystin content (discussed below) should not exceed 1 mcg of dry weight for consumption.
- *Spirulina* has typically been studied in daily dosage of 1–10 g for 2–12 months; however, there is insufficient clinical data to officially guide dosing [58–62].

- **Evidence for or against its use:**

- While cyanobacteria and microalgae are marketed as food supplements with numerous effects on human health, these claims are all largely based on *in vitro* experiments or on experiments involving animal [56].

- **Safety concerns, side effects, and precautions:**

- The vast majority of cyanotoxin poisoning (cyanobacterial blooms from blue algae) occur in dogs and livestock [63]
- A comprehensive literature review dating from 1920s to 2020s demonstrated that half of the incidences were from a contaminated drinking water supply and the other half were from recreational exposure [63]. Nowadays, blue-green algae are produced in controlled cultivation processes, harvested within their natural habitats, or in specialized bioreactors [55].
- Cyanobacteria also produce several potent hepatotoxins and neurotoxins. The most well-known is microcystin, which is readily taken up by hepatocytes and cause structural damage. Microcystin is also linked to liver cancer in humans [64]. The main routes which human health can be affected include ingestion, inhalation, and skin contact [65].
- While microcystin is the most encountered and well studied, there is a large array of other toxins that may be present in these supplements. These include BMAA (a neurotoxic amino acid) which has been suggested to be associated with amyotrophic lateral sclerosis/parkinsonism dementia complex or ALS/PDC [55].
- There is also a large quantity of nucleic acids within algae, which metabolize to uric acid. This can increase the risk of gout or kidney stones, among other

adverse health effects. However, the current recommended dose of various blue algae (15 of *Scenedesmus* daily, up to 50 g of Chorella should not pose a concern to increased uric acid—but cautions away from consuming large quantities [57].

- **Interactions with other medications:**

- There have been no well-documented interactions. There has been antiplatelet effects documented in vitro but not in vivo [66].

Caffeine

- **How it works?**

- Caffeine is a central nervous stimulant, found in more than 60 plants such as coffee beans, tea leaves, cola nuts, and cocoa pods. Caffeine is believed to act in three ways. First, it acts as a central nervous stimulation via an adenosine blockade which in turn releases neurotransmitters such as dopamine, catecholamines, and acetylcholine. The second mechanism is via enhancement of muscle contraction via improved calcium output from the sarcoplasmic reticulum to the sarcoplasm after a muscle action potential. Finally, it acts by inhibiting phosphodiesterases which in turn inhibits the degradation of cAMP and stimulates lipolysis, causing the activity of hormone-sensitive lipase which plays a vital role in the adrenaline cascade.

- **What is it used for?**

- There is a consensus regarding the effects of caffeine consumption on aerobic performance with high doses, there has been pronounced effects on physiological responses to exercise, including increased heart rates, doubling of catecholamine levels, higher blood lactate levels, and increased blood-free fatty acids. These effects have also been studied at medium and lower doses, and recent work shows that lower caffeine doses taken before exercise can also increase athletic performance, improved vigilance, alertness and mood, and cognitive processes during and following strenuous exercise [67].

- **Evidence for or against its use:**

- A recent meta-analysis conducted in 2020 examined the effects of caffeine ingestion on exercise performance. This meta-analysis contained 11 reviews and showed that caffeine ingestion improves exercises on a broad range of exercise tasks. It also demonstrated ergogenic effects on muscle endurance, muscle strength, anaerobic power, and aerobic endurance [68].
 - Another study examined the effects of supplement identification on exercise performance with caffeine supplementation. Caffeine improved performance over the control group or placebo group [69].

- Another randomized double-blind, placebo-controlled crossover designed study investigated the effects of caffeine supplementation on anaerobic performance, neuromuscular efficiency, and upper and lower limb extremity fatigue in Olympic level boxers. The resulting conclusion showed that caffeine supplementation improved anaerobic performance without affecting EMG activity and fatigue levels in the lower limbs [70].

- **Safety concerns, side effects, and precautions:**

- The ingestion of high doses can produce gastrointestinal upset, nervousness, mental confusion, inability to focus, and disturbing sleeping in some subjects [67].
- In many lethal cases, caffeine had been introduced as a dietary supplement in conjunction with other substances such as stimulant drugs and alcohol. The acute toxic level of caffeine isn't well established, but for adults is approximately 10 g of caffeine a day, which would be equivalent to approximately 100 cups of coffee [71].

- **Interactions with other medications:**

- The enzyme P450 1A2 participates in the metabolism of caffeine. There are several medications that inhibit this enzyme, including the selective serotonin reuptake inhibitor fluvoxamine, the antiarrhythmic mexiletine, the antipsychotic clozapine, psoralens, idrocilamide and phenylpropanolamine, bronchodilators furafylline and theophylline, and the quinolone enoxacin. Due to these drugs acting as potent inhibitors of this enzyme, this could lead to toxic effects of caffeine, especially if concomitantly being taken with other drugs that are metabolized by this same enzyme [72].

Calcium

- **How it works?**

- Calcium is the most plentiful mineral in the human body, found mainly in bones and teeth. It is also found in blood, muscles, and other tissues with a variety of functions within the body. Physical activity such as weight-bearing exercises, loss of calcium via sweat, and the female athlete triad (disordered eating, amenorrhea, and osteoporosis) are all important factors to consider for supplementation as it relates to physical activity [73].

- **What is it used for?**

- Calcium is involved in a myriad of processes within the human body. While its most well-known function for bone health and prevention of osteoporosis, it is utilized for many other functions within the human body that would be of interest to an athlete. It is involved in muscle contraction, regulation of

heartbeat, nerve impulse conduction, blood pressure, and balance of water within the body, energy and fat metabolism, and general transport of nutrients across cell membranes [73].

- **Evidence for or against its use:**

- A large placebo-controlled study involving 33,000 women administered 1000 mg calcium carbonate and 400 mg Vitamin D3 compared to placebo examining physical performance and exercise measures after 1, 2, and 4 years. The results showed no improvement in subjective or objective physical function [74].
- Another study found elevated urinary calcium losses after a high impact training program, suggesting that calcium is utilized in higher amounts in high impact physical exercise. However, the current literature reviewed did not conclude the need for calcium supplementation greater than what can be obtained via diet [75].

- **Safety concerns, side effects, and precautions:**

- In a study reviewing randomized control trial evidence of adverse events from calcium supplementation, gastrointestinal events were the most common described. This included constipation, abdominal cramping, bloating, upper GI events, GI disease, and severe diarrhea (for calcium there was an incidence of 14.1%, for placebo 10.0%, with a relative risk (RR) of 1.43, and a confidence interval of 1.28–1.59, $p < 0.001$) [76].
- Two trials also examined self-reported myocardial infarctions with dietary calcium supplementation at 3.6% rate in the calcium supplementation group and 2.1% in the placebo group. However, after undergoing an adjudication process by the reviewers, the adjusted rates were 2.4% in the calcium group and 1.6% in the placebo group [76].

- **Interactions with other medications:**

- An absolute contraindication to being prescribed calcium carbonate is concomitant use of ceftriaxone due to increased risk of end-organ failure and death [77].

Catechin

- **How it works?**

- Green tea extract contains catechins (CA), which are polyphenolic compounds, the major being epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-3-gallate [78]. These fall within the family of flavonoids, and are thought to have antioxidative potential, but these studies have often only been demonstrated in vitro studies [79].

- It is also proposed that catechins upregulate lipid-metabolizing enzymes via the NF-κB activation by inhibiting the peroxisome proliferator-activated receptors (PPARs) that are important transcription factors for lipid metabolism, and in theory mRNA expression of lipid-metabolizing enzymes would be upregulated [80].

- **What is it used for?**

- Catechin is a frequent ingredient in herbal and dietary supplements, typically labeled as green tea extract. It is typically marketed as an antioxidant and a weight loss supplement [78].

- **Evidence for or against its use:**

- The European food safety authority had a safety meeting regarding the safety of consuming green tea catechins. The conclusion was that green tea infusions, prepared in a traditional way, are in general safe for consumption; however, there is evidence from interventional clinical trials that doses equal or above 800 mg a day can induce a statistically significant increase of serum transaminases [81].
- One study evaluated the influence of green tea catechin beverage on body composition and fat distribution in overweight and obese adults during exercised-induced weight loss. 107 participants were assigned to receive a beverage containing ~625 mg of catechins with 39 mg of caffeine or a control beverage for 12 weeks and participate in similar amounts of moderate intensity exercise.
- Percentage changes in fat mass did not differ between the catechin group compared to the control group, but percentage changes in total abdominal fat area and fasting serum triglycerides were greater in the catechin group. These findings suggest that the consumption of a beverage containing green tea catechins (625 mg/day) may enhance exercise-induced loss of abdominal fat and improve circulating free fatty acids and triglyceride levels [82].
- However, a meta-analysis of six studies on 532 participants produced a very small, statistically non-significant mean difference in weight loss [83].

- **Safety concerns, side effects, and precautions:**

- Catechins were implicated in several case reports regarding hepatotoxicity. A further investigative report assayed herbal dietary supplements that were implicated in human hepatotoxicity and screened for catechins. The results were that many of these supplements may commonly contain catechins even if their presence is not listed on the drug label, but there was no statistically significant association between presence of catechin or the dose consumed in liver or causality score, severity, or pattern of liver injury [78].
- Additionally, the US Pharmacopeia conducted a systematic review to determine the safety of green tea extracts with the conclusion that these extracts can contain hepatotoxic solvent residues, pesticide residues, pyrrolizidine alkaloids, and elemental impurities, but no evidence of involvement in actual

green tea extract induced injury. Therefore, the official conclusion from this review was to include a cautionary label that recommends not to use if patients have any pre-existing liver problem [84].

Chitosan

- **What is it?**

- Chitosan is a natural polysaccharide derived from chitin which is a widely used biopolymer [85]. They are a large component of arthropod shells such as crabs, shrimps, and insects, and are also produced extracellularly by various fungi and algae [86].

- **How does it work in the body?**

- Studies have shown that Chitosan taken as a food supplement forms a gel in the intestinal tract which binds dietary lipids and other nutrients, resulting in a reduction in intestinal lipid absorption as well as other vitamins and minerals, this in turn causes lower serum cholesterol and triglycerides [86]. Chitosan also displays hormonal and protein-modulating properties such as increasing serum leptin concentration and leading to a reduction in C-reactive protein [87].

- **What is it used for?**

- Chitosan is used as a weight loss and anti-obesity supplement. A 2019 meta-analysis showed that Chitosan supplementation led to a clinically significant reduction in body weight, BMI, and body fat [88]. Chitosan supplementation is also used as a cholesterol-lowering agent [86]. There have also been reports of its use for treating hypertension, wound healing, and for antimicrobial purposes [85, 86]. Notably, further studies in human participants are needed to solidify the evidence to support these claims.

- **Evidence for and against:**

- A 2018 meta-analysis showed that Chitosan supplementation can lead to minimal weight loss and an improvement in serum lipid and cardiovascular factors [85].
 - In animal studies, short-term chitosan administration was shown to cause a reduction in the absorption of vitamins and minerals including fat-soluble vitamins, calcium, and Vitamin E. This led to a reduction in bone mineral content and growth restriction [86].

- **Precautions/side effects:**

- Adverse effects of Chitosan include a reduction in Vitamin E levels in plasma, reduction in bone mineral content, growth retardation, and reduced absorption of fat-soluble vitamins and minerals [86]. These may lead to symptoms

such as weakness, nausea, diarrhea, constipation, increased bone fragility, and steatorrhea.

- **Dosage:**

- A meta-analysis which included 14 studies showed a mean dosage of 2 g/day p.o [85].

- **Interactions:**

- Chitosan has been shown to potentiate the anticoagulant effect of warfarin if used together, likely due to reduced absorption of fat-soluble vitamins, namely Vitamin K [89].
 - Individuals with shellfish allergies should avoid chitosan [90].

Chlorogenic Acid

- **What is it?**

- Chlorogenic acid is a polyphenol compound that is sourced from coffee beans as well as various fruits and vegetables [91].

- **How does it work in the body?**

- A 2017 systematic review showed that chlorogenic acids counteract oxidative stress by scavenging free radicals, acting as a metal chelator, reducing lipid peroxidation, and inhibiting NADPH oxidase activity. It also inhibits alpha glucosidase which limits digestive uptake of carbohydrates. This leads to a combination of antidiabetic, anti-carcinogenic, anti-inflammatory, and anti-bacterial effects [91, 92].

- **What is it used for?**

- Chlorogenic acids are mainly used for weight loss and to lower blood pressure, but studies have shown that it may also be beneficial as an anti-bacterial agent, as a blood sugar-lowering agent, and to improve mood [91].

- **Evidence for and against:**

- A 2019 systematic review and meta-analysis found that chlorogenic acid supplementation led to statistically significant reductions in systolic and diastolic blood pressure although they mention that further studies should be conducted. Of the five studies included, no adverse events were reported following chlorogenic acid intake [93].
 - A 2017 article found that chlorogenic acid may have a role in the treatment of metabolic syndrome through antioxidant, anti-inflammatory, and antilipidemic properties. They suggest that this supplement may also have antimicrobial properties, making it a useful nutritional supplement [94].

- **Dosage:**

- There is no official dose of CGA supplementation, but user dosing typically ranges anywhere from 240 to 3000 mg/day.

- **Precautions/side effects:**

- Individuals with green coffee bean extract allergies may have an adverse reaction to this supplement in the form of an asthmatic response, studies suggest that this is likely due to the surrounding compounds in the coffee beans rather than chlorogenic acid itself [95].

- **Interactions:**

- Chlorogenic acids may elicit adverse interactions with antihypertensives since it has blood pressure lowering effects as well. Chlorogenic acids may also be shown to enhance the effects of metformin in lowering blood sugar. This can cause episodes of hypotension and hypoglycemia, respectively, so precautions should be taken [96].

Chromium

- **What is it?**

- Chromium is a trivalent trace element and essential nutrient that is commonly found in many foods and used as a nutritional supplement in humans and animals [97].

- **How does it work in the body?**

- In the body, 95% of chromium is bound to proteins such as transferrin, the remainder is unbound and can accumulate in the liver, bone, soft tissue, and spleen. Chromium may enhance insulin activity, leading to increased metabolism of carbohydrates, lipids, and proteins. The exact mechanism is still unclear, but studies suggest that this may occur through chromium binding to chromodulin, a substance that can directly bind to insulin receptors and enhance its activity. Chromium is excreted in the urine [98].

- **What is it used for?**

- Studies have shown that chromium deficiency can cause a diabetic-like state with features such as elevated blood sugars, impaired growth, elevated serum lipids, decreased fertility, and nerve damage. Chromium supplementation is used to treat and prevent chromium deficiency which is usually only seen in severely malnourished individuals or patients undergoing total parenteral nutrition without added chromium [99, 100]. Supplementation with chromium is also used for prevention and control of diabetes and hyperlipidemia as studies suggest improved glycemic and lipid profiles with its use [100,

[101]. There have been claims that chromium supplementation can also aid in weight loss, cognitive function, and bone health but there is insufficient evidence to support these claims at this time.

- **Evidence for and against:**

- Chromium has been shown to improve blood glucose and related variables in diabetes mellitus type 1 and 2, gestational diabetes, and corticosteroid-induced diabetes [100].
- A 2014 meta-analysis showed that chromium mono and combined supplementation significantly reduced HbA1c and fasting plasma glucose (FPG) levels. It also showed that chromium mono-supplementation elevated HDL-c levels and lowered triglycerides. These effects were most notably enhanced with the combination of chromium-picolinate [101].
- A 2016 meta-analysis of 13 randomized controlled trials showed that chromium significantly reduced FPG levels by an average of -29.26 mg/dL and significantly lowered total cholesterol at an average of -6.7 mg/dL [102].
- A 2015 meta-analysis with 875 participants showed that chromium yeast and chromium-picoline did not show significant effects on HbA1c or FPG [103].

- **Dosage:**

- Dietary reference intake suggests an adequate intake of 35 and 25 mcg, respectively, in men and women aged 19–50 (30 and 20 mcg, respectively, in men and women aged 51 or older) [98]. A 2014 systematic review suggests that $>200 \text{ mcg}$ of chromium mono-supplementation may improve glycemic control [101]. Doses typically should not exceed 1000 mcg daily [104].

- **Precautions/side effects:**

- Chromium supplementation is typically safe with mild adverse effects reported in the form of headaches, sleep disturbances, and irritability [101, 102, 104].

- **Interactions:**

- Chromium may interact with insulin, metformin, or other blood-glucose-lowering antidiabetic medications to cause hypoglycemia so simultaneous use should be discussed with a health care provider. Chromium may also reduce levothyroxine absorption [98].

Coenzyme Q10

- **What is it?**

- Coenzyme Q10 (CoQ10) is a naturally occurring quinone that is found in many aerobic organisms such as bacteria and mammals. It functions primarily

to aid in energy production, augment the immune system, and combat oxidative damage in the body. It is found in abundance in tissues with significant metabolic activity such as the heart, lungs, liver, kidneys, spleen, pancreas, and adrenal glands. It is typically sourced through oily fish such as tuna and salmon, organ meats, and whole grains; however, it can also be supplemented in the form of oral tablets, capsules, and sprays [105].

- **How does it work in the body?**

- In mitochondria, CoQ10 functions primarily as a cofactor in the electron transport chain during the formation of adenosine triphosphate (ATP) for cellular energy [105]. It is also found on cell membranes and transport lipoproteins such as LDL and HDL where it functions as an antioxidant to combat oxidative damage [106]. CoQ10 exists in the body in two forms: Ubiquinone (oxidized form) or Ubiquinol (reduced form). Most of its antioxidant properties are carried out in its Ubiquinol form, and it does so by neutralizing free radicals and reactive oxygen species [105, 107].

- **What is it used for?**

- Supplementation with CoQ10 is typically used to improve its deficiency as well as diseases related to mitochondrial dysfunction and oxidative stress such as fibromyalgia, diabetes, chronic fatigue syndrome, and heart diseases. It can also be used for performance enhancement and to prevent adverse effects of statins [108, 109].

- **Evidence for and against:**

- *CoQ10 deficiency*: Deficiency can lead to symptoms such as weakness, fatigue, seizures, encephalopathy, and nephrotic syndrome. Oral CoQ10 supplementation has been shown to reduce these symptoms and reverse the progression of some [110].
- *Mitochondrial encephalomyopathy (MELAS)*: Studies show that CoQ10 supplementation can improve symptoms of mitochondrial dysfunction such as nerve dysfunction, muscle weakness, tremors, cramps, and muscle stiffness [111, 112].
- *Heart disease*: Studies show that CoQ10 supplementation has significant benefits for heart health. CoQ10 was shown to reduce heart wall thickness, regulate heart rate, improve heart function, and quality of life in patients with hypertrophic cardiomyopathy [113]. In heart failure studies inclusive of 420 and 639 participants, oral CoQ10 supplementation was shown to reduce mortality, hospitalizations, and significant complications from heart failure [114, 115]. Another study also found that supplementation reduced heart failure mortality but that it did not improve heart function or symptoms [116].
- *Vascular health*: CoQ10 was shown to increase nitric oxide levels through its antioxidant effects leading to improved blood vessel dilation and increased circulation [117, 118].

- *Blood pressure:* Many studies inclusive of over 280 participants show that CoQ10 supplementation reduces systolic and diastolic blood pressure [119, 120]. Other studies suggest that supplementation with 200 mg/day for 12 weeks had no effect on blood pressure [118].
- *Inflammation:* A systematic review found that CoQ10 supplementation significantly reduced inflammatory markers such as TNF- α but had no effect on CRP and IL-6 [121].
- *Diabetes mellitus:* 400 mg of CoQ10 daily was shown to reduce nerve damage and improved nerve function in diabetic mice. CoQ10 also has been shown to protect organs such as the kidneys and heart from elevated blood sugar levels [122, 123]. A meta-analysis also showed that low doses of CoQ10 (<200 mg) reduced blood sugar levels when given for 12 weeks or less [124].
- *Migraines:* CoQ10 supplementation has been shown to reduce migraine duration, frequency, and severity [125].
- *Fibromyalgia:* Patients with fibromyalgia have been shown to have reduced and dysfunctional CoQ10, supplementation has been shown to improve headache, depression, and fatigue symptoms associated with this disorder [126].
- *Multiple sclerosis:* 500 mg/day of CoQ10 has been shown to improve fatigue and depression associated with multiple sclerosis [127].

- **Dosage:**

- 100–300 mg of CoQ10 twice daily has proven to be effective for most of its usages. It has been shown to be safe and well tolerated at dosages up to 1200 mg daily [128].

- **Precautions/side effects:**

- Studies show that CoQ10 does not cause serious harmful effects in humans, but mild side effects may include diarrhea, nausea, loss of appetite, headache, or rash. It is metabolized by the liver and eliminated through bile so people with liver or biliary pathology may be at a higher risk of experiencing these side effects due to poor elimination from the body [129].

- **Interactions:**

- *Warfarin:* CoQ10 has structural similarity to procoagulant Vitamin K so may reduce Warfarin's effect [130].
- *Blood pressure:* CoQ10 has been shown to lower blood pressure so should be taken with caution by those taking antihypertensives [119].
- *Blood sugar:* CoQ10 has been shown to lower blood-glucose levels so should be taken with caution by those taking glucose-lowering medications [124].

Colostrum

- **What is it?**

- Colostrum is a milk that is secreted by mammals in the initial post-partum period that contains nutrients such as carbohydrates, growth factors, proteins, enzymes, enzyme inhibitors, antibodies, nucleotides and nucleosides, cytokines, fats, vitamins, and minerals [131]. Colostrum is produced during the first week following birth and provides significant protection for newborns with developing immune systems, it eventually transitions into mature milk [132].

- **How does it work in the body?**

- Colostrum has a wide range of mechanisms in the body. These include boosting immunity by activating natural killer cells and stimulating IFN-gamma and IL-2 release [133]. Suppressing myeloperoxidase activity to reduce oxidative damage [134]. It protects the gastrointestinal system through its anti-inflammatory and antimicrobial properties [135]. It can also raise IGF-1 levels allowing for better glucose utilization and storage [136].

- **What is it used for?**

- Colostrum supplementation is frequently used for modulating immune defense, aiding in gastrointestinal issues such as diarrhea and leaky gut, stimulating exercise enhancement, and aiding in Alzheimer's disease and memory loss [135].

- **Evidence for and against:**

- *Diarrhea and respiratory infections:* A study of 160 children showed that bovine colostrum significantly reduced the number of upper respiratory tract infections, diarrheal episodes, and number of hospital admissions. Another study with 605 children showed similar results [137, 138]. In a study of 74 people, there were fewer reports of respiratory tract infections reported when taking colostrum [139].
 - *Immune:* In a study of 18 participants Colostrum was shown to enhance IgA antibodies and increase mucosal protection [140]. Another study with 198 participants showed that consumption of colostrum had no effect on immunological parameters [141]. In mice, colostrum was shown to enhance natural killer cell activity [142]. In a study of 35 long distance runners, Colostrum supplementation was shown to increase IgA levels [143]. A study found that Colostrum supplementation was more effective than vaccination for preventing influenza in both healthy and high-risk cardiovascular subjects.
 - *Muscle enhancement:* One study showed significantly increased lean body weight when taking Colostrum supplementation compared to whey protein. Another study showed that both whey protein and colostrum equally increased lean body mass, total body mass, and strength [144].

- *Alzheimer's and memory loss:* Studies have shown that long-term colostrinin, which is a component of colostrum, may slow memory loss and cognitive deficits associated with Alzheimer's disease [145].

- **Dosage:**

- Doses varied from as low as 500 mg/day for leaky gut to as high as 60 g/day for upper respiratory tract infections [139, 146].

- **Precautions/side effects:**

- Colostrum is generally a safe supplement and tolerated well. Mild side effects include nausea, gas, skin rash, diarrhea, and stomach pain [135].

- **Interactions:**

- Colostrum may alter the effectiveness of NSAIDs due to its lactoferrin content which can bind NSAIDs [147].

Conjugated Linoleic Acid

- **What is it?**

- Conjugated linoleic acids (CLA) are poly-unsaturated fatty acids with various bonding structures within them. They are found mainly in meat and dairy products but can also be used as supplements [148, 149].

- **How does it work in the body?**

- CLAs contain cis, trans, and double bonds. In foods like meat and dairy, they are found in the CLA cis-9, trans-11 form but in supplements they are found in the trans-10, cis-12 form [148].

- **What is it used for?**

- Supplemental CLA are primarily used as anti-obesity and anti-hypertensive agents regularly [148–150].

- **Evidence for and against:**

- *Blood pressure:* One study that included 80 obese individuals showed that CLA supplementation significantly enhanced the effect of Ramipril on systolic and diastolic blood pressure reduction [151].

- *Cholesterol:* In a study of 61 healthy women, high intake of supplemental CLA was shown to significantly elevate HDL levels [152].

- *Heart disease:* Cardiomyocyte exposure to high glucose levels can result in structural and functional damage to the heart, one study in rat cells found that cells pre-treated with CLA can prevent this cardiomyocyte damage in the setting of hyperglycemia [153].

- *Obesity*: CLA supplementation was shown to significantly improve weight loss in a 63-subject study over a 12-week period, this led to reduced body weight, BMI, total fat mass, and a reduced fat percentage. Subjects' waist to hip ratio and subcutaneous fat mass also significantly decreased [154]. Some studies have not shown any relationship between CLA and weight loss [155].
- *Fatty liver disease*: Non-alcoholic fatty liver disease (NAFLD) can be seen in obese patients and lead to liver failure. A study consisting of 38 obese individuals showed that CLA supplementation improved insulin resistance, lipid disturbances, oxidative stress, and liver function in NAFLD [156].
- *Cancer*: There have been claims that CLA can be beneficial against certain types of cancer but further studies on human subjects need to be conducted to further explore the role of CLA in cancer treatment and prevention.

- **Dosage:**

- There is no standardized dosing for CLA as an adequately powered study to address this has not yet been conducted. For many of its usages that were explored, 5 g/day of CLA was shown to be safe and effective.

- **Precautions/side effects:**

- Side effects of CLA are normally mild and include excessive flatulence, bloating, nausea, and diarrhea [148].
 - Men with metabolic syndrome that were taking supplemental CLA had increased insulin resistance and oxidative stress which led to increased inflammation and diabetes [157].
 - Animal studies which showed adverse effects with supplemental CLA include:

Kidney damage and enlargement in obese rats with pre-existing kidney disease that were given CLA [158].

Supplemental CLA in large doses was shown to lead to fat accumulation in the liver of rodents [159].

- **Interactions:**

- There are no known interactions for CLA.

Copper

- **What is it?**

- Copper is an essential trace element in the human body. It is required for growth, bone strength, immune function, heart function, brain development, cholesterol and glucose metabolism. Its daily requirement is typically met by the North American standard diet [160].

- **How does it work in the body?**

- Copper is a cofactor for a group of enzymes called cuproenzymes which includes cytochrome c oxidase, lysyl oxidase, ferroxidase, dopamine β -hydroxylase, superoxide dismutase, ceruloplasmin, and tyrosinase [161, 162].

- **What is it used for?**

- Copper supplementation is used for copper deficiency, skin health, bone loss, heart health, immune function, and anxiety and depression [160].

- **Evidence for and against:**

- *Copper deficiency*: Copper deficiency can present as anemia, heart disease, neutropenia, myelopathy, peripheral neuropathy, and myelodysplasia-like effects. Deficiency is typically only seen when on parenteral nutrition [163]. Copper supplementation in the setting of deficiency has been shown to stimulate bone formation and reduce bone abnormalities in infants and elderly. It was also shown to improve heart function in deficient individuals [164–166].
 - *Skin*: Copper supplementation has been shown to increase collagen and elastin production for strength and elasticity of skin, respectively. Copper also showed antimicrobial properties in the setting of athlete's foot in a study consisting of 56 subjects. Copper prevented skin infections and ulcer wounds in long-standing diabetics [167–169].
 - *Bone loss*: Through its action as a cofactor for various enzymes, Copper has a vital role in the formation of bone [160]. In a study consisting of 73 women, Copper was shown to significantly reduce the loss of vertebral trabecular bone mineral density over the course of 2 years [170].
 - There have been further studies that suggest Copper supplementation may have a role in heart health, immune function, and anxiety and depression but larger clinical studies involving humans would need to be conducted to support these claims.

- **Dosage:**

- The recommended daily copper intake for children: 0.3–0.9 mg/day, adults: 0.9 mg/day, and pregnant or breastfeeding mothers: 1–1.3 mg/day. The safe upper limit for copper supplementation is 10 mg/day [171].

- **Precautions/side effects:**

- *Copper toxicity*: Copper toxicity is normally seen with ingestion of more than 1 g of copper, and it can lead to erosive gastropathy, intravascular hemolysis, methemoglobinemia, hepatitis, acute kidney injury, and rhabdomyolysis [172]. Chronic copper toxicity is typically seen in those with inherited disorders of copper metabolism such as Wilson's disease or idiopathic copper toxicosis, supplementation should not be used in these individuals. Chronically elevated copper levels may be linked to oxidative damage, Alzheimer's disease, Parkinson's disease, and diabetes [173–176].

- **Interactions:**

- *Increased absorption:* Things shown to increase copper absorption include high protein diet and amino acids glycine, L-tryptophan, and L-methionine [177, 178].
- *Decreased absorption:* Copper absorption has been shown to be reduced with amino acids L-histidine and L-cystine, zinc, iron, carbohydrates, and dietary fiber [178–180].

Creatine

- **What is it?**

- Creatine is a natural substance derived from amino acids that is stored in muscles and released upon physical activity. It is widely used to elevate exercise performance and strengthen muscles and is naturally found in sources such as meat and fish [181, 182].

- **How does it work in the body?**

- Creatine is mainly stored in the skeletal muscle as phosphocreatine, the remainder of the body's creatine is stored in the brain, kidney, and liver. The phosphocreatine stored in muscle has high-energy phosphate groups attached to it which allow it to release energy and significantly enhance the formation of new ATP molecules. This allows for a high-energy burst lasting only a short duration (5–10 s) until a drop in phosphocreatine levels occurs. Supplementation with creatine bolsters strength and performance by regenerating ATP that gets used during exercise as well as regenerating phosphocreatine supplies following exercise during recovery [181, 182].

- **What is it used for?**

- Creatine is one of the most popular supplements in the world and is mainly used for exercise performance and muscle strength, preventing muscle damage and fatigue, protecting against age-related muscle loss, and enhancing cognitive function [182].

- **Evidence for and against:**

- *Exercise performance and muscle strength:* Creatine supplementation bolsters phosphocreatine stores which increase ATP energy utilization, especially in muscles during short high intensity workouts [181, 182]. In a meta-analysis of 22 studies, creatine supplementation during resistance training was found to significantly increase muscle strength by 8%, weightlifting performance by 14%, and 1 rep max bench press by a high of 45% when compared with just resistance training alone [183]. Another meta-analysis of 100 studies found that creatine supplementation significantly increased lean body mass when

doing short-term, repetitive exercises, this same study also found that creatine did not improve endurance-based exercise such as running or swimming, which is consistent with other studies [184]. In a study of 32 healthy men undergoing heavy resistance training, creatine supplementation (6–24 g/day) significantly increased muscle growth better than daily protein (20 g/day) [185]. Creatine was also shown to lower myostatin-induced muscle growth impairment [186].

- *Muscle damage and fatigue:* Creatine has been shown to protect against muscle damage and fatigue and aid in its recovery. One study inclusive of 14 men showed that creatine supplementation significantly increased isokinetic and isometric knee-extension strength during recovery from exercise-induced muscle damage, plasma creatine kinase which is a marker of myocyte damage was also lower [187]. Another study on 22 men showed that oral creatinine supplementation did not lower skeletal muscle damage or aid in muscle recovery after a hypoxic resistance exercise challenge [188].
- *Age-related muscle loss:* Studies suggest that creatine supplementation can protect against age-related muscle loss. In a study on elderly individuals, creatine supplementation was shown to reduce muscle atrophy, increase muscle strength and endurance, and increase bone strength even in the absence of resistance training [189].
- *Cognitive function:* Studies suggest that creatine may have a role in preventing mental fatigue and improving cognitive function. One study found that in sleep-deprived athletes, creatine supplementation improved cognitive skills after 1 week of supplementation. Another study showed that creatine supplementation improved complex cognitive skills, it was taken along with moderate intensity exercise for 1 week prior to sleep deprivation [190, 191]. In another study, creatine supplementation was shown to improve cognitive performance and quality of life in elderly individuals after only 2 weeks [192].
- There have been further studies that suggest that creatine supplementation may play a role in elevating testosterone levels, stabilizing musculoskeletal manifestations of Parkinson's disease, improving heart health, lowering blood glucose levels, and increasing bone health. Further clinical studies with human participants should be conducted to explore these claims in more depth.

- **Dosage:**

- Creatine dosing typically occurred in phases. The first phase was the loading phase in which patients received a larger amount in about 20 g/day for the first 5–7 days. The second phase was the maintenance phase in which the dose would reduce to 3–5 g/day. This was done to adequately bring creatine levels to an effective concentration [193].

- **Precautions/side effects:**

- Creatine is likely safe in doses below 30 g/day. Side effects typically include stomach pain and cramping. This supplement can also lead to water retention and weight gain [194]. Creatine has not been shown to damage the kidneys in the short or long term [193].

- **Interactions:**

- *Fenugreek*: Creatine has been shown to maximize strength and training adaptation when taken in conjunction with fenugreek [195].
- *Coenzyme Q10*: Creatine paired with CoQ10 was shown to delay cognitive decline in subjects with mild cognitive impairment and Parkinson's disease [196].

References

Sources for Acarbose

1. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, STOPNIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet. 2002;359(9323):2072–7. [https://doi.org/10.1016/S0140-6736\(02\)08905-5](https://doi.org/10.1016/S0140-6736(02)08905-5). PMID: 12086760
2. Yu AQ, Le J, Huang WT, Li B, Liang HX, Wang Q, Liu YT, Young CA, Zhang MY, Qin SL. The effects of acarbose on non-diabetic overweight and obese patients: a meta-analysis. Adv Ther. 2021;38(2):1275–89. <https://doi.org/10.1007/s12325-020-01602-9>. Epub 2021 Jan 9. Erratum in: Adv Ther. 2021 Aug;38(8):4603–4604. PMID: 33421022
3. Khalili N, Safavipour A. Evaluation of the effects of acarbose on weight and metabolic, inflammatory, and cardiovascular markers in patients with obesity and overweight [J]. Int J Prev Med. 2020;11:140.
4. Serrano JS, Jiménez CM, Serrano MI, et al. A possible interaction of potential clinical interest between digoxin and acarbose. Clin Pharmacol Ther. 1996;60:589–92.
5. Gerard J, Lefebvre PJ, Luyckx AS. Glibenclamide pharmacokinetics in acarbose-treated type 2 diabetics. Eur J Clin Pharmacol. 1984;27:233–6.
6. Scheen AJ, de Magalhaes AC, Salvatore T, Lefebvre PJ. Reduction of the acute bioavailability of metformin by the alpha-glucosidase inhibitor acarbose in normal man. Eur J Clin Invest. 1994;24:50–4.

Sources for 3-Acetyl-7-Oxo-Dehydroepiandrosterone

7. Kaiman DS, Colker CM, Swain MA, Torina GC, Shi Q. A randomized, double-blind, placebo-controlled study of 3-acetyl-7-oxo-dehydroepiandrosterone in healthy overweight adults. Current Therapeutic Research. 2000;61(7):435–42., ISSN 0011-393X (<https://www.sciencedirect.com/science/article/pii/S0011393X00800260>). [https://doi.org/10.1016/S0011-393X\(00\)80026-0](https://doi.org/10.1016/S0011-393X(00)80026-0).
8. Wang F, He Y, Santos HO, Sathian B, Price JC, Diao J. The effects of dehydroepiandrosterone (DHEA) supplementation on body composition and blood pressure: a meta-analysis of randomized clinical trials. Steroids. 2020;163:108710., ISSN 0039-128X. <https://doi.org/10.1016/j.steroids.2020.108710>.
9. Zenk JL, Helmer TR, Kassen LJ, Kuskowski MA. The effect of 7-Keto Naturalean™ on weight loss: A randomized, double-blind, placebo-controlled trial. Current Therapeutic Research - Clinical and Experimental, 2002;63(4):263–72. [https://doi.org/10.1016/S0011-393X\(02\)80031-5](https://doi.org/10.1016/S0011-393X(02)80031-5).

Sources for ATP

10. Ng S, Lim HS, Ma Q, Gao Z. Optical aptasensors for adenosine triphosphate. *Theranostics*. 2016;6(10):1683–702. <https://doi.org/10.7150/thno.15850>. PMID: 27446501; PMCID: PMC4955066
11. Jordan AN, Jurca R, Abraham EH, Salikhova A, Mann JK, Morss GM, Church TS, Lucia A, Earnest CP. Effects of oral ATP supplementation on anaerobic power and muscular strength. *Med Sci Sports Exerc*. 2004;36:983–90. <https://doi.org/10.1249/01.MSS.0000128198.97260.8B>.
12. Purpura M, Rathmacher JA, Sharp MH, Lowery RP, Shields KA, Partl JM, Wilson JM, Jäger R. Oral adenosine-5'-triphosphate (ATP) administration increases postexercise ATP levels, muscle excitability, and athletic performance following a repeated sprint bout. *J Am Coll Nutr*. 2017;36(3):177–83. <https://doi.org/10.1080/07315724.2016.1246989>. Epub 2017 Jan 12. PMID: 28080323

Sources for Alpha Lipoic Acid

13. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivighn S, Johnson RJ. Elevated uric acid increases blood pressure in the rat by a novel crystalindependent mechanism. *Hypertension*. 2001;38:1101–6. <https://doi.org/10.1161/hy1101.092839>.
14. Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schütte K, Kerum G, Malessa R. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-lipoic acid in diabetic neuropathy. *Diabetes Care*. 1999;22(8):1296–301. <https://doi.org/10.2337/diacare.22.8.1296>. PMID: 10480774
15. Boriani F, Granchi D, Roatti G, Merlini L, Sabattini T, Baldini N. Alpha-lipoic acid after median nerve decompression at the carpal tunnel: a randomized controlled trial. *J Hand Surg Am*. 2017;42(4):236–42. <https://doi.org/10.1016/j.jhsa.2017.01.011>. Epub 2017 Feb 28
16. Xia D, Zhai X, Wang H, Chen Z, Fu C, Zhu M. Alpha lipoic acid inhibits oxidative stress-induced apoptosis by modulating of Nrf2 signalling pathway after traumatic brain injury. *J Cell Mol Med*. 2019;23(6):4088–96. <https://doi.org/10.1111/jcmm.14296>.
17. Baziar N, Nasli-Esfahani E, Djafarian K, Qorbani M, Hedayati M, Mishani MA, Faghfoori Z, Ahmaripour N, Hosseini S. The beneficial effects of alpha lipoic acid supplementation on Lp-PLA2 mass and its distribution between HDL and apoB-containing lipoproteins in type 2 diabetic patients: a randomized, double-blind, placebo-controlled trial. *Oxid Med Cell Longev*. 2020;9(2020):5850865.
18. Kucukgoncu S, Zhou E, Lucas KB, Tek C. Alpha-lipoic acid (ALA) as a supplementation for weight loss: results from a meta-analysis of randomized controlled trials. *Obes Rev*. 2017;18(5):594–601. <https://doi.org/10.1111/obr.12528>. Epub 2017 Mar 13. PMID: 28295905; PMCID: PMC5523816
19. Yukina M, Nuralieva N, Solov'yev M, Troshina E, Vasilyev E. Insulin autoimmune syndrome. *Endocrinol Diabetes Metab Case Rep*. 2020;2020:19–0159. <https://doi.org/10.1530/EDM-19-0159>.
20. Phua LC, New LS, Goh CW, et al. Investigation of the drug–drug interaction between α -lipoic acid and valproate via mitochondrial β -oxidation. *Pharm Res*. 2008;25:2639–49. <https://doi.org/10.1007/s11095-008-9681-5>.

Sources for Alpha-Tocopherol

21. Rizvi S, Raza ST, Ahmed F, Ahmad A, Abbas S, Mahdi F. The role of vitamin e in human health and some diseases. *Sultan Qaboos Univ Med J*. 2014;14(2):e157–65.
22. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. *JAMA*. 2014;311(1):33–44. <https://doi.org/10.1001/jama.2013.282834>.
23. Glynn RJ, Ridker PM, Goldhaber SZ, Zee RY, Buring JE. Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: report from the Women's Health Study. *Circulation*. 2007;116(13):1497–503. <https://doi.org/10.1161/CIRCULATIONAHA.107.716407>. Epub 2007 Sep 10. PMID: 17846285
24. Klein EA, Thompson IM, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306(14):1549–56. <https://doi.org/10.1001/jama.2011.1437>.
25. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebocontrolled trial. *Lancet*. 2006;367(9517):1145–54.
26. Loh WQ, Youn J, Seow WJ. Vitamin E intake and risk of prostate cancer: a meta-analysis. *Nutrients*. 2022;15(1):14. <https://doi.org/10.3390/nu15010014>. PMID: 36615673; PMCID: PMC9824720

Sources for Arginine-Alpha-Ketoglutarate

27. Reid J, Skelton G, Clark M, Boucher A, Willoughby DS. Effects of 7 days of argininealpha-ketoglutarate supplementation using NO2 platinum on brachial artery blood flow and the levels of plasma Larginine, nitric oxide, and eNOS after resistance exercise. *J Int Soc Sports Nutr*. 2010;7 <https://doi.org/10.1186/1550-2783-7-S1-P22>.
28. Prosser JM, Majlesi N, Chan GM, Olsen D, Hoffman RS, Nelson LS. Adverse effects associated with arginine [alpha]-ketoglutarate containing supplements. *Hum Exp Toxicol*. 2009;28(5):259–62. <https://doi.org/10.1177/0960327109104498>.
29. Randhawa S, Abowd M, Sharma A, Weiss JS. Anterior segment complications of a nutritional supplement. *J Cataract Refract Surg*. 2007;33:918–20.
30. Campbell B, Roberts M, Kerksick C, et al. Pharmacokinetics, safety, and effects on exercise performance of l-arginine α -ketoglutarate in trained adult men. *Nutrition*. 2006;22(9):872–81. <https://doi.org/10.1016/j.nut.2006.06.003>.

Sources for Ascorbic Acid

31. Henry J, Benzie IFF. Advances in food and nutrition research, vol. Seventy One. Academic Press; 2014.
32. American Society of Health-Systems Pharmacists. Ascorbic acid. In: Snow EK, editor. AHFS drug information 2020. Bethesda, MD: American Society of Health-Systems Pharmacists; 2020.
33. Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. *Cochrane Database Syst Rev*. 2013;(CD005532)
34. Age-Related Eye Disease Study Research Group. A randomized, placebocontrolled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss. *Arch Ophthalmol*. 2001;119:1417–36.
35. Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary reference

- intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000.
- 36. Mason SA, Rasmussen B, van Loon LJC, Salmon J, Wadley GD. Ascorbic acid supplementation improves postprandial glycaemic control and blood pressure in individuals with type 2 diabetes: findings of a randomized cross-over trial. *Diabetes Obes Metab*.
 - 37. Luitpold Pharmaceuticals, Inc. Ascorbic acid injection prescribing information. Shirley, NY; 2000.

Sources for Biotin

- 38. Saleem F, Soos MP. Biotin deficiency. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
- 39. Patel DP, Swink SM, Castelo-Soccio L. A review of the use of biotin for hair loss. *Skin Appendage Disord*. 2017;3:166–9. <https://doi.org/10.1159/000462981>.
- 40. Bistas KG, Tadi P. Biotin [updated 29 Sep 2021]. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554493/>.
- 41. The FDA warns that biotin may interfere with lab tests: FDA safety communication. Published 28 Nov 2017. Updated 5 Nov 2019.
- 42. Katzman BM, Lueke AJ, Donato LJ, Jaffe AS, Baumann NA. Prevalence of biotin supplement usage in outpatients and plasma biotin concentrations in patients presenting to the emergency department. *Clin Biochem*. 2018;60:11–6. ISSN: 0009-9120. <https://doi.org/10.1016/j.clinbiochem.2018.07.004>.
- 43. Piketty ML, Polak M, Flechtnner I, Gonzales-Briceño L, Souberbielle JC. False biochemical diagnosis of hyperthyroidism in streptavidin-biotin-based immunoassays: the problem of biotin intake and related interferences. *Clin Chem Lab Med*. 2017;55(6):780–8.

Sources for Bitter Orange

- 44. Fugh-Berman A, Myers A. Citrus aurantium, an ingredient of dietary supplements marketed for weight loss: current status of clinical and basic research. *Exp Biol Med*. 2004;229:698–704.
- 45. Bent S, Padula A, Neuhaus J. Safety and efficacy of citrus aurantium for weight loss. *Am J Cardiol*. 2004;94:1359–61.
- 46. Penzak SR, Jann MW, Cold JA, Hon YY, Desai HD, Gurley BJ. Seville (sour) orange juice: synephrine content and cardiovascular effects in normotensive adults. *J Clin Pharmacol*. 2001;41:1059–63.

Sources for Blue-Green Algae

- 47. Ulbricht C, Costa D, Giese N, et al. An evidence-based systematic review of bitter orange (*Citrus aurantium*) by the Natural Standard Research Collaboration. *J Diet Suppl*. 2013;10(4):391–431.
- 48. Allison DB, Cutter G, Poehlman ET, Moore DR, Barnes S. Exactly which synephrine alkaloids does citrus aurantium (bitter orange) contain? *Int J Obes*. 2005;29:443–6.
- 49. Colker CM, Kaiman DS, Torina GC, Perlis T, Street C. Effects of *Citrus aurantium* extract, caffeine, and St. John's wort on body fat loss, lipid levels, and mood states in overweight healthy adults. *Curr Ther Res Clin Exp*. 1999;60:145–53.
- 50. Bui LT, Nguyen DT, Ambrose PJ. Blood pressure and heart rate effects following a single dose of bitter orange. *Ann Pharmacother*. 2006;40(1):53–7.
- 51. Kaats GR, Miller H, Preuss HG, Stohs SJ. A 60-day double-blind, placebo-controlled safety study involving *Citrus aurantium* (bitter orange) extract. *Food Chem Toxicol*. 2013;55:358–62. <https://doi.org/10.1016/j.fct.2013.01.013>.

52. Bouchard NC, Howland MA, Greller HA, Hoffman RS, Nelson LS. Ischemic stroke associated with use of an ephedra-free dietary supplement containing synephrine. Mayo Clin Proc. 2005;80(4):541–5.
53. Firenzuoli F, Gori L, Galapai C. Adverse reaction to an adrenergic herbal extract (*Citrus aurantium*). Phytomedicine. 2005;12(3):247–8.
54. Burke J, Seda G, Allen D, Knee TS. A case of severe exercise-induced rhabdomyolysis associated with a weight-loss dietary supplement. Mil Med. 2007;172(6):656–8.

Sources for Blue Green Algae

55. Gantar M, Svirčev Z. Microalgae and cyanobacteria: food for thought. J Phycol. 2008;44:260–8. <https://doi.org/10.1111/j.1529-8817.2008.00469.x>.
56. Kent M, Welladsen HM, Mangott A, Li Y. Nutritional evaluation of Australian microalgae as potential human health supplements. PLoS One. 2015;10(2):e0118985. <https://doi.org/10.1371/journal.pone.0118985>.
57. Cohen Z. Products from microalgae. In: Richmond A, editor. CRC handbook of microalgal mass culture. Boca Raton, FL: CRC Press; 1986. p. 421–54.
58. Labbe RU, Mani UV, Iyer UM, Mishra M, Jani K, Bhattacharya A. The effect of spirulina in the treatment of bronchial asthma. J Nutraceut Funct Med Foods. 2001;3(Pt 4):53–62.
59. Simpore J, Kabore F, Zongo F, et al. Nutrition rehabilitation of undernourished children utilizing Spiruline and Misola. Nutr J. 2006;5:3.
60. Grobler L, Siegfried N, Visser ME, Mahlungulu SSN, Volmink J. Nutritional interventions for reducing morbidity and mortality in people with HIV. Cochrane Database Syst Rev. 2013;2:CD004536. <https://doi.org/10.1002/14651858.CD004536.pub3>.
61. Torres-Durán PV, Ferreira-Hermosillo A, Ramos-Jiménez A, Hernández-Torres RP, Juárez-Oropeza MA. Effect of *Spirulina maxima* on postprandial lipemia in young runners: a preliminary report. J Med Food. 2012;15(8):753–7.
62. Serban MC, Sahebkar A, Dragan S, et al. A systematic review and meta-analysis of the impact of spirulina supplementation on plasma lipid concentrations. Clin Nutr. 2016;35(4):842–51.
63. Wood R. Acute animal and human poisonings from cyanotoxin exposure—a review of the literature. Environ Int. 2016;91:276–82. <https://doi.org/10.1016/j.envint.2016.02.026>.
64. Eriksson JE, Toivola D, Meriluoto JOA, Karaki H, Han Y-G, Hartshorne D. Hepatocyte deformation induced by cyanobacterial toxins reflects inhibition of protein phosphatases. Biochem Biophys Res Commun. 1990;173:1347–53.
65. Codd GA, Testai E, Funari E, Svirčev Z. Cyanobacteria, cyanotoxins, and human health. In: Water treatment for purification from cyanobacteria and cyanotoxins. Wiley; 2020. p. 37–68. <https://doi.org/10.1002/9781118928677>.
66. Hsiao G, Chou PH, Shen MY, Chou DS, Lin CH, Sheu JR. C-phycocyanin, a very potent and novel platelet aggregation inhibitor from *Spirulina platensis*. J Agric Food Chem. 2005;53(20):7734–40.

Sources for Caffeine

67. Spriet LL. Exercise and sport performance with low doses of caffeine. Sports Med (Auckland). 2014;44(Suppl 2):175–84. <https://doi.org/10.1007/s40279-014-0257-8>.
68. Grgic J, Grgic I, Pickering C, Schoenfeld BJ, Bishop DJ, Pedisic Z. Wake up and smell the coffee: caffeine supplementation and exercise performance—an umbrella review of 21 published meta-analyses. Br J Sports Med. 2020;54(11):681–8. <https://doi.org/10.1136/bjsports-2018-100278>.
69. Saunders B, Oliveira LF, Silva RP, et al. Placebo in sports nutrition: a proof-of-principle study involving caffeine supplementation. Scand J Med Sci Sports. 2017;27(11):1240–7.

70. San Juan AF, López-Samanes Á, Jodra P, et al. Caffeine supplementation improves anaerobic performance and neuromuscular efficiency and fatigue in olympic-level boxers. *Nutrients*. 2019;11(9):2120. <https://doi.org/10.3390/nu11092120>.
71. Greden JF. Anxiety or caffeineism: a diagnostic dilemma. *Am J Psychiatry*. 1974;131(10):1089–92.
72. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet*. 2000;39(2):127–53.

Sources for Calcium

73. Kunstel K. Calcium requirements for the athlete. *Curr Sports Med Rep*. 2005;4(4):203–6. <https://doi.org/10.1097/01.CSMR.0000306208.56939.01>.
74. Brunner RL, Cochrane B, Jackson RD, Larson J, Lewis C, Limacher M, et al. Calcium, vitamin D supplementation, and physical function in the Women's Health Initiative. *J Am Diet Assoc*. 2008;108(9):1472–9.
75. Nemoseck T, Kern M. The effects of high-impact and resistance exercise on urinary calcium excretion. *Int J Sport Nutr Exerc Metab*. 2009;19(2):162–71.
76. Lewis JR, Zhu K, Prince RL. Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. *J Bone Miner Res*. 2012;27(3):719–22. <https://doi.org/10.1002/jbmr.1484>. PMID: 22139587
77. Steadman E, Raisch DW, Bennett CL, Esterly JS, Becker T, Postelnick M, McKoy JM, Trifilio S, Yarnold PR, Scheetz MH. Evaluation of a potential clinical interaction between ceftriaxone and calcium. *Antimicrob Agents Chemother*. 2010;54(4):1534–40.

Sources for Catechin

78. Navarro VJ, Bonkovsky HL, Hwang SI, Vega M, Barnhart H, Serrano J. Catechins in dietary supplements and hepatotoxicity. *Dig Dis Sci*. 2013;58:2682–90.
79. Lamprecht M, editor. Antioxidants in sport nutrition. Taylor & Francis; 2015. <https://doi.org/10.1201/b17442>.
80. Janssens PLH, Hursel R, Westerterp-Plantenga MS. Nutraceuticals for body-weight management: the role of green tea catechins. *Physiol Behav*. 2016;162:83–7. <https://doi.org/10.1016/j.physbeh.2016.01.044>.
81. Younes M, Aggett P, Aguilar F, et al. Scientific opinion on the safety of green tea catechins. *EFSA J*. 2018;16(4):e05239. <https://doi.org/10.2903/j.efsa.2018.5239>.
82. Maki KC, Reeves MS, Blumberg JB, et al. Green tea catechin consumption enhances exercise-induced abdominal fat loss in overweight and obese adults. *J Nutr*. 2009;139(2):264–70. <https://doi.org/10.3945/jn.108.098293>.
83. Jurgen TM, Whelan AM, Killian L, et al. Green tea for weight loss and weight maintenance in overweight or obese adults. *Cochrane Database Syst Rev*. 2012;2012(12):CD008650. <https://doi.org/10.1002/14651858.CD008650.pub2>.
84. Oketch-Rabah HA, Roe AL, Rider CV, et al. United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Toxicol Rep*. 2020;7:386–402.

Sources for Chitosan

85. Moraru C, Mincea MM, Frandes M, Timar B, Ostafe V. A meta-analysis on randomised controlled clinical trials evaluating the effect of the dietary supplement chitosan on weight loss, lipid parameters and blood pressure. *Medicina*. 2018;54(6):109. <https://doi.org/10.3390/medicina54060109>.

86. Koide SS. Chitin-chitosan: properties, benefits and risks. *Nutr Res*. 1998;18(6):1091–101., ISSN 0271-5317. [https://doi.org/10.1016/S0271-5317\(98\)00091-8](https://doi.org/10.1016/S0271-5317(98)00091-8).
87. Walsh AM, Sweeney T, Bahar B, O'Doherty JV. Multi-functional roles of chitosan as a potential protective agent against obesity. *PLoS One*. 2013;8(1):e53828. <https://doi.org/10.1371/journal.pone.0053828>.
88. Huang H, Liao D, Zou Y, Chi H. The effects of chitosan supplementation on body weight and body composition: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr*. 2020;60(11):1815–25. <https://doi.org/10.1080/10408398.2019.1602822>.
89. Huang SS, Sung SH, Chiang CE. Chitosan potentiation of warfarin effect. *Ann Pharmacother*. 2007;41(11):1912–4. <https://doi.org/10.1345/aph.1K173>. Epub 2007 Oct 9.
90. Miller K. Chitosan uses and risks. 5 Feb 2021. <https://www.webmd.com/vitamins-and-supplements/chitosan-uses-and-risks>. Accessed 1 May 2022.

Sources for Chlorogenic Acid

91. Tajik N, Tajik M, Mack I, et al. The potential effects of chlorogenic acid, the main phenolic components in coffee, on health: a comprehensive review of the literature. *Eur J Nutr*. 2017;56:2215–44. <https://doi.org/10.1007/s00394-017-1379-1>.
92. Tunnicliffe JM, Eller LK, Reimer RA, Hittel DS, Shearer J. Chlorogenic acid differentially affects postprandial glucose and glucose-dependent insulinotropic polypeptide response in rats. *Appl Physiol Nutr Metab*. 2011;36(5):650–9. <https://doi.org/10.1139/h11-072>. Epub 2011 Oct 6.
93. Onakpoya IJ, Spencer EA, Thompson MJ, Heneghan CJ. The effect of chlorogenic acid on blood pressure: a systematic review and meta-analysis of randomized clinical trials. *J Hum Hypertens*. 2015;29(2):77–81. <https://doi.org/10.1038/jhh.2014.46>. Epub 2014 Jun 19.
94. Santana-Gálvez J, Cisneros-Zevallos L, Jacobo-Velázquez DA. Chlorogenic acid: recent advances on its dual role as a food additive and a nutraceutical against metabolic syndrome. *Molecules*. 2017;22(3):358. <https://doi.org/10.3390/molecules22030358>.
95. Zuskin E, Kanceljak B, Skurić Z, Butković D. Bronchial reactivity in green coffee exposure. *Br J Ind Med*. 1985;42(6):415–20. <https://doi.org/10.1136/oem.42.6.415>.
96. Prabhakar PK, Doble M. Interaction of phytochemicals with hypoglycemic drugs on glucose uptake in L6 myotubes. *Phytomedicine*. 2011;18(4):285–91. <https://doi.org/10.1016/j.phymed.2010.06.016>. Epub 2010 Aug 19.

Sources for Chromium

97. Eastmond DA, Macgregor JT, Slesinski RS. Trivalent chromium: assessing the genotoxic risk of an essential trace element and widely used human and animal nutritional supplement. *Crit Rev Toxicol*. 2008;38(3):173–90. <https://doi.org/10.1080/10408440701845401>.
98. <https://ods.od.nih.gov/factsheets/Chromium-HealthProfessional/#ref>.
99. Wallach S. Clinical and biochemical aspects of chromium deficiency. *J Am Coll Nutr*. 1985;4(1):107–20. <https://doi.org/10.1080/07315724.1985.10720070>.
100. Anderson RA. Chromium in the prevention and control of diabetes. *Diabetes Metab*. 2000;26(1):22–7.
101. Suksomboon N, Poolsup N, Yuwanakorn A. Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes. *J Clin Pharm Ther*. 2014;39(3):292–306. <https://doi.org/10.1111/jcpt.12147>. Epub 2014 Mar 17.
102. San Mauro-Martin I, Ruiz-León AM, Camina-Martín MA, Garicano-Vilar E, Collado-Yurrita L, de Mateo-Silleras B, De Paz Redondo Del Río M. [Chromium supplementation in patients with type 2 diabetes and high risk of type 2 diabetes: a meta-analysis of randomized controlled trials]. *Nutr Hosp*. 2016;33(1):27. Spanish. <https://doi.org/10.20960/nh.v33i1.27>.

103. Yin RV, Phung OJ. Effect of chromium supplementation on glycated hemoglobin and fasting plasma glucose in patients with diabetes mellitus. *Nutr J.* 2015;14:14. <https://doi.org/10.1186/1475-2891-14-14>.

Sources for Coenzyme Q10

104. Tian H, Guo X, Wang X, He Z, Sun R, Ge S, Zhang Z. Chromium picolinate supplementation for overweight or obese adults. *Cochrane Database Syst Rev.* 2013;2013(11):CD010063. <https://doi.org/10.1002/14651858.CD010063.pub2>.
105. Saini R. Coenzyme Q10: the essential nutrient. *J Pharm Bioallied Sci.* 2011;3(3):466–7. <https://doi.org/10.4103/0975-7406.84471>.
106. Thomas SR, Neuzil J, Stocker R. Inhibition of LDL oxidation by ubiquinol-10. A protective mechanism for coenzyme Q in atherogenesis? *Mol Asp Med.* 1997;18(Suppl):S85–103. [https://doi.org/10.1016/s0098-2997\(97\)00031-9](https://doi.org/10.1016/s0098-2997(97)00031-9).
107. Petillo D, Hultin HO. Ubiquinone-10 as an antioxidant. *J Food Biochem.* 2008;32:173–81. <https://doi.org/10.1111/j.1745-4514.2008.00151.x>.
108. Hernández-Camacho JD, Bernier M, López-Lluch G, Navas P. Coenzyme Q10 supplementation in aging and disease. *Front Physiol.* 2018;9:44. <https://doi.org/10.3389/fphys.2018.00044>.
109. Mancini A, Festa R, Raimondo S, Pontecorvi A, Littarru GP. Hormonal influence on coenzyme Q(10) levels in blood plasma. *Int J Mol Sci.* 2011;12(12):9216–25. <https://doi.org/10.3390/ijms12129216>. Epub 2011 Dec 9.
110. Salvati L, Trevisson E, Doimo M, et al. Primary coenzyme Q10 deficiency. 26 Jan 2017. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews®. Seattle, WA: University of Washington; 1993–2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK410087/>.
111. Ihara Y, Namba R, Kuroda S, Sato T, Shirabe T. Mitochondrial encephalomyopathy (MELAS): pathological study and successful therapy with coenzyme Q10 and idebenone. *J Neurol Sci.* 1989;90(3):263–71. [https://doi.org/10.1016/0022-510x\(89\)90112-3](https://doi.org/10.1016/0022-510x(89)90112-3).
112. Nishikawa Y, Takahashi M, Yorifuji S, Nakamura Y, Ueno S, Tarui S, Kozuka T, Nishimura T. Long-term coenzyme Q10 therapy for a mitochondrial encephalomyopathy with cytochrome c oxidase deficiency: a 31P NMR study. *Neurology.* 1989;39(3):399–403. <https://doi.org/10.1212/wnl.39.3.399>.
113. Adarsh K, Kaur H, Mohan V. Coenzyme Q10 (CoQ10) in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM). *Biofactors.* 2008;32(1– 4):145–9. <https://doi.org/10.1002/biof.5520320117>.
114. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, Littarru GP, Q-SYMBIO Study Investigators. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *JACC Heart Fail.* 2014;2(6):641–9. <https://doi.org/10.1016/j.jchf.2014.06.008>. Epub 2014 Oct 1.
115. Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. *Clin Investig.* 1993;71(8 Suppl):S134–6. <https://doi.org/10.1007/BF00226854>.
116. Lei L, Liu Y. Efficacy of coenzyme Q10 in patients with cardiac failure: a meta-analysis of clinical trials. *BMC Cardiovasc Disord.* 2017;17(1):196. <https://doi.org/10.1186/s12872-017-0628-9>.
117. Hadi HA, Carr CS, Al Suwaidi J. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. *Vasc Health Risk Manag.* 2005;1(3):183–98.
118. Watts GF, Playford DA, Croft KD, Ward NC, Mori TA, Burke V. Coenzyme Q(10) improves endothelial dysfunction of the brachial artery in Type II diabetes mellitus. *Diabetologia.* 2002;45(3):420–6. <https://doi.org/10.1007/s00125-001-0760-y>.
119. Burke BE, Neuenschwander R, Olson RD. Randomized, double-blind, placebo-controlled trial of coenzyme Q10 in isolated systolic hypertension. *South Med J.* 2001;94(11):1112–7. <https://doi.org/10.1097/00007611-200111000-00015>.

120. Singh RB, Niaz MA, Rastogi SS, Shukla PK, Thakur AS. Effect of hydrosoluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery disease. *J Hum Hypertens.* 1999;13(3):203–8. <https://doi.org/10.1038/sj.jhh.1000778>.
121. Zhai J, Bo Y, Lu Y, Liu C, Zhang L. Effects of coenzyme Q10 on markers of inflammation: a systematic review and meta-analysis. *PLoS One.* 2017;12(1):e0170172. <https://doi.org/10.1371/journal.pone.0170172>.
122. Hernández-Ojeda J, Cardona-Muñoz EG, Román-Pintos LM, Troyo-Sanromán R, Ortiz-Lazareno PC, Cárdenas-Meza MA, Pascoe-González S, Miranda-Díaz AG. The effect of ubiquinone in diabetic polyneuropathy: a randomized double-blind placebo-controlled study. *J Diabetes Complicat.* 2012;26(4):352–8. <https://doi.org/10.1016/j.jdiacomp.2012.04.004>. Epub 2012 May 16.
123. Chen PP, Xu HL, Ting-Yue, ZhuGe DL, Jin BH, Zhu QY, Shen BX, Wang LF, Lu CT, Zhao YZ, Li XK. CoQ10-loaded liposomes combined with UTMD prevented early nephropathy of diabetic rats. *Oncotarget.* 2018;9(14):11767–82. <https://doi.org/10.18632/oncotarget.24363>.
124. Stojanović M, Radenković M. A meta-analysis of randomized and placebo-controlled clinical trials suggests that coenzyme Q10 at low dose improves glucose and HbA1c levels. *Nutr Res.* 2017;38:1–12. <https://doi.org/10.1016/j.nutres.2016.12.001>. Epub 2016 Dec 8.
125. Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, Shechter AL, Silberstein SD. Open label trial of coenzyme Q10 as a migraine preventive. *Cephalgia.* 2002;22(2):137–41. <https://doi.org/10.1046/j.1468-2982.2002.00335.x>.
126. Cordero MD, Santos-García R, Bermejo-Jover D, Sánchez-Domínguez B, Jaramillo-Santos MR, Bullón P. Coenzyme Q10 in salivary cells correlate with blood cells in Fibromyalgia: improvement in clinical and biochemical parameter after oral treatment. *Clin Biochem.* 2012;45(6):509–11. <https://doi.org/10.1016/j.clinbiochem.2012.02.001>. Epub 2012 Feb 10.
127. Sanoobar M, Dehghan P, Khalili M, Azimi A, Seifar F. Coenzyme Q10 as a treatment for fatigue and depression in multiple sclerosis patients: a double blind randomized clinical trial. *Nutr Neurosci.* 2016;19(3):138–43. <https://doi.org/10.1179/1476830515Y.0000000002>. Epub 2015 Jan 20.
128. Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos JL, Nutt J, Shoulson I, Carter J, Kompoliti K, Perlmuter JS, Reich S, Stern M, Watts RL, Kurlan R, Molho E, Harrison M, Lew M, Parkinson Study Group. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol.* 2002;59(10):1541–50. <https://doi.org/10.1001/archneur.59.10.1541>.
129. Garrido-Maraver J, Cordero MD, Oropesa-Ávila M, Fernández Vega A, de la Mata M, Delgado Pavón A, de Miguel M, Pérez Calero C, Villanueva Paz M, Cotán D, Sánchez-Alcázar JA. Coenzyme q10 therapy. *Mol Syndromol.* 2014;5(3–4):187–97. <https://doi.org/10.1159/000360101>.
130. Zhou Q, Zhou S, Chan E. Effect of coenzyme Q10 on warfarin hydroxylation in rat and human liver microsomes. *Curr Drug Metab.* 2005;6(2):67–81. <https://doi.org/10.2174/1389200053586091>.

Sources for Colostrum

131. McGrath BA, Fox PF, McSweeney PLH, et al. Composition and properties of bovine colostrum: a review. *Dairy Sci Technol.* 2016;96:133–58. <https://doi.org/10.1007/s13594-015-0258-x>.
132. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. *Pediatr Clin N Am.* 2013;60(1):49–74. <https://doi.org/10.1016/j.pcl.2012.10.002>.
133. Shing CM, Peake JM, Suzuki K, Jenkins DG, Coombes JS. Bovine colostrum modulates cytokine production in human peripheral blood mononuclear cells stimulated with lipopolysaccharide and phytohemagglutinin. *J Interf Cytokine Res.* 2009;29(1):37–44. <https://doi.org/10.1089/jir.2008.0015>.
134. Buescher ES, McIlheran SM. Antioxidant properties of human colostrum. *Pediatr Res.* 1988;24(1):14–9. <https://doi.org/10.1203/00006450-198807000-00005>.

135. Rathe M, Müller K, Sangild PT, Husby S. Clinical applications of bovine colostrum therapy: a systematic review. *Nutr Rev.* 2014;72(4):237–54. <https://doi.org/10.1111/nure.12089>. Epub 2014 Feb 26.
136. Guaragna MA, Albanesi M, Stefani S, Pasqualone A, Angelini A, Alfieri S, Barbaro SP. The effectiveness of oral goat colostrum in the treatment of patients with type 2 diabetes mellitus: our preliminary experience. *Clin Ter.* 2013;164(2):111–4. <https://doi.org/10.7417/CT.2013.1527>.
137. Saad K, Abo-Elela MGM, El-Baseer KAA, Ahmed AE, Ahmad FA, Tawfeek MSK, El-Houfey AA, Aboul Khair MD, Abdel-Salam AM, Abo-Elgehit A, Qubaisy H, Ali AM, Abdel-Mawgoud E. Effects of bovine colostrum on recurrent respiratory tract infections and diarrhea in children. *Medicine (Baltimore).* 2016;95(37):e4560. <https://doi.org/10.1097/MD.00000000000004560>.
138. Patel K, Rana R. Pedimune in recurrent respiratory infection and diarrhoea—the Indian experience—the pride study. *Indian J Pediatr.* 2006;73(7):585–91. <https://doi.org/10.1007/BF02759923>.
139. Brinkworth GD, Buckley JD. Concentrated bovine colostrum protein supplementation reduces the incidence of self-reported symptoms of upper respiratory tract infection in adult males. *Eur J Nutr.* 2003;42(4):228–32. <https://doi.org/10.1007/s00394-003-0410-x>.
140. He F, Tuomola E, Arvilommi H, Salminen S. Modulation of human humoral immune response through orally administered bovine colostrum. *FEMS Immunol Med Microbiol.* 2001;31(2):93–6. <https://doi.org/10.1111/j.1574-695X.2001.tb00504.x>.
141. Wolvers DA, van Herpen-Broekmans WM, Logman MH, van der Wielen RP, Albers R. Effect of a mixture of micronutrients, but not of bovine colostrum concentrate, on immune function parameters in healthy volunteers: a randomized placebo-controlled study. *Nutr J.* 2006;5:28. <https://doi.org/10.1186/1475-2891-5-28>.
142. Wong EB, Mallet JF, Duarte J, Matar C, Ritz BW. Bovine colostrum enhances natural killer cell activity and immune response in a mouse model of influenza infection and mediates intestinal immunity through toll-like receptors 2 and 4. *Nutr Res.* 2014;34(4):318–25. <https://doi.org/10.1016/j.nutres.2014.02.007>. Epub 2014 Mar 6.
143. Crooks CV, Wall CR, Cross ML, Rutherford-Markwick KJ. The effect of bovine colostrum supplementation on salivary IgA in distance runners. *Int J Sport Nutr Exerc Metab.* 2006;16(1):47–64. <https://doi.org/10.1123/ijsnem.16.1.47>.
144. Antonio J, Sanders MS, Van Gammeren D. The effects of bovine colostrum supplementation on body composition and exercise performance in active men and women. *Nutrition.* 2001;17(3):243–7. [https://doi.org/10.1016/s0899-9007\(00\)00552-9](https://doi.org/10.1016/s0899-9007(00)00552-9).
145. Leszek J, Inglot AD, Janusz M, Byczkiewicz F, Kiejna A, Georgiades J, Lisowski J. Colostrinin proline-rich polypeptide complex from ovine colostrum—a long-term study of its efficacy in Alzheimer’s disease. *Med Sci Monit.* 2002;8(10):PI93–6.
146. Halasa M, Maciejewska D, Baśkiewicz-Hałasa M, Machaliński B, Safranow K, Stachowska E. Oral supplementation with bovine colostrum decreases intestinal permeability and stool concentrations of zonulin in athletes. *Nutrients.* 2017;9(4):370. <https://doi.org/10.3390/nu9040370>.
147. Mir R, Singh N, Vikram G, Kumar RP, Sinha M, Bhushan A, Kaur P, Srinivasan A, Sharma S, Singh TP. The structural basis for the prevention of nonsteroidal antiinflammatory drug-induced gastrointestinal tract damage by the C-lobe of bovine colostrum lactoferrin. *Biophys J.* 2009;97(12):3178–86. <https://doi.org/10.1016/j.bpj.2009.09.030>.

Sources for Conjugated Linoleic Acid

148. den Hartigh LJ. Conjugated linoleic acid effects on cancer, obesity, and atherosclerosis: a review of pre-clinical and human trials with current perspectives. *Nutrients.* 2019;11(2):370. <https://doi.org/10.3390/nu11020370>.

149. Lehnens TE, da Silva MR, Camacho A, Marcadenti A, Lehnens AM. A review on effects of conjugated linoleic acid (CLA) upon body composition and energetic metabolism. *J Int Soc Sports Nutr.* 2015;12:36. <https://doi.org/10.1186/s12970-015-0097-4>.
150. Gaullier JM, Halse J, Høye K, Kristiansen K, Fagertun H, Vik H, Gudmundsen O. Conjugated linoleic acid supplementation for 1 y reduces body fat mass in healthy overweight humans. *Am J Clin Nutr.* 2004;79(6):1118–25. <https://doi.org/10.1093/ajcn/79.6.1118>.
151. Zhao WS, Zhai JJ, Wang YH, Xie PS, Yin XJ, Li LX, Cheng KL. Conjugated linoleic acid supplementation enhances antihypertensive effect of ramipril in Chinese patients with obesity-related hypertension. *Am J Hypertens.* 2009;22(6):680–6. <https://doi.org/10.1038/ajh.2009.56>. Epub 2009 Mar 19.
152. Wanders AJ, Brouwer IA, Siebelink E, Katan MB. Effect of a high intake of conjugated linoleic acid on lipoprotein levels in healthy human subjects. *PLoS One.* 2010;5(2):e9000. <https://doi.org/10.1371/journal.pone.0009000>.
153. Aloud BM, Raj P, O’Hara K, Shao Z, Yu L, Anderson HD, Netticadan T. Conjugated linoleic acid prevents high glucose-induced hypertrophy and contractile dysfunction in adult rat cardiomyocytes. *Nutr Res.* 2016;36(2):134–42. <https://doi.org/10.1016/j.nutres.2015.11.012>. Epub 2015 Nov 19.
154. Chen SC, Lin YH, Huang HP, Hsu WL, Houng JY, Huang CK. Effect of conjugated linoleic acid supplementation on weight loss and body fat composition in a Chinese population. *Nutrition.* 2012;28(5):559–65. <https://doi.org/10.1016/j.nut.2011.09.008>. Epub 2012 Jan 20.
155. Larsen TM, Toustrup S, Gudmundsen O, Astrup A. Conjugated linoleic acid supplementation for 1 y does not prevent weight or body fat regain. *Am J Clin Nutr.* 2006;83(3):606–12. <https://doi.org/10.1093/ajcn.83.3.606>.
156. Ebrahimi-Mameghani M, Jamali H, Mahdavi R, Kakaei F, Abedi R, Kabir-Mamdooh B. Conjugated linoleic acid improves glycemic response, lipid profile, and oxidative stress in obese patients with non-alcoholic fatty liver disease: a randomized controlled clinical trial. *Croat Med J.* 2016;57(4):331–42. <https://doi.org/10.3325/cmj.2016.57.331>.
157. Lamarche B, Desroches S. Metabolic syndrome and effects of conjugated linoleic acid in obesity and lipoprotein disorders: the Québec experience. *Am J Clin Nutr.* 2004;79(6 Suppl):1149S–52S. <https://doi.org/10.1093/ajcn/79.6.1149S>.
158. Zhan Y, Shi H, Caligiuri SP, Wu Y, Declercq V, Taylor CG, Zahradka P, Ogborn MR, Aukema HM. Trans-10,cis-12-conjugated linoleic acid worsens renal pathology and alters cyclooxygenase derived oxylipins in obesity-associated nephropathy. *J Nutr Biochem.* 2015;26(2):130–7. <https://doi.org/10.1016/j.jnutbio.2014.09.011>. Epub 2014 Oct 25.
159. Vyas D, Kadegowda AKG, Erdman RA. Dietary conjugated linoleic acid and hepatic steatosis: species-specific effects on liver and adipose lipid metabolism and gene expression. *J Nutr Metab.* 2012;2012:932928, 13 p. <https://doi.org/10.1155/2012/932928>.

Sources for Copper

160. Olivares M, Uauy R. Copper as an essential nutrient. *Am J Clin Nutr.* 1996;63(5):791S–6S. <https://doi.org/10.1093/ajcn/63.5.791>.
161. Prohaska JR. Impact of copper limitation on expression and function of multicopper oxidases (ferroxidases). *Adv Nutr.* 2011;2(2):89–95. <https://doi.org/10.3945/an.110.000208>. Epub 2011 Mar 10.
162. Prohaska JR, Gybina AA. Intracellular copper transport in mammals. *J Nutr.* 2004;134(5):1003–6. <https://doi.org/10.1093/jn/134.5.1003>.
163. Wazir SM, Ghobrial I. Copper deficiency, a new triad: anemia, leucopenia, and myeloneuropathy. *J Community Hosp Intern Med Perspect.* 2017;7(4):265–8. <https://doi.org/10.1080/20009666.2017.1351289>.
164. Allen TM, Manoli A 2nd, LaMont RL. Skeletal changes associated with copper deficiency. *Clin Orthop Relat Res.* 1982;168:206–10.

165. Kawada E, Moridaira K, Itoh K, Hoshino A, Tamura J, Morita T. In long-term bedridden elderly patients with dietary copper deficiency, biochemical markers of bone resorption are increased with copper supplementation during 12 weeks. *Ann Nutr Metab.* 2006;50(5):420–4. <https://doi.org/10.1159/000094633>. Epub 2006 Jul 17.
166. Al-Bayati MA, Jamil DA, Al-Aubaidy HA. Cardiovascular effects of copper deficiency on activity of superoxide dismutase in diabetic nephropathy. *N Am J Med Sci.* 2015;7(2):41–6. <https://doi.org/10.4103/1947-2714.152077>.
167. Sajithlal GB, Chithra P, Chandrasekaran G. An *in vitro* study on the role of metal catalyzed oxidation in glycation and crosslinking of collagen. *Mol Cell Biochem.* 1999;194(1–2):257–63. <https://doi.org/10.1023/a:1006988719374>.
168. Zatcoff RC, Smith MS, Borkow G. Treatment of tinea pedis with socks containing copper-oxide impregnated fibers. *Foot (Edinb).* 2008;18(3):136–41. <https://doi.org/10.1016/j.foot.2008.03.005>. Epub 2008 May 19.
169. Borkow G, Zatcoff RC, Gabbay J. Reducing the risk of skin pathologies in diabetics by using copper impregnated socks. *Med Hypotheses.* 2009;73(6):883–6. <https://doi.org/10.1016/j.mehy.2009.02.050>. Epub 2009 Jun 25.
170. Eaton-Evans J, McIlrath E, Jackson W, McCartney H, Strain J. Copper supplementation and the maintenance of bone mineral density in middle-aged women. *J Trace Elem Exp Med.* 1996;9:87–94. [https://doi.org/10.1002/\(SICI\)1520-670X\(1996\)9:3<87::AID-JTEA1>3.0.CO;2-E](https://doi.org/10.1002/(SICI)1520-670X(1996)9:3<87::AID-JTEA1>3.0.CO;2-E).
171. <https://ods.od.nih.gov/factsheets/Copper-HealthProfessional/#ref>.
172. Gamakaranage CS, Rodrigo C, Weerasinghe S, Gnanathasan A, Puvanaraj V, Fernando H. Complications and management of acute copper sulphate poisoning; a case discussion. *J Occup Med Toxicol.* 2011;6(1):34. <https://doi.org/10.1186/1745-6673-6-34>.
173. Bremner I. Manifestations of copper excess. *Am J Clin Nutr.* 1998;67(5):1069S–73S. <https://doi.org/10.1093/ajcn/67.5.1069S>.
174. Bush AI, Tanzi RE. Therapeutics for Alzheimer's disease based on the metal hypothesis. *Neurotherapeutics.* 2008;5(3):421–32. <https://doi.org/10.1016/j.nurt.2008.05.001>.
175. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, Richardson RJ. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. *Neurotoxicology.* 1999;20(2–3):239–47.
176. Ferdousi S, Mia AR. Serum levels of copper and zinc in newly diagnosed type-2 diabetic subjects. *Mymensingh Med J.* 2012;21(3):475–8.
177. Greger JL, Snedeker SM. Effect of dietary protein and phosphorus levels on the utilization of zinc, copper and manganese by adult males. *J Nutr.* 1980;110(11):2243–53. <https://doi.org/10.1093/jn/110.11.2243>.
178. Wapnir RA, Balkman C. Intestinal absorption of copper: effect of amino acids. *Nutr Res.* 1990;10(5):589–95. ISSN: 0271-5317. [https://doi.org/10.1016/S0271-5317\(05\)80068-5](https://doi.org/10.1016/S0271-5317(05)80068-5).
179. Collins JF, Prohaska JR, Knutson MD. Metabolic crossroads of iron and copper. *Nutr Rev.* 2010;68(3):133–47. <https://doi.org/10.1111/j.1753-4887.2010.00271.x>.
180. Turnlund JR. Copper nutriture, bioavailability, and the influence of dietary factors. *J Am Diet Assoc.* 1988;88(3):303–8.

Sources for Creatine

181. Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. *Pharmacol Rev.* 2001;53(2):161–76.
182. Bird SP. Creatine supplementation and exercise performance: a brief review. *J Sports Sci Med.* 2003;2(4):123–32.
183. Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. *J Strength Cond Res.* 2003;17(4):822–31. [https://doi.org/10.1519/1533-4287\(2003\)017<0822:eoecsar>2.0.co;2](https://doi.org/10.1519/1533-4287(2003)017<0822:eoecsar>2.0.co;2).

184. Branch JD. Effect of creatine supplementation on body composition and performance: a meta-analysis. *Int J Sport Nutr Exerc Metab.* 2003;13(2):198–226. <https://doi.org/10.1123/ijsnem.13.2.198>.
185. Olsen S, Aagaard P, Kadi F, Tufekovic G, Verney J, Olesen JL, Suetta C, Kjaer M. Creatine supplementation augments the increase in satellite cell and myonuclei number in human skeletal muscle induced by strength training. *J Physiol.* 2006;573(Pt 2):525–34. <https://doi.org/10.1113/jphysiol.2006.107359>. Epub 2006 Mar 31. Erratum in: *J Physiol.* 2006 Sep 15;575(Pt 3):971.
186. Saremi A, Gharakhanloo R, Sharghi S, Gharaati MR, Larijani B, Omidfar K. Effects of oral creatine and resistance training on serum myostatin and GAS-1. *Mol Cell Endocrinol.* 2010;317(1–2):25–30. <https://doi.org/10.1016/j.mce.2009.12.019>. Epub 2009 Dec 22.
187. Cooke MB, Rybalka E, Williams AD, Cribb PJ, Hayes A. Creatine supplementation enhances muscle force recovery after eccentrically-induced muscle damage in healthy individuals. *J Int Soc Sports Nutr.* 2009;6:13. <https://doi.org/10.1186/1550-2783-6-13>.
188. Rawson ES, Conti MP, Miles MP. Creatine supplementation does not reduce muscle damage or enhance recovery from resistance exercise. *J Strength Cond Res.* 2007;21(4):1208–13. <https://doi.org/10.1519/R-21076.1>.
189. Moon A, Heywood L, Rutherford S, Cobbold C. Creatine supplementation: can it improve quality of life in the elderly without associated resistance training? *Curr Aging Sci.* 2013;6(3):251–7. <https://doi.org/10.2174/1874609806666131204153102>.
190. McMorris T, Harris RC, Swain J, Corbett J, Collard K, Dyson RJ, Dye L, Hodgson C, Draper N. Effect of creatine supplementation and sleep deprivation, with mild exercise, on cognitive and psychomotor performance, mood state, and plasma concentrations of catecholamines and cortisol. *Psychopharmacology (Berl).* 2006;185(1):93–103. <https://doi.org/10.1007/s00213-005-0269-z>. Epub 2006 Jan 17.
191. McMorris T, Harris RC, Howard AN, Langridge G, Hall B, Corbett J, Dicks M, Hodgson C. Creatine supplementation, sleep deprivation, cortisol, melatonin and behavior. *Physiol Behav.* 2007;90(1):21–8. <https://doi.org/10.1016/j.physbeh.2006.08.024>. Epub 2006 Oct 13.
192. McMorris T, Mielcarz G, Harris RC, Swain JP, Howard A. Creatine supplementation and cognitive performance in elderly individuals. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn.* 2007;14(5):517–28. <https://doi.org/10.1080/13825580600788100>.
193. Buford TW, Kreider RB, Stout JR, Greenwood M, Campbell B, Spano M, Ziegenfuss T, Lopez H, Landis J, Antonio J. International Society of Sports Nutrition position stand: creatine supplementation and exercise. *J Int Soc Sports Nutr.* 2007;4:6. <https://doi.org/10.1186/1550-2783-4-6>.
194. Kilduff LP, Lewis S, Kingsley MI, Owen NJ, Dietzig RE. Reliability and detecting change following short-term creatine supplementation: comparison of two-component body composition methods. *J Strength Cond Res.* 2007;21(2):378–84. <https://doi.org/10.1519/R-19245.1>.
195. Taylor L, Poole C, Pena E, Lewing M, Kreider R, Foster C, Wilborn C. Effects of combined creatine plus fenugreek extract vs. creatine plus carbohydrate supplementation on resistance training adaptations. *J Sports Sci Med.* 2011;10(2):254–60.
196. Li Z, Wang P, Yu Z, Cong Y, Sun H, Zhang J, Zhang J, Sun C, Zhang Y, Ju X. The effect of creatine and coenzyme q10 combination therapy on mild cognitive impairment in Parkinson's disease. *Eur Neurol.* 2015;73(3–4):205–11. <https://doi.org/10.1159/000377676>. Epub 2015 Mar 10.
197. Cesarone MR, Belcaro G, Di Renzo A, Dugall M, Cacchio M, Ruffini I, Pellegrini L, Del Boccio G, Fano F, Ledda A, Bottari A, Ricci A, Stuard S, Vinciguerra G. Prevention of influenza episodes with colostrum compared with vaccination in healthy and high-risk cardiovascular subjects: the epidemiologic study in San Valentino. *Clin Appl Thromb Hemost.* 2007;13(2):130–6. <https://doi.org/10.1177/1076029606295957>.

Chapter 2

Green Tea



German Valdez, Abid Haque, Craig Silverberg, Morgen Owens, Daniel Weng, and Farrah Asaad

Dandelion

- **Other names:** *Taraxacum officinale*, lion's tooth, blowball.
- **Mechanism of action:**
 - The components of the dandelion plant (flower, leaves, stems, and root) contain various chemical compounds which have been studied for their medicinal properties. These include anti-inflammatory, anti-diabetic, and anti-carcinogenic properties.
 - These compounds include: taraxasterol, chicoric acid (CRA), and chlorogenic acid (CGA).
- **Common indications/uses:**
 - Dandelion leaves and flowers are commonly used as a salad green and to make wine and teas. The root can be roasted and used as a coffee substitute. Some of the earlier mentioned chemical compounds have been studied for their anti-hyperglycemic and anti-inflammatory benefits.
- **Dosing:**
 - Dandelion root supplements may be found in doses between 500 and 2000 mg.
- **Evidence:**
 - Chicoric acid is found in high concentrations in all parts of the dandelion plant and has been studied for its anti-hyperglycemic effects. It has been

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shown to improve glucose tolerance and reduce insulin resistance in diabetic mice. Furthermore, chicoric acid can prevent the endothelial damage caused by hyperglycemia-induced oxidative stress via its antioxidant properties. Ma et al. found this to be related to activation of the AMP-activated protein kinase signaling pathway.

- Taraxasterol and taraxerol have been isolated in the natural root extract of *Taraxacum officinale* during chemical analysis. Taraxasterol has anti-inflammatory properties, and there is some interest in studying its potential for anti-carcinogenic activity.

- **Safety concerns:**

- *Adverse reactions:* Allergic reaction.

- **Drug interactions:**

- May interact with lithium and quinolone antibiotics.

Fennel

- **Other names:** *Foeniculum vulgare*.

- **Mechanism of action:**

- Fennel is a good source of vitamin C, potassium, plant flavanoids, and beta-carotene which. Vitamin C and flavanoids (discussed further in their own section) have antioxidant activity which in turn are anti-inflammatory. Other compounds found in fennel seeds—including anethole and estragole—are thought to make it a possible galactogogue. For this reason, fennel seeds/fennel seed oils are included in some lactation supplements, but there have not been large randomized trials to prove its efficacy.
 - One randomized trial testing the effects of curcumin and fennel essential oil on IBS symptoms also had positive results. This study is discussed further in the evidence section.

- **Common indications/uses:**

- Fennel and fennel seeds are commonly used in a normal diet. As noted above, the oils of fennel seeds have compounds which are thought to be beneficial to lactation.

- **Dosing:**

- 50 mg fennel essential oil was used in Portincasa et al., but fennel is otherwise used unmeasured in its vegetable form which is not concentrated.

- **Evidence:**

- Portincasa et al. studied the combination of curcumin and fennel in patients with IBS. Curcumin has anti-inflammatory properties, and fennel has anti-

spasmodic and anti-inflammatory effects which the authors wanted to assess together for improvement of IBS symptoms. Over 30 days, patients in the experimental group reported improvement in their IBS symptoms and better quality of life.

- **Safety concerns:**

- *Adverse reactions:* Allergic reactions, photosensitivity.

- **Drug interactions:**

- Ciprofloxacin absorption, distribution, and elimination were affected by fennel ingestion in a small randomized study.

Fenugreek

- **Other names:** *Trigonella foenum-graecum.*

- **Mechanism of action:**

- The seeds of fenugreek are a source of multiple chemical compounds and have been used historically in foods and drinks. They have been used around the world as a possible galactagogue and are thought to increase insulin and oxytocin secretion; however, there is no definitive evidence for its effects in humans and because of history of birth defects, may not be safe for use during lactation.
 - Fenugreek is also thought to have anti-hyperglycemic properties.

- **Common indications/uses:**

- Fenugreek is an herb-like plant which is used in foods and drinks in its leaf form and seed form. The seeds have also been used historically as a medicine thought to aid with lactation.

- **Dosing:**

- In one randomized controlled clinical trial by Najdi et al., patients were given 2 g of fenugreek daily spread out over three doses as suggested by the GNC company. However, fenugreek is widely used as a seasoning and herb in unmeasured smaller amounts.

- **Evidence:**

- In a small randomized controlled study by Najdi et al., the effect of fenugreek supplementation versus glibenclamide supplementation was studied in 12 type 2 diabetic patients over a 12-week period. This study resulted in a significantly increased fasting insulin level and HDL/LDL ratio in the fenugreek group. Fasting blood glucose was not significantly different between the groups. These results are similar to other studies of fenugreek effects on fast-

ing blood glucose, insulin, and lipid profiles and suggest some benefits of fenugreek use in patients with diabetes and otherwise affected by metabolic syndrome. These anti-hyperglycemic benefits do still require confirmation by larger randomized controlled studies.

- In a systematic review, fenugreek was compared with other substances to determine its effectiveness as a galactagogue. In their pairwise comparisons of fenugreek to placebo, control, and other galactagogues, fenugreek did significantly increase breast milk production but was not better than other galactagogues including *Coleus amboinicus* and palm date. They concluded that this lack of significant benefit did not outweigh the safety profile, especially as it relates to pregnant and lactating women.

- **Safety concerns:**

- *Adverse reactions:* Acute hypoglycemia can occur with higher doses of fenugreek. It is otherwise considered generally safe to take but may cause gastrointestinal upset, dizziness, or allergic reactions. Fenugreek is not considered safe for use in pregnancy as it may be teratogenic.

- **Drug interactions:**

- Fenugreek can interact with anticoagulant and antiplatelet medication.

Docosahexaenoic Acid

- **Other names:** DHA.

- **Mechanism of action:**

- Docosahexaenoic acid (DHA) is a poly-unsaturated fatty acid found in the phospholipids of neuronal cell membranes. For this reason, there is evidence for it as beneficiary for cognitive and visual development and function. There is also evidence for DHA having a role in innate immunity as an M2 macrophage regulator.

- **Common indications/uses:**

- DHA is not found in high concentrations in a normal human diet and is therefore taken as a supplement either separately or can be in fish oil supplements. It is often taken along with eicosapentaenoic acid (EPA). Like fish oil, DHA as a supplement is recommended for cognitive and psychological disorders as well as heart disease.

- **Dosing:**

- Hyperlipidemia: 1.5 g/day.
 - Breastfeeding women: 200–300 mg/day.
 - It is recommended to take DHA in conjunction with EPA, and they are often sold as a combined supplement.

- **Evidence:**

- Fatty acids are known to be beneficial for cognitive development. DHA in particular is a component of phospholipids found in neuronal cell membranes.
- DHA is not readily produced in large quantities from its precursor alpha linoleic acid in the human body, so intake in the diet or supplementation are required to maintain adequate levels.
- A study by Kawano et al. found that DHA upregulates krüppel-like factor-4 which is involved in the regulation of macrophage polarization. This in turn shows some involvement of DHA in the MAP kinase pathway of M2 macrophages and innate immunity.

- **Safety concerns:**

- *Adverse reactions:* Fishy taste, abdominal upset, and increased risk of bleeding have been reported with use of fish oil and DHA/EPA supplements.

- **Drug interactions:**

- May interact with antihypertensive, anticoagulant, and antiplatelet drugs.

Fiber

- **Other names:** Inulin, wheat bran, beta-glucan, psyllium.

- **Mechanism of action:**

- Postprandial glycemic control: Gel-forming fibers, such as psyllium or B-glucan will increase viscosity of chyme in the small intestine. By increasing the viscosity, it slows the interactions of digestive enzymes with nutrients, thus slowing down the absorption of glucose, leading to reduced peak of post-prandial blood glucose concentration. Long term, it has been shown to improve glycemic control in type 2 diabetics.
- The physical increase in chyme viscosity can also lower elevated serum cholesterol concentration by trapping and eliminating bile. As chyme becomes more viscous, bile's window for reuptake becomes smaller, causing bile to be lost in stool. Reduction of bile acid causes hepatocytes to stimulate LDL-receptor expression leading to increased LDL-cholesterol clearance from blood to synthesize more bile acids.
- Laxative effect in two ways: Insoluble fiber (wheat bran) does not dissolve in water well; thus they mechanically irritate the gut mucosa, stimulating water secretion helping to soften stool and secondly, soluble gel-forming fiber retains high water hold capacity, helping to resist dehydration in the large bowel. Both result in soft and easy-to-pass stools.

- **Common indications/uses:**

- The use of viscous gel-forming fiber (aka psyllium) is indicated for lowering cholesterol, improving glycemic control, constipation, and IBS.

- **Dosing:**

- 25 g of fiber per day for women, 38 g of fiber per day for men.

- **Evidence:**

- A study done by the American college of Gastroenterology Chronic Constipation Task Force systematically reviewed clinical evidence and concluded that only psyllium was sufficient for the treatment of chronic constipation.
 - A 6-month study was done to compare the effects of viscosity on weight loss by assessing a viscous, gel-forming, nonfermented fiber (psyllium) versus a less viscous, readily fermented fiber (partially hydrolyzed guar gum). In this randomized control study, the psyllium treatment group showed gradual and sustained weight loss across the entire 6-month test period. After 6-months, there was significant improvement in fasting plasma glucose, hemoglobin A1C, and LDL-cholesterol levels.

- **Safety concerns:**

- *Adverse reactions:* Abdominal bloating and gas.

- **Drug interactions:**

- May interact with tricyclic antidepressants, glyburide, metformin, carbamazepine, cholestyramine, colestipol, digoxin, lithium.

Fish Oil

- **Mechanism of action:**

- Fish oil is a source of omega-3 fatty acids—specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

- **Common indications/uses:**

- Fish oil is taken as a supplement. 1–4 g/day.

- **Dosing:**

- The only omega-3 fatty acid which has a proven recommended amount is alpha linoleic acid.

- **Evidence and Safety Concerns are discussed above in the section “Docosahexaenoic Acid.”**

Flavonoid

- **Other names:** Polyphenols.
 - Subcategories: Flavones, Flavonols, Flavanones, Flavanonols, Chalcones, Catechins, Anthocyanins.
- **Description:**
 - Flavonoids are a large group of natural substances found in numerous fruits, vegetables, grains, bark, roots, stems, flowers, and teas.
- **Mechanism of action:**
 - Generally, their health benefits are attributed to their antioxidative, anti-inflammatory, and anti-carcinogenic properties. Flavonoids are understood to contain these properties via numerous mechanisms of action. Each flavonoid exerts its health effects via varying use of different mechanisms. Some well understood and studied mechanisms of action are listed below:
 1. Anticholinesterase activity via Inhibition of Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE)
 2. Anti-inflammatory activity via inhibition of COX-2
 3. Antioxidant via free radical scavenging
- **Common indications/uses:**
 - Flavonoids are used to either prevent or treat a wide array of disease processes. Ongoing investigation in their efficacy has led to a growing list of potential indications. A list of common and well-studied indications are listed below:
 1. Hypertension prevention and management
 2. Lipid management
 3. Chronic venous disease management
 4. Hemorrhoids
- **Dosing:**
 - In many studies, flavonoid consumption is marked as products high in flavonoid content. There is a lack of data regarding precise dosing.
 - Chronic venous disease management

Micronized Purified Flavonoid Fraction (MPFF)
Two 500 mg tablets daily
- **Evidence:**
 - *Mechanisms*

Anticholinesterase activity: In vitro inhibitory studies performed showed that quercetin and macluraxanthone possess concentration-dependent inhib-

bition against AChE and Butyrylcholinesterase (BChE). Macluraxanthone was found to inhibit both enzymes with 50% inhibitory concentration (IC₅₀) values of 8.47 and 29.8 μm, respectively.

Anti-inflammatory activity: Studies observing binding modes of flavonoids, demonstrated that some flavonols and flavones contain a 2,3-double bound which acts as a preferential inhibitor of COX-2. This discovery led to the creation selective COX-2 inhibitors.

Antioxidant activity: Flavanoids are oxidized by free radicals resulting in a more stable, less reactive radical. Research by Hanasaki found that some flavonoids can directly scavenge superoxides while other flavonoids can scavenge high reactive oxygen-derived radicals.

– Indications and efficacy

Hypertension: A Cochrane meta-analysis revealed that ingestion of flavanol-rich cocoa products significantly reduced both systolic and diastolic pressure compared with low flavonol containing cocoa powder or flavonol-free interventions (1.8/1.8 mmHg).

Chronic venous disease: a meta-analysis comparing micronized purified flavonoid fraction (MPFF) to placebo revealed a significant reduction in pain, heaviness, cramps, paresthesias, leg circumference, leg redness, and improvement in skin changes and quality of life. Seven trials examining MPFF and ulcer healing revealed that MPFF significantly improved the rate of ulcer healing at 6 months (61.3% versus 47.6%) as well as time to healing (16 versus 21 weeks).

Lipid: A trial of 200 men examining virgin olive oil (high in polyphenols) versus refined olive oil (low in polyphenols) on serum lipids revealed a dose-response effect of virgin olive oil on both LDL- and HDL-cholesterol; raising HDL- and lowering LDL-cholesterol.

Hemorrhoids: Flavanoids such as hydroxyethylrutoside function as phlebotonics which improve venous tone, microvascular permeability, lymphatic activity, and microcirculatory nutritive flow. Studies have shown its utility in reducing acute and recurrent hemorrhoidal attacks, as well as useful in bridging patients to surgery.

- **Safety concerns:**

- No adverse effects have been associated with high dietary intake of flavonoids from plant-based food. This is thought to be related to its low bioavailability, rapid metabolism, and elimination of most flavonoids.

- **Adverse reactions:**

- Drug-induced liver injury: Flavocoxid, a blend of two flavonoids (baicalin and catechins) has been used to treat osteoarthritis. The FDA has recommended it be discontinued due to drug-induced liver injury. One study revealed an incidence of 0.4%.

- **Drug interactions:**

- Many anthocyanins and anthocyanidins have been described as inhibitors of BRCP-mediated transport thus theoretically affecting anticancer drugs such as mitoxantrone, topotecan, tyrosine kinase inhibitor, fluoroquinolones, prazosin, and sulfasalazine.
- High intake of flavonoids from grape juice and dark chocolate has been found to inhibit platelet aggregation and thus can theoretically increase the risk of bleeding when also taken with anticoagulant and antiplatelet drugs.
- Consumption of flavonoid-rich grapefruit inhibits cytochrome P450 and increase the bioavailability and the risk of toxicity of more than 85 drugs.

Flax Seed

- **Other names:** Linseed, *Linum usitatissimum*.

- Common forms: whole flaxseed, ground flaxseed, flaxseed oil.

- **Description:**

- Flaxseed is a seed that comes from the flax plant.

- **Mechanism of action:**

- It is thought that Alpha-Linolenic Acid (ALA) contained within flaxseed is responsible for its anti-hypertensive effect. ALA inhibits the enzyme Soluble Epoxide Hydrolase (seH) which in turn is responsible for the metabolism of Epoxy-eicosatrienoic acid (EpETre) into Dihydroxy-eicosatrienoic acid (DiHETre). Because EpETre contains vasodilatory properties via nitric oxide synthase, the inhibition of its degradation may lead to more vasodilation and its anti-hypertensive effect.
- Flaxseed is thought to exert anti-atherogenic effect via anti-inflammatory and antiproliferative actions which include a reduction in the expression of IL-6, VCAM-1 and PCNA.

- **Common indications/uses:**

- Anti-hypertensive
- Anti-atherogenic

- **Dosing:**

- Flaxseed fiber: 7.0–18.9 g/day for anti-hypertensive consumption
- Ground flaxseed in food: 30 g for anti-hypertensive consumption

- **Evidence:**

- In a year-long randomized, double-blinded study (FLAX-PAD) revealed that consumption of 30 g of ground flaxseed was associated with a 10 and 7 mmHg

reduction in systolic and diastolic blood pressure, respectively. The effect was even larger, with a reduction of 15 mmHg in SBP, in participants who entered the study with elevated blood pressure.

- A meta-analysis of 25 randomized controlled trials evaluating flaxseed fiber consumption and blood pressure reported a significant reduction of SBP (3.4 mmHg) and DBP (1.97 mmHg) with fiber disease between 7.2 and 18.9 g/day.

- **Safety concerns:**

- In a double-blind study examining BeneFlax consumption and safety, there were no incidents of hypoglycemia or hypotension observed.
- Contraindicated in acute or chronic diarrhea, esophageal stricture, inflammatory bowel disease.

- **Adverse reactions:**

- Adverse reactions from flaxseed are limited. Of reported reactions, they are often due to drug interactions leading to an increased risk of bleeding.

- **Drug interactions:**

- May have a synergistic antiplatelet and anticoagulation effect with antiplatelet medications such as Aspirin and Warfarin, respectively. There have been case reports of elevated INR, anemia, rectal bleeding, and melena.

Folic Acid

- **Other names:** Folate, vitamin B9.

- **Description:**

- Folate is a water-soluble vitamin which plays an essential role in DNA synthesis.

- **Mechanism of action:**

- Participates in transfer/methylation reactions which are important in synthesizing nitrogenous bases in DNA and RNA. This is an essential process in the maturation of red blood cells [1].
- It has been proposed that folate prevents neural tube defects through its complex relationship with ubiquitination and expression of neural tube closure-related genes [1].
- Folate functions as an important regulator of homocysteine, with its consumption inversely related to homocysteine blood concentration.

- **Common indications/uses:**

- Neural tube defect prevention
- Macrocytic and megaloblastic anemia due to folate deficiency

- Vitiligo treatment
- Cognitive performance
- Prevention of folic acid deficiency in hemodialysis (HD) patients
- Stroke prevention

- **Dosing:**

- Neural tube defect prevention: 0.4–0.5 mg daily beginning 5–6 months before conception
- Macrocytic anemia: 1–5 mg daily
- Prevention of folic acid deficiency in HD dependence: 1–5 mg daily

- **Evidence:**

- The US preventive service task force recommends periconceptional folic acid supplementation for the prevention of neural tube defects. It has a grade A recommendation, the highest recommendation grading based on reviewed evidence.
- Randomized controlled trials have documented that dietary supplementation of folic acid reduces blood levels of homocysteine. Since 1969, there has been substantial evidence linking homocysteine plasma and risk of cardiovascular disease via its impact on the atherosclerotic process.
- The Hope 2 study revealed folic acid supplementation reduced risk of stroke by 24%. While a meta-analysis indicated that folic acid supplementation can significantly reduce the risk of stroke in individuals without a history of stroke, and thus should be considered for primary prevention.
- Folic acid and its role in improving cognitive function remains unclear, but it may improve cognitive function by reducing levels of homocysteine.
- Folic acid may also have a therapeutic role in the treatment of Vitiligo via its effect on homocysteine.

- **Safety concerns:**

- Folic acid is generally considered a safe and non-toxic supplement. There is debate whether it is associated with an increased cancer risk.

- **Adverse reactions:**

- Increased seizure risk through its interaction with antiepileptic medications.

- **Drug interactions:**

- Interacts with the metabolism of antiepileptic drugs such as phenytoin, carbamazepine, and phenobarbital, reducing serum levels, and increasing the likelihood of seizure.
- In addition, folic acid interacts with anti-folate drugs such as the chemotherapy and autoimmune agent methotrexate. Folate may render these drugs less effective.

Gamma-Aminobutyric Acid

- **Other names:** GABA; GABA-A GABA-B.
- **Description:**
 - An amino acid.
- **Mechanism of action:**
 - GABA is an amino acid which functions as the main inhibitory neurotransmitter in the central nervous system. It is packaged in synaptic vesicles and released into synaptic cleft to target GABA receptors on the postsynaptic surface [2].
 - Interestingly, it has long been believed that GABA is unable to pass the blood-brain barrier (BBB).
- **Common indications/uses:**
 - Improve cognition/mental focus
 - Anxiety management and stress reduction
 - Promote relaxation and sleep agent
 - Anti-hypertensive
- **Dosing:**
 - GABA 50–100 mg/day.
- **Evidence:**
 - Anti-anxiety: One study reported reduced heart rate variability and salivary chromagin A, a salivary catecholamine marker, during an arithmetic task compared to a control group after administration of GABA-enriched chocolate. A second study reported reduced salivary cortisol and Cga during a psychological stress-inducing arithmetic task. In another study, participants who consumed 50 mg of GABA reported less psychological fatigue after task completion compared to placebo. However, this evidence is questionable as many of these authors are affiliated with the company producing the GABA supplement.
 - Relaxation and sleep: A randomized double-blind, placebo-controlled study sought to examine the impact of GABA on sleep in 40 patients with insomnia. After 4 weeks of GABA supplementation, sleep latency was decreased and sleep efficacy was increased as compared to placebo.
 - Anti-hypertensive: In a double-blind, placebo-controlled study examining the effect of GABA on blood pressure in 177 participants, results revealed a reduction in average systolic blood pressure by 4.6 mmHg in the GABA treated groups as compared to the control groups. Multiple other studies have also noted a small reduction in systolic blood pressure.

- The currently held belief is that GABA is unable to cross the blood-brain barrier, but there have been a few recent studies revealing conflicting evidence, implying it may potentially be able to cross the barrier in small amounts.
- **Safety concerns:**
 - Caution is advised for pregnant and lactating women since GABA can affect neurotransmitter and the endocrine system.
- **Adverse reactions:**
 - No serious adverse events have been associated with GABA intake with up to 120 mg for 12 weeks. Mild side effects include abdominal discomfort, headache, drowsiness, and transient burning sensation in the throat.
- **Drug interactions:**
 - As GABA is associated with a small reduction in blood pressure, it may work synergistically with anti-hypertensive medication.

Garcinia Cambogia

- **Other names:** Garcinia, Malabar Tamarind, Brindle berry.
- **Description:**
 - Small pumpkin-like fruit native to Southeast Asia and Africa.
- **Mechanism of action:**
 - The rind of Garcinia cambogia contains a chemical called hydroxycitric acid (HCA). It is thought that HCA promotes weight loss via its effect on lipogenesis, appetite suppression via serotonin, and fat absorption.
 - HCA inhibits adenosine triphosphate citrate lyase enzyme which converts citrate to citrate to acetyl coenzyme A and oxaloacetate which contributes to lipogenesis. Thus, suppression of this enzyme HCA prevents de novo fatty acid and cholesterol biosynthesis, thereby alleviating subcutaneous and visceral fat deposition and causing weight loss.
 - HCA raises the level of serotonin in the brain and suppresses appetite and food intake.
 - HCA also improves fat and carbohydrate metabolism by suppressing intestinal absorption of fat.
- **Common indications/uses:**
 - Weight loss
 - Athletic performance

- **Dosing:**

- Garcinia 1500–5000 mg/day
 - HCA 900–2800 mg/day

- **Evidence:**

- Weight loss: A 2020 systematic review examining eight trials of Garcinia cambogia supplementation and its relationship with obesity revealed a non-linear association between Garcinia cambogia dosage and change in body weight. Despite this, the study revealed that Garcinia cambogia had a significant effect on body weight (-1.34 kg), BMI (-0.99 kg/m^2), percentage of fat mass (-0.42%), and waist circumference (-4.16 cm).
 - Athletic performance: In a study examining HCA consumption and glycogen stores, results revealed that HCA supplementation can effectively increase the rate of glycogen storage formation in skeletal muscle. This translates to athletic performance as glycogen stores typically take greater than 1 day to be replete, thus accelerated glycogen repletion may be advantageous for training in endurance athletes [3].

- **Safety concerns:**

- Liver injury
 - Serotonin toxicity

- **Adverse reactions:**

- There have been multiple case reports connecting Garcinia cambogia and liver injury and hepatotoxicity, with some cases leading to fulminant hepatic failure requiring liver transplantation. Due to these reported effects, the FDA has warned against using products containing Garcinia cambogia.
 - Minor adverse effects include headache, nausea, upper respiratory tract symptoms, and gastrointestinal symptoms.

- **Drug interactions:**

- *SSRIs*: Garcinia cambogia may increase serotonin concentrations; thus, it may synergistically interact with serotonin reuptake inhibitors further increase serotonin concentrations, potentially leading to serotonin toxicity.

Garlic

- **Other names:** *Allium sativum*.

- **Description:**

- Garlic is the edible bulb from a plant in the lily family.

- **Mechanism of action:**

- Diallyl disulfide is a component of garlic oil that has been found to inhibit 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase in a concentration-dependent manner. HMG CoA reductase is a key enzyme in the formation of cholesterol synthesis; thus, its inhibition reduces cholesterol formation, similar to the mechanism of action of statin medication.
- It is hypothesized that garlic improves blood pressure through inhibition of angiotensin-converting enzyme (ACE), down regulation of angiotensin II receptor, and through stimulation of nitric oxide formation.
- Garlic is also thought to have antimicrobial and anti-viral properties.

- **Common indications/uses:**

- Hyperlipidemia
- Hypertension
- Common cold prevention

- **Dosing:**

- 2–5 g of fresh raw garlic
- 300–2400 mg/day

- **Evidence:**

- The most comprehensive meta-analysis conducted to date included 39 primary trials evaluating the effect on garlic preparation on total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. The study revealed that garlic was effective in reducing total serum cholesterol and LDL-cholesterol in individuals with elevated total cholesterol levels if used for longer than 2 months. The observed mean reduction of total serum cholesterol was 8% and was associated with a 38% reduction in risk of coronary events at 50 years of age. HDL-cholesterol levels improved only slightly and triglycerides were not influenced significantly. Despite these findings, there continues to be ongoing controversy whether garlic supplementation can truly and significantly impact hyperlipidemia.
- Most clinical trial support the assumption that garlic may moderately decrease arterial blood pressure in hypertensive subjects. A meta-analysis of seven randomized placebo-controlled trials reported a significant lowering effect of garlic on both systolic and diastolic blood pressure, by 6.7 and 4.8 mmHg, respectively.
- In one 12-week randomized controlled trial of 146 participants evaluating cold prevention with garlic supplementation versus placebo and standard treatment demonstrated 24 occurrences of the common cold in the intervention group as compared to 65 in the placebo group. The trial also revealed a few days of illness (111 versus 366). Seeing as there is only one randomized controlled trial supporting Garlic's effect on cold prevention, more evidence is needed.

- **Safety concerns:**

- Garlic is generally considered a safe supplement. The known adverse effects are considered mild, nevertheless attention should be paid to its few herb-drug interactions.

- **Adverse reactions:**

- Side effects are more noticeable with raw garlic. The most commonly documented side effects are breath and body odor. Other side effects include heartburn, upset stomach, and applied directly on skin; burns are possible. As like many other substances, there is also a risk of allergic reaction.

- **Drug interactions:**

- As garlic supplementation may increase the risk of bleeding, bleeding risk may be further exacerbated with concurrent use of anticoagulants such as Warfarin.
 - Garlic may reduce the efficacy of anti-AIDS drugs such as Saquinavir.

Ginger

- **What is it and how does it work in the body?**

- Ginger is the spicy and flavorful root of the flowering plant *Zingiber officinale*. The exact origins of the plant are unknown, but it is likely that ginger is native to Southeast Asia. Ginger's current name comes from the Middle English *gingivere*, but this spice dates back over 3000 years to the Sanskrit word *srngaveram*, meaning "horn root," based on its appearance. In Greek, it was called *zingiberis*, and in Latin, *zingiberi*.
 - Ginger is not only an extremely popular dietary condiment used for flavoring food but also an herb that has been used for thousands of years as a medicinal supplement to treat a variety of ailments.
 - It is believed that Indians and Chinese have produced ginger as a tonic root for over 5000 years to treat many ailments, and this plant is now cultivated throughout the humid tropics, with India being the largest producer.
 - It was an exceedingly important article of trade and was exported from India to the Roman Empire over 2000 years ago, where it was especially valued for its medicinal properties.
 - In the thirteenth and fourteenth centuries, the value of a pound of ginger was equivalent to the cost of a sheep. By medieval times, it was being imported in preserved form to be used in sweets.
 - When you consume ginger, you are eating the thick root, also known as the rhizome which is the edible portion of the plant. It is available in the produce section of most grocery stores. Dried and ground ginger can also commonly be found in the herbs and spices aisle.

- Ginger is used in numerous forms, including fresh, dried, pickled, preserved, crystallized, candied, and powdered or ground. The flavor is somewhat peppery and slightly sweet, with a strong and spicy aroma. The concentration of essential oils increases as ginger ages and, therefore, the intended use of the rhizome determines the time when it is harvested. If extracting the oil is the main purpose, then ginger can be harvested at 9 months or longer. Ginger is commonly pickled in sweet vinegar, which turns it into a pink color, which is popular with sushi. Ginger harvested at 8–9 months has a tough skin that must be removed before eating, and the root is more pungent and is usually dried or pulverized into ground ginger. This is the form found in spice bottles and used in cookies, cakes, and curry mixes.
- Candied or crystallized ginger is cooked in sugar syrup and coated with granulated sugar. Ginger harvested at 5 months is not yet mature and has a very thin skin, and the rhizomes are tender with a mild flavor and are best used in fresh or preserved forms.

- **What is it used for and at what dosage?**

- The unique compounds within ginger are thought to be the primary source of its health benefits. The oleoresin (i.e., oily resin) from the rhizomes, the edible root, of ginger contains many bioactive components. Ginger has been fractionated into at least 14 bioactive compounds, including [4]-gingerol, [6]-gingerol, [8]-gingerol, [10]-gingerol, [6]-paradol, [14]-shogaol, [6]-shogaol, 1-dehydro-[10]-gingerdione, [10]-gingerdione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone A, 1,7-bis-(4'-hydroxy-3'-methoxyphenyl)-5-methoxyheptan-3-one, and methoxy-[10]-gingerol. The proportion of each individual component in a sample of ginger depends on country of origin, commercial processor, and whether the ginger is fresh, dried, or processed.
- The primary component of these is gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone) which is the primary pungent ingredient that is believed to exert a variety of remarkable pharmacological and physiological activities. In general, ginger is deemed safe but the lack of a full understanding of its mechanism of action is the reason why there is some caution in its therapeutic properties.
- However, ginger has been used for medicinal use for thousands of years. It has shown to contain antioxidant properties and reduces inflammatory enzymes.
- Therefore, ginger is thought to be beneficial for pain relief, specifically arthritis-based conditions, and menstrual cramps. Ginger has been linked to treating chronic pain rather than alleviating acute pain symptoms.
- One study showed that ginger oil (33 mg/kg), administered orally to rats for 26 days, caused a significant repression of paw and joint swelling associated with severe chronic adjuvant arthritis. More recently, the effectiveness of a crude ginger extract was compared with a fraction containing only gingerols and derivatives to inhibit joint swelling in the streptococcal cell wall-induced arthritis animal model of rheumatoid arthritis.

- The most common and well-established use of ginger throughout history is probably its utilization in alleviating symptoms of nausea and vomiting. The benefits and dangers of herbal treatment of liver and gastrointestinal distress have been reviewed, and several controlled studies have reported that ginger is generally effective as an antiemetic. The effectiveness of ginger as an antiemetic has been attributed to its carminative effect, which helps to break up and expel intestinal gas. This idea was supported by the results of a randomized, double-blind trial in which healthy volunteers reported that ginger effectively accelerated gastric emptying and stimulated antral contractions.
- The cases where ginger has been shown to be most effective are nausea and vomiting associated with pregnancy, chemotherapy, and some types of surgery. The clinical data undoubtedly indicate that ginger is at least as effective and may be better than vitamin B6 in treating these symptoms. Again, mechanisms are lacking, but no reports indicate that ginger has any adverse side effects or that it can worsen illness in pregnant women or patients.
- In addition, ginger helps with blood sugar regulation by reducing enzymes that break down carbohydrates. Studies have found that ginger helps with glucose absorption without the need of increased insulin.

- **Safety concerns, side effects, and precautions?**

- Ginger is recognized by the US Food and Drug Administration (FDA) as a food additive that is “generally recognized as safe.” However, and notably, in 1930, thousands of Americans were poisoned and paralyzed by an illicit extract of Jamaican ginger (jake) that was used to circumvent prohibition laws. The extract had been adulterated with a neurotoxic organophosphate compound, triorthocresyl phosphate. The extract was banned in 1931.
- One study showed that oral administration of a ginger extract (1000 mg/kg) to pregnant rats had no adverse effects on the mothers or in the development of fetuses. However, this result differed from an earlier study, in which administration of ginger tea to pregnant rats resulted in twice the loss of embryos but heavier surviving fetuses compared to untreated controls.
- In a more recent study, male and female rats that were fed ginger powder (500, 1000, or 2000 mg/kg BW) by gavage for 35 days did not exhibit any overall mortalities or abnormalities in behavior, growth, or food and water consumption. No overt organ abnormalities were observed and hematological and blood biochemical parameters in treated and untreated control animals were similar.

- **Conclusion:**

- More studies are needed on the long-term effects ginger has on health and better ways to utilize it in our everyday diet. Specific molecular targets and mechanisms of action need to be identified to understand what interactions this supplement has with other medications or dietary limitations. Ginger

- clearly has a vast number of components and metabolites, many of which have not been studied in detail.
- Overall, ginger has many beneficial effects and has a myriad of enhancements in many areas of life.

Goji

- **Other names:** *Lycium barbarum*.
- **Mechanism of action:**
 - Contains a very high amount of anthocyanins which gives it its antioxidant activity, anti-inflammatory and antilipidemic activity by increasing the production of antioxidant enzymes, suppressing inflammatory factors and raising serum HDL levels.
- **Common indications/uses:**
 - Antioxidant, benefits vision by protecting from hypopigmentation and soft drusen accumulation in the macula (shown in a study done on elderly patients).
- **Dosing:**
 - Insufficient data to recommend.
- **Evidence:**
 - A study done on lipid-lowering effects showed that the group of mice supplemented with goji extract had significantly lower concentrations of triglycerides and total cholesterol compared to the diabetic control group.
 - Tang et al. (2012) tested goji berries and found to have pro-apoptotic and anti-proliferative activity against cancer cells. Gan et al. (2004) confirmed that goji polysaccharide fractions could inhibit the growth of transplantable sarcoma in mice, increase macrophage phagocytosis and antibody secretion by spleen cells.
 - Yu et al. (2013) showed that bioactive compounds present in *L. barbarum* enhance the expression of zeaxanthin and luteolin genes in diabetic mice, thus having neuroprotective properties on a diabetic animal's retina.
 - Chemical analysis of the goji berry shows its high antioxidative activity, showing its scavenging activity against free radicals. Goji antioxidative activity is mainly due to carotenoid pigments, flavonoids, polysaccharide fraction, and vitamin analog C-2-O ascorbic acid.
- **Safety concerns:**
 - The high content of atropine (0.95%) present in goji fruit was tested in berries from India in 1989. However, published case reports do not describe people who have experienced atropine poisoning. There was no detected atropine in both studies using HPLC-PAD and TLC methods. Using HPLC-MS method, a small amount of atropine found, with a maximum concentration of 19 ppb, well below toxic level.

- **Adverse reactions:**

- Allergic reaction—only seen in a few cases. Led to anaphylaxis, urticaria on hands, palms and lips, edema, dyspnea, and acute rhinitis. Skin prick testing show a high degree of cross-reactivity between goji berry and peach and tomato.

- **Drug interactions:**

- Warfarin (elevates INR, increased bleeding from rectum and nose shown in three case reports).

Glucosamine

- **Other names:** Brand names: glucosamine and chondroitin, osteo bi-flex advanced.

- **Mechanism of action:**

- D-Glucosamine from exogenous sources was shown to incorporate into the metabolic pathway of glycosaminoglycan synthesis. In vitro studies show that glucosamine stimulates the production of proteoglycans and increases the sulfate uptake by articular cartilage.

- **Common indications/uses:**

- Osteoarthritis.

- **Dosing:**

- Recommended dosage is 500 mg three times daily because of greater experience in clinical trials

- **Evidence:**

- Braham et al. [4] did a study and showed that glucosamine supplementation (2000 mg/day, for 12 weeks) may result in decreased pain ratings and self-reported improvements in functional ability of patients with chronic knee pain.

- **Safety concerns:**

- One case report discussed a case of asthma being exacerbated by the use of glucosamine supplement for OA, and the physician should keep underlying conditions in mind when discussing supplementation.

- **Adverse reactions:**

- Overall adverse effects from glucosamine are minimal, mainly consisting of minor GI symptoms (nausea, vomiting, GI cramps, headache, bloating, dry mouth).

- **Drug interactions:**

- No drug interactions were found.

Glutamine

- **Other names:** Endari, Nutrestore, Enterex Glutapak-10, Resource Glutasolve, Symp-X.

- **Mechanism of action:**

- Glutamine is an amino acid that is normally produced in the body and has a large variety of biochemical functions which include: (1) synthesis of proteins, DNA precursors, lipids; (2) energy production in ATP synthesis; (3) regulation of intestinal mucosa, and many others. The lungs, liver, brain, skeletal muscles, and adipose tissue have glutamine synthesis activity. Glutamine is considered a conditionally essential amino acid as endogenous synthesis does not meet bodily demands in certain catabolic conditions such as cancer, sepsis, infections, surgeries, traumas, and prolonged intense exercise. Skeletal muscles play a fundamental role in glutamine metabolism as intramuscular glutamine content corresponds to 50–60% of the total free amino acids found in skeletal muscles.

- **Common indications/uses:**

- Exhaustive and prolonged exercise
 - Oral mucositis prevention secondary to chemo
 - Short gut syndrome
 - Sickle cell disease

- **Dosing:**

- *Exhaustive prolonged exercise:* 20–30 g have been tolerated without any adverse concerns. Typically dosed 10 g a day on current nutritional supplements.
 - *Oral mucositis prevention secondary to chemo:* 10–30 g daily [5].
 - *Short bowel syndrome:* 30 g daily with other nutritional supplemental and growth hormone for up to 4 weeks [6].
 - *Sickle cell disease:* FDA approved (Endari)—dosing based on weight [7].

Weight in kg	Dose
Less than 30 kg	5 g PO twice a day
30–60 kg	10 g PO twice a day
>65 kg	15 g PO twice a day

- **Evidence:**

- *Exhaustive/prolonged exercise:* A review by Coqueiro et al. [8] consisting of 55 studies looking at the anti-fatigue effects of glutamine after exercise showed that glutamine supplementation increased muscle glycogen synthesis and reduced ammonia accumulation induced by exercise and attenuated markers of muscle damage such as blood CK and LDH levels. However, there was limited effect on physical performance.
- *Oral mucositis prevention secondary to chemo:* The most recent MASCC/ISOO guidelines for management of mucositis secondary to cancer therapy suggested oral glutamine tablets in patients with head and neck cancer receiving RT-CT, based on two RCTs showed that glutamine dosed between 10 and 30 daily during RT-CT may prevent oral mucositis [5].
- *Short gut syndrome:* A study by Guo et al. [6] showed that among 12 patients with short bowel syndrome, oral glutamine (30 g daily), growth hormone (0.05 mg/kg/day), and enteral supplementation for 4 weeks resulted in improved intestinal absorptive capacity, plasma level of proteins, and overall nutrition status.
- *Sickle cell disease:* The FDA approved Endari (L-glutamine supplement) in 2017 to reduce acute sickle cell flares in adult and pediatric patients older than 5 years old, based on a multicenter phase 3 trial looking at glutamine supplementation among 230 patients with sickle cell disease, showing a significant decrease in pain crises and fewer hospitalizations [7].

- **Safety concerns:**

- There are minimal safety concerns if taken at the recommended dose (<40 mg/day).
- In one case study, a female athlete who had increased alcohol consumption experienced hepatotoxicity with chronic glutamine supplementation [9], warranting furthering research.

- **Adverse reactions:**

- Commonly reported side effects through FDA reporting include: constipation, nausea, headaches, abdominal pain, cough, and muscle/joint pain.

- **Drug interactions:**

- *Lactulose:* Glutamine may reduce the ammonia-lowering effects of lactulose when used for conditions like hepatic encephalopathy. Should be monitored [10].

Glutathione

- **Other names:** (2S)-2-Amino-5-((2R)-1-[(carboxymethyl)amino]-1-oxo-3-sulfanylpropan-2-yl}amino)-5-oxopentanoic acid, γ -L-glutamyl-L-cysteinylglycine (2S)-2-amino-4-((1R)-1-[(carboxymethyl)carbamoyl]-2-sulfanylethyl}carbamoyl)butanoic acid.

- **Mechanism of action:**

- Glutathione is a tripeptide, a substance consisting of three amino acids: cysteine, glutamate, and glycine.
 - The critical roles of glutathione include:
 - Direct chemical neutralization of singlet oxygen, hydroxyl radicals, and superoxide radicals
 - Cofactor for several antioxidant enzymes
 - Regeneration of vitamins C and E
 - Neutralization of free radicals produced by Phase I liver metabolism of chemical toxins
 - One of approximately seven liver Phase II reactions, which conjugate the activated intermediates produced by Phase I to make them water soluble for excretion by the kidneys
 - Transportation of mercury out of cells and the brain
 - Regulation of cellular proliferation and apoptosis
 - Vital to mitochondrial function and maintenance of mitochondrial DNA (mtDNA)

- **Common indications/uses:**

- People take glutathione for its antioxidant power and as a detoxification agent. There are multiple diseases associated with low levels of glutathione, including: Alzheimer's, Parkinson's, COPD, asthma, HIV, hypertension, myocardial infarction, macular degeneration, glaucoma, cystic fibrosis, and the aging process itself. Direct administration of glutathione has been proved to be effective in the diseases mentioned above.

- **Dosing:**

- Insufficient data to recommend.

- **Evidence (by indication):**

- Insufficient data to recommend.

- **Safety concerns:**

- Long-term use of glutathione is linked to low zinc levels. In addition, inhaled glutathione can cause wheezing and exacerbate asthma attacks. It is unknown if this substance is safe to take during pregnancy.

- **Adverse reactions:**

- Insufficient data to recommend.

- **Drug interactions:**

- Insufficient data to recommend.

Green Tea

- **Other names:** *Camellia sinensis*.
- **Mechanism of action:**
 - Ohishi et al. state that green tea's main component epigallocatechin-3-gallate, or EGCG, is a major reason for the anti-inflammatory benefits of green tea. EGCG works as an antioxidant and also suppresses expression of inflammatory cytokines and enzymes. Some of the anti-inflammatory benefits of green tea are likely a benefit of their polyphenol content [11]. One type of polyphenol are flavanoids which are discussed in depth earlier in this chapter. In short, flavanoids have a variety of mechanisms of action which may contribute to their anti-inflammatory properties including acting as antioxidants via COX-2 inhibition and inhibiting acetylcholinesterase.
- **Common indications/uses:**
 - People drink variations of green tea world-wide for cultural, recreational, and medicinal reasons.
- **Dosing:**
 - The composition of green tea varieties has been studied many times and varies depending on the growing conditions and processing of the leaves. For example, Japanese Matcha tea may typically contain about 6.5% polyphenols by weight.
- **Adverse reactions:**
 - Adverse reactions to green tea are more likely when it is used in concentrated forms such as green tea extract. For example, a case report by Molinari et al. [12] reported acute liver failure resulting in liver transplant following the use of green tea extract at 720 mg/day for 6 months.
- **Drug interactions:**
 - Green tea may interact with some common medications including statins, folic acid, and lisinopril.

References

1. Merrell BJ, McMurry JP. Folic acid. 2020.
2. Ngo DH, Vo TS. An updated review on pharmaceutical properties of gamma-aminobutyric acid. *Molecules*. 2019;24(15):2678.
3. Cheng I, Huang S, Lu H, Wu C, Chu Y, Lee S, et al. Oral hydroxycitrate supplementation enhances glycogen synthesis in exercised human skeletal muscle. *Br J Nutr.* 2012;107(7):1048–55. <https://doi.org/10.1017/S0007114511003862>.
4. Braham R, Dawson B, Goodman C. The effect of glucosamine supplementation on people experiencing regular knee pain. *Br J Sports Med.* 2003;37:45–9.

5. Elad S, Cheng KKF, Lalla RV, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2020;126(19):4423–31. <https://doi.org/10.1002/cncr.33100>.
6. Guo M, Li Y, Li J. Effect of growth hormone, glutamine, and enteral nutrition on intestinal adaptation in patients with short bowel syndrome. *Turk J Gastroenterol*. 2013;24(6):463–8. <https://doi.org/10.4318/tjg.2013.0555>.
7. Niihara Y, Miller ST, Kanter J, et al. A phase 3 trial of L-glutamine in sickle cell disease. *N Engl J Med*. 2018;379(3):226–35. <https://doi.org/10.1056/NEJMoa1715971>.
8. Coqueiro AY, Rogero MM, Tirapegui J. Glutamine as an anti-fatigue amino acid in sports nutrition. *Nutrients*. 2019;11(4):863. <https://doi.org/10.3390/nu11040863>.
9. Hatami B, Saffaei A, Jamali F, Abbasinazari M. Glutamine powder-induced hepatotoxicity: it is time to understand the side effects of sports nutritional supplements. *Gastroenterol Hepatol Bed Bench*. 2020;13(1):86–9. <http://www.ncbi.nlm.nih.gov/pubmed/32190229>.
10. Rai R, Saraswat VA, Dhiman RK. Gut microbiota: its role in hepatic encephalopathy. *J Clin Exp Hepatol*. 2015;5(Suppl 1):S29–36. <https://doi.org/10.1016/j.jceh.2014.12.003>.
11. Cabrera C, Artacho R, Gimenez R. Beneficial effects of green tea—a review. *J Am Coll Nutr*. 2006;25(2):79–99. <https://doi.org/10.1080/07315724.2006.10719518>.
12. Molinari M, Watt KD, Kruszyna T, Nelson R, Walsh M, Huang WY, Nashan B, Peltekian K. Acute liver failure induced by green tea extracts: case report and review of the literature. *Liver Transpl*. 2006;12(12):1892–5. <https://doi.org/10.1002/lt.21021>.

Chapter 3

Hawthorn–Lysine



Esha Jain, Chibuike Ezeibe, and Glenn Adesoji

Hawthorn

- **What Is It?**

- Hawthorn (*Crataegus monogyna*, *Crataegus laevigata*) is a flowering shrub or tree of the Rosaceae (rose) family [1]. It is known to develop and thrive in temperate regions throughout the world [2].

- **How Does It Work in the Body?**

- Derived from the flower, leaves, and fruits of the plant, hawthorn is also known in Asia as Shan Zha. It is used in traditional Chinese medicine to improve digestion and treat heart problems. Hawthorn also has a long history in European medicine as a heart tonic [1].
- Studies in the lab suggest a range of anti-inflammation, heart-protective, and digestion-improving properties. Studies in humans show benefits in patients with congestive heart failure although a few trials did not [1].
- More studies are needed to confirm safety and effectiveness of hawthorn. In addition, it should not be used in place of conventional heart failure therapies and its use should be monitored by the treating physician [1].

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- **What Is It Used for?**

- In traditional Chinese medicine, hawthorn fruits are used for relieving indigestion and promoting stomach function, improving blood circulation, and removing blood stasis; however, clinical studies are lacking [1, 3, 4].
- In European herbal medicine, hawthorn flowers have been used as an astringent, antispasmodic, cardiotonic, and diuretic; hawthorn has been thought to aid as a hypotensive and/or anti-atherosclerotic agent; data are conflicting. More research is needed [1, 3, 5].
- In some studies, hawthorn extract used as add-on therapy was found to be beneficial in heart failure patients. More definitive data are needed [1, 3, 4, 6].

- **Precautions/Side Effects:**

- Generally, hawthorn is well tolerated. However, individuals may experience dizziness (most common) and nausea, cardiac and gastrointestinal complaints (infrequent and mild) with use [1].
- Overdose can potentially cause hypotension and irregular heartbeat (arrhythmia) [1].

- **Evidence for and Against:**

- In a study on 2681 patients suffering from congestive heart failure, the administration of hawthorn extract (900 mg/day) for 6 months showed no positive clinical effects in inflammation, oxidative stress, neurohormones, functional capacity, and quality-of-life measures, but modest change in left ventricular ejection fraction was found [7].
- However, according to the findings of Trexler et al. [8], 160 mg of hawthorn supplementation in adult subjects for a week could not influence electrocardiographic indices [7].
- Moeini et al. showed that 5 mL of hawthorn fruit extract after each meal in male and female patients with gastroesophageal reflux disease controlled the main symptoms over 4 weeks, as well as causing a 94.2% and 93.5% alleviation in regurgitation and heartburn, respectively [7].

- **Dosage:**

- The recommended daily dose of hawthorn is 160–900 mg of a native water-ethanol extract of the leaves or flowers (equivalent to 30–169 mg of epicatechin or 3.5–19.8 mg of flavonoids) administered in two or three doses [6].
- At therapeutic dosages, hawthorn may cause a mild rash, headache, sweating, dizziness, palpitations, sleepiness, agitation, and gastrointestinal symptoms [6].

- **Interactions:**

- Use of hawthorn with phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil) may lead to hypotension [9].

- Because hawthorn can be used to help with hypertension, it may interact with drugs used to treat high blood pressure (e.g., beta blockers such as atenolol, calcium channel blockers such as diltiazem) and result in hypotension [9].
- Taking hawthorn along with digoxin and/or nitrates may increase the effects of such cardiogenic drugs and increase the risk of cardiotoxic side effects [9].

Hazelnut Extract/Oil

- **What Is It?**

- Also known as *Corylus avellana*, hazelnut is a species of flowering plant in the birch family *Betulaceae* and is native to Europe and Western Asia [10].

- **How Does It Work in the Body?**

- Hazelnuts contain high amounts of protein, dietary fiber, vitamin E, iron, thiamin, phosphorus, manganese, and magnesium [11].
 - Hazelnuts are a significant source of total fat, accounting for 93% DV in a 100-g amount [11].

- **What Is It Used for?**

- Hazelnut has been used for high cholesterol and other forms of hyperlipidemia (high levels of fats in the blood), heart disease, dementia, and obesity; however, there is insufficient data to support these medicinal uses [12, 13].

- **Precautions/Side Effects:**

- Hazelnut is likely safe for most people in food amounts. But some people are allergic to hazelnuts and have had life-threatening allergic reactions (anaphylaxis) [12, 13].

- **Evidence for and Against:**

- In a study, the nutraceutical potential of two hazelnut varieties (Turkey and Italy) were examined [14]:
 - Turkish hazelnut had the higher concentration of phenolic acids, flavonoids, higher antioxidant capacity and enzyme inhibition properties, and lower saturated fatty acid concentration than the Italian sample.

In vivo studies showed that compared to the Italian hazelnuts, the addition of Turkish hazelnuts to high-fat diet was associated with a more significant decrease in body weight, food consumption, atherogenic index, lipid peroxidation levels and biochemical/morphological markers of liver injury. The two hazelnut varieties were protective against β -amyloid-induced neurochemical changes and high-fat diet-induced alteration of metabolic indices.

- **Dosage:**

- The appropriate dose of hazelnut depends on several factors such as the user's age, health, and several other conditions. There is not sufficient scientific data to determine an appropriate range of doses for hazelnut [12, 13].

- **Interactions:**

- There is currently no information on hazelnut drug-drug interactions [12, 13].

Hemp Seed Oil (HSO)

- **What Is It?**

- Hemp seed oil is extracted from cold pressing seeds of the hemp plant. It is derived from the cannabis plants originated from Central Asia, but it differs from cannabis in that HSO does not contain significant amounts of tetrahydrocannabinol (THC) [15, 16].

- **How Does It Work in the Body?**

- Hemp contains chemicals that may affect the heart and might help reduce blood pressure [17, 18].
 - Hemp also contains terpenes, which have may have the following benefits [18, 19]:

- Neuroprotective or brain-protective benefits.

- Anti-inflammatory benefits.

- Anti-tumor properties.

- **What Is It Used for?**

- Hemp seed oil contains a 3:1 ratio of omega-6 (Linoleic Acid (LA)) to omega-3 (Alpha-Linolenic Acid (ALA)) Polyunsaturated Fatty Acids (PUFAs) and has anti-inflammatory properties which help with pain reduction [15, 16].
 - Hemp seed oil contains gamma-linolenic acid (GLA); studies have shown that natural herbs rich in GLA are effective in relieving symptoms of inflammatory conditions, such as irritable bowel syndrome (IBS), rheumatoid arthritis (RA), and multiple sclerosis (MS) [15, 16].
 - Hemp seed oil is high in omega-3 fatty acid. While omega-3 fatty acids are vital during pregnancy as they support healthy brain and eye development for the baby, there is not enough evidence to prove the safety of hemp during pregnancy or while breastfeeding [15, 18].

- **Precautions/Side Effects:**

- Hemp seed oil is used lower blood pressure. However, in individuals with chronic hypotension, the use of HSO may potentiate hypotensive effects [15].

- **Evidence for and Against:**

- Callaway et al performed a randomized, single blind crossover study with patients diagnosed with atopic dermatitis. They found after 8 weeks, patients reported significant improvement in skin dryness and itchiness ($p = 0.027$) and dermal medications decreased ($p = 0.024$) [20].

- **Dosage:**

- The Food and Drug Administration has not issued a recommended daily allowance (RDA) for hemp seed oil. However, one should be advised to never exceed the recommended dosage on the package insert [15, 18].
- Researchers estimate that three tablespoons of hemp seed oil per day can provide the amount of 3:1 fatty acid ratio needed for a healthy diet [15].
- One tablespoon (15 mL) of hemp seed oil contains [15]:

Calories: 125.

Total fat: 14 g.

Saturated fatty acids: 1 g.

Monounsaturated fatty acids: 2 g.

Polyunsaturated fatty acids: 11 g.

- **Interactions:**

- The combination of cardiac glycosides (digoxin) and hemp seed may potentiate bradycardia effects and cause arrhythmias [18].
- The use of diuretics and hemp together may result in severely hypokalemia (low potassium levels). This may lead to arrhythmias [18].

Horny Goat Weed

- **What Is It?**

- Horny goat weed is an over-the-counter herb with the active ingredient Icariin, an extract of Epimedium, is a genus of flowering plants in the family *Berberidaceae* [21]. It is used in traditional Chinese medicine to treat fatigue, arthritic pain, nerve pain, and sexual dysfunction [22].

- **How Does It Work in the Body?**

- The active ingredient in horny goat weed is Icariin, a weak phosphodiesterase type 5 (PDE5) inhibitor, allowing blood to fill the arteries and the three cylinders in the penis and create an erection [23, 24].

- **What Is It Used for?**

- Horny goat weed is traditionally used in herbal formulas for sexual dysfunction, due to its weak PDE5 inhibition. However, additional research is needed to verify such effects [22].
- *Epimedium* is traditionally used for fatigue, but it has not been studied in clinical trials [22].
- A small, randomized trial shows that *Epimedium* may help prevent bone loss in women who have had menopause for a long time [22].

- **Precautions/Side Effects:**

- Excessive dosages of horny goat weed may cause diaphoresis (sweating) and hot flashes—however, safety evaluations are scarce [22, 25].

- **Evidence for and Against:**

- As per Shindel et al., rats treated with low-dose icariin (ICA) demonstrated significantly higher intracavernous pressure/mean arterial pressure (ICP/MAP) and area under the curve/mean arterial pressure (AUC/MAP) ratios compared with control and single-dose ICA animals. Immunohistochemistry and Western blot were revealing of significantly greater positivity for neuronal nitrous oxide synthase (nNOS) and calponin in penile tissues of all rats treated with ICA. ICA led to significantly greater neurite length in cultured specimens of pelvic ganglia [24].
- A case study of an elderly man with congestive heart failure presenting with shortness of breath, angina, and new-onset symptomatic arrhythmia after taking horny goat weed daily for 2 weeks to increase sexual pleasure. The side effects and drug interactions of horny goat weed are difficult to interpret considering variability in the contents of herbal formulations. Herbal products may contain a host of other pharmacologically active substances, including coumarins, glycosides, alkaloids, and flavonoids, some of which have been demonstrated to inhibit cytochrome P450 enzymes [22, 26].

- **Dosage:**

- There is no FDA recommended dosage for horny goat weed other than the recommended serving size as set by the manufacturer [23].
- Thus, the amount of horny goat weed varies—generally 500 to 1000 mg per serving—depending on the brand [23].

- **Interactions:**

- Prolonged use of *Epimedium* can induce CYP3A4 through the activation of pregnane X receptor. The clinical relevance is unknown [22].
- Icariin enhances the action of aromatase, which may reduce the effect of aromatase inhibitors, like anastrozole, exemestane, and letrozole. The clinical relevance is unknown [22, 27].

Hydroxymethylbutyrate (HMB)

- **What Is It?**

- Beta-hydroxy-beta-methylbutyrate (HMB) is a metabolite of the amino acid leucine and is often used as a body building supplement to improve muscle strength while reducing protein breakdown [28].

- **How Does It Work in the Body?**

- HMB is a by-product of the amino acid leucine. Along with arginine and glutamine, these compounds prevent or reduce damage to muscle cells that occurs with intense exercise or in advanced cancers and AIDS [28, 29].

- **What Is It Used for?**

- HMB can be used to prevent or reverse cancer- or HIV-related weight loss and weakness; however, there is limited research in these populations with conflicting results [28].
 - HMB is used historically to increase muscle mass. As mentioned before, HMB is an amino acid metabolite that aids in building muscle with halting protein breakdown. However, meta-analyses currently suggest that any benefits with HMB supplementation are small [28].

- **Precautions/Side Effects:**

- HMB appears to be generally safe and well tolerated, with little to no known side effects. HMB appears to be generally safe in standard doses of 3 g daily or less up to 1 year [30, 31].

- **Evidence for and Against:**

- A study by Asjodi et al. demonstrated that hydroxymethylbutyrate supplementation can decrease serum creatine kinase and delay the onset of muscle soreness, while increasing the range of motion in certain joints. The use of HMB may also be able to repair cell wall damage during the activities [32].

- **Dosage:**

- The standard dose of HMB is a maximum of 3 g daily [30, 31].

- **Interactions:**

- Studies indicate that the stimulating effect of HMB on mammalian target of rapamycin (mTOR) is reduced by rapamycin, an mTOR inhibitor. HMB's ability to reduce the effectiveness of these drugs is unknown [28].

Indole-3-Carbinol (I3C)

- **What Is It?**

- Indole-3-carbinol (I3C) is formed from the breakdown of a substance called glucosinolate glucobrassicin. Glucobrassicin is found in vegetables such as broccoli, brussels sprouts, cabbage, collards, cauliflower, kale, mustard greens, turnips, and rutabagas [33].

- **How Does It Work in the Body?**

- I3C is known to stimulate detoxifying enzymes in the gut and liver. Diets high in these vegetables slow cancer growth in animals, believing I3C to be a good candidate for cancer prevention [34].

- **What Is It Used for?**

- Cancer Prevention

Studies indicate that I3C may have protective qualities against various cancers; however, some animal studies suggest that I3C supplementation might have tumor-promoting effects. Further research is required [34].

- Treatment of Viral Infections

Lab studies suggest immune function and antiviral effects, but no studies have been conducted in humans [34].

- **Precautions/Side Effects:**

- Mild adverse events have been reported dependent on dosage and use: abdominal discomfort, bloating, nausea, vomiting, asthma, breast tenderness, chest pain, constipation, diarrhea/loose stools, dizziness, headache, musculoskeletal complaints, rash, sciatic nerve pain, and upper respiratory symptoms [35].

- **Evidence for and Against:**

- New anticancer agents with overlapping underlying mechanisms have emerged via structural optimization of I3C and its metabolite 3,3'-diindolylmethane (DIM), which may provide therapeutic advantages with respect to chemical stability and anti-tumor potency [36].
 - Numerous *in situ* studies have implicated indole-3-carbinol as one of the phytochemicals with anticancer properties. Recent studies on the role of I3C in *Arabidopsis* (rockcress) opens the door for cross-kingdom comparisons that can help in understanding the role of this chemical in both plant biology and combatting cancer [37].

- **Dosage:**

- There is not enough scientific information to determine an appropriate range of doses for I3C [33].

- **Interactions:**

- Laboratory studies suggest I3C induces CYP 1A2; however, the clinical relevance is unproven [34].

Inosine

- **What Is It?**

- Inosine is a purine nucleoside in RNA formed by hypoxanthine linked by its N9 nitrogen to the C1 carbon of ribose [38].

- **How Does It Work in the Body?**

- When people take inosine by mouth, it is changed in the body to make a chemical called uric acid. Uric acid acts like an antioxidant and might protect cells in the brain [39].

- **What Is It Used for?**

- Although there is some theoretical rationale, available studies indicate that inosine supplementation has no apparent effect on aerobic or anaerobic exercise performance [40].

- **Precautions/Side Effects:**

- When taken by mouth, inosine is considered safe. Inosine becomes uric acid when taken by mouth. High levels of inosine can result in uric acid in the blood and urine, leading to possible kidney or bladder stones [39].

- **Evidence for and Against:**

- Studies have shown that in adult rats with unilateral cortical infarcts, inosine stimulated neurons on the undamaged side of the brain to extend new projections to denervated areas of the midbrain and spinal cord. The growth was paralleled by improved performance on several behavioral measures [41].

- **Dosage:**

- Inosine has most often been used by adults at a dose of 1–3 g by mouth daily for up to 2 years [39].

- **Interactions:**

- Inosine increases levels of uric acid. High levels of uric acid might make gout worse. Taking inosine along with chronic gout medications and uricosuric drugs might reduce their effects [39].

Inositol Nicotinate

- **What Is It?**

- Inositol nicotinate, also known as Inositol hexaniacinate/hexanicotinate or “no-flush niacin,” is a niacin ester and vasodilator [42].

- **How Does It Work in the Body?**

- Inositol nicotinate releases niacin, or vitamin B3, when processed in the body. Niacin causes vasodilation, lowers blood levels of fats such as cholesterol, LDL, and triglycerides, and breaks up a protein needed for the clotting of blood [43, 44].

- **What Is It Used for?**

- Some research suggests that taking a specific product of inositol nicotinate (Hexopal) by mouth for several weeks modestly improves symptoms of Raynaud’s syndrome [43, 45].

- **Precautions/Side Effects:**

- Inositol nicotinate is generally safe for most people. However, it can cause adverse effects such as stomach upset, intestinal gas, and nausea [43].

- **Evidence for and Against:**

- According to a systematic review in 2008, certain drug treatments, such as nicardipine, inositol nicotinate, and prazosin may successfully treat primary Raynaud’s phenomenon, but there are no large studies available to effectively draw these conclusions [46].

- **Dosage:**

- General Dosing: Some supplements may not list inositol nicotinate separately. Instead it may be listed as niacin. Niacin is measured in niacin equivalents (NE). 1 mg of inositol nicotinate equals 1 mg NE [43].
 - Raynaud’s Phenomenon: Up to 4 g daily of inositol nicotinate can be used; however, it might take several weeks before effects are seen [43].

- **Interactions:**

- Long-term use of inositol nicotinate can increase blood glucose and may decrease effectiveness of hypoglycemic medications [43].
 - Inositol nicotinate may have potential action in anticoagulation. When coupled with other anticoagulation medication, the chance for bleeding and bruising may increase [43].
 - Inositol nicotinate is converted to niacin within the body. The use of statins and niacin together may increase the risk of muscle problems (e.g., myositis) [43].

- When Inositol nicotinate converted to niacin, flushing and dizziness can occur. Nicotine patches can also cause flushing and dizziness. The use of both medications can worse potential side effects [43].

Ipriflavone

- **What Is It?**

- Ipriflavone is a synthetic isoflavone, used to prevent bone resorption, maintain bone density, and manage osteoporosis [47, 48].

- **How Does It Work in the Body?**

- Ipriflavone works by inhibiting calcium-dependent protease throughout the body [49].

- **What Is It Used for?**

- There is evidence that ipriflavone (in conjunction with estrogen and/or calcium) may strengthen bones in postmenopausal women with osteoporosis [47, 48, 50].

- **Precautions/Side Effects:**

- Per a systematic review by Hu et al., mild gastrointestinal symptoms were noted. Additionally, a mild decrease in lymphocyte count was observed but resolved with discontinuation of ipriflavone [51].

- **Evidence for and Against:**

- According to Hu et al., ipriflavone significantly increases bone mineral density and has inhibitory effects on bone resorption markers in postmenopausal women with osteopenia or osteoporosis [51].
 - Several studies have shown that genistein and ipriflavone have beneficial effects on bone density and are safe in postmenopausal women. This may be considered as a complementary or alternative option in the prevention and treatment of menopause-related osteoporosis [52].

- **Dosage:**

- Osteoporosis: 200 mg of ipriflavone by mouth, three times daily.
 - Paget disease: 600–1200 mg of ipriflavone by mouth, daily.

- **Interactions:**

- Ipriflavone is contraindicated in individuals with an existing history of hypersensitivity to any of its ingredients (Ipriflavone, Hypromellose, Leucine, or Magnesium Citrate) [49].

Iodine

- **What Is It?**

- Iodine is a mineral found in some foods. It is critical for the formation of thyroid hormone [53].

- **How Does It Work in the Body?**

- Iodine is not readily made in the human body and must be obtained through diet. Iodine in the blood is transported into the follicular cell along with sodium by a sodium-iodine symporter pump. Once in follicular cells, it binds with tyrosine and thyroglobulin and later iodized and coupled to form thyroid hormone [54].

- **What Is It Used for?**

- Taking iodine supplements by mouth, including iodized salt, is effective for preventing and treating iodine deficiency, treating an overactive thyroid gland, and/or preventing thyroid cancer secondary to radiation [55, 56].

- **Precautions/Side Effects:**

- High levels of iodine can cause some of the same symptoms as iodine deficiency, including goiter (an enlarged thyroid gland) [53].
 - High iodine intakes can also cause thyroid gland inflammation and thyroid cancer [53].
 - Getting a very large dose of iodine (e.g., several grams) can cause burning of the mouth, throat, and stomach; fever; stomach pain; nausea; vomiting; diarrhea; weak pulse; and coma [53].

- **Evidence for and Against:**

- There is insufficient evidence to support current recommendations for iodine supplementation in pregnancy in areas of mild-to-moderate iodine deficiency. Well-designed randomized control trials, with child cognitive outcomes, are needed in pregnant women who are moderately deficient in iodine [57].
 - Thyroid hormone receptors have been identified and characterized in placental and embryonic tissues, allowing us to elucidate the maternal-fetal transfer of thyroid hormones. Experimental studies have demonstrated that the architecture of the cerebral cortex can be irreversibly disturbed in iodine deficiency causing abnormal neuron migratory patterns associated with cognitive impairment in children [58].

- **Dosage:**

- The amount of iodine you need each day depends on your age. Average daily recommended amounts are listed below in micrograms (mcg) [53].

Life Stage	Recommended Amount
Birth to 6 months	110 mcg
Infants 7–12 months	130 mcg
Children 1–8 years	90 mcg
Children 9–13 years	120 mcg
Teens 14–18 years	150 mcg
Adults	150 mcg
Pregnant teens and women	220 mcg
Breastfeeding teens and women	290 mcg

- **Interactions:**

- Iodine supplements might interact with anti-thyroid medications such as methimazole, used to treat hyperthyroidism. The two medications combined may potentiate hypothyroid effects [53].
- Taking potassium iodide with medicines for high blood pressure (e.g., ACE inhibitors) or with potassium-sparing diuretics could raise the amount of potassium in your blood to an unsafe level [53].

Iron

- **What Is It?**

- Iron is a mineral and an essential component of hemoglobin. It is naturally present in many foods, added to some food products, and available as a dietary supplement [59].

- **How Does It Work in the Body?**

- Iron is a crucial component of heme synthesis. The iron in the blood is transported to the mitochondria and inserted into heme precursor, protoporphyrin IX, via the enzyme ferrochelatase. This produces heme [60].

- **What Is It Used for?**

- Iron is a key building block for hemoglobin formation. Its primary purpose is to prevent anemia. Hemoglobin resides on red blood cells, a mineral in the human body, is one of the components of hemoglobin, the substance in red blood cells that helps blood carry oxygen throughout the body. If you do not have enough iron, your body cannot make hemoglobin and you may develop anemia [59–61].

- **Precautions/Side Effects:**

- Iron is generally safe with doses below the tolerable upper intake level (UL) of 45 mg elemental iron daily [61].
- High doses of iron can cause gastrointestinal issues including upset stomach, nausea, diarrhea, and vomiting; however, taking iron supplements with food seems to reduce side effects [59, 61].
- Iron is likely unsafe when taken in excessive doses. Acute intakes of more than 20 mg/kg iron (about 1365 mg iron for a person weighing 150 lb) from supplements or medicines can lead to corrosive necrosis of the intestine, which might lead to fluid and blood loss, shock, tissue damage, and organ failure, especially if food is not taken at the same time as the iron [59, 61].

- **Evidence for and Against:**

- Recent evidence indicates that low doses of iron sulfate are more effective and better tolerated than the traditionally recommended dose (100–200 mg daily) [62].
- Studies now suggest switching from daily to alternate-day schedules and from divided to morning single doses increases iron absorption and may reduce side effects. Providing morning doses of 60–120 mg iron as a ferrous salt given with ascorbic acid on alternate days may be an optimal oral dosing regimen for women with iron-deficiency and mild IDA [63].

- **Dosage:**

- The amount of iron needed daily depends on your age. Average daily recommended amounts of iron for non-vegetarians are listed below [59].

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	0.27 mg*	0.27 mg*		
7–12 months	11 mg	11 mg		
1–3 years	7 mg	7 mg		
4–8 years	10 mg	10 mg		
9–13 years	8 mg	8 mg		
14–18 years	11 mg	15 mg	27 mg	10 mg
19–50 years	8 mg	18 mg	27 mg	9 mg
51+ years	8 mg	8 mg		

- The recommended daily allowance for vegetarians is 1.8 times higher than individuals who eat meat because iron is more bioavailable in meat compared to plants [59].

- **Interactions:**

- Evidence exists that indicates that iron supplements may reduce the absorption of levodopa, thus, diminish its clinical effectiveness [59].

- Simultaneous ingestion of iron and levothyroxine can result in significant reductions in levothyroxine efficacy [59, 64].
- Proton pump inhibitors reduce the acidity of stomach contents and thus, can reduce iron absorption [59].

Java Tea

- **What Is It?**

- Java Tea (*Orthosiphon stamineus*) is a medicinal herb predominantly found in Southeast Asia and Africa.

- **How Does It Work in the Body, Usage, and Evidence?**

- A study from Yuliana et al. has been shown that Java Tea antagonizes the adenosine A1 receptors which induces diuresis and natriuresis which regulates urine flow rate and absolute excretion of sodium [65, 66].
 - A study from Zhong et al. (2010) showed that Java Tea can increase urinary calcium and oxalate excretion thus reducing the synthesis of calcium-based kidney stones [65, 67].
 - Yam et al. (2009) studied *Orthosiphon stamineus* and noted a marked histological improvement in the healing of mucosal damage in the GI tract. This is based off its ability to inhibit lipid peroxidation and stimulate gastric secretion [65, 68].

- **Dosage:**

- A study from Yam et al. (2007) analyzed effects of Java Tea for liver protection by monitoring ALT and AST levels which showed good results. Study suggests Java Tea was found effective at doses higher than 250 mg/kg [65, 67].
 - Further studies must be done to know the correct therapeutic dosage [65].

- **Adverse Effects:**

- Patients that are on a hypertensive therapy when taking *Orthosiphon stamineus* should be monitored for an orthostatic hypotensive attack [65].

- **Interactions:**

- Should not be taken with other diuretics because the combination and lead to possible hypertension and congestive heart failure. Adam et al. (2009) noted that a combination of *Orthosiphon stamineus* and antidiabetic drugs can cause hypoglycemia [65, 69].

Jimson Weed

- **What Is It?**

- Plant known as a member of the nightshade family. Its leaves and seeds are used to make medicine but also known to have hallucinogenic affects if taken inappropriately [70].
- Scientific name goes by *Datura stramonium* [71].

- **How Does It Work in the Body?**

- The leaves that are used contain antispasmodic properties that help with the treatment of asthma [70].
- Jimson weed contains chemicals such as atropine, hyoscyamine and scopolamine that interfere with the acetylcholine in the brain and nerves [70].

- **What It Is Used for?**

- Jimson weed can be used to make medicine and have been used to treat asthma, diarrhea, intestinal cramps, and nocturia due to its anticholinergic affects [70].

- **What Dosage?**

- Dosages exceeding 10 mg is considered potentially lethal. The seeds can contain approximately 6 mg of atropine [70, 72].
- Further studies are needed to have a set dosage on what is considered safe for medicinal purposes.

- **Evidence for or Against Its Different Uses:**

- A study was done to show the benefits of Jimson weed for asthma in pregnant patients along with potential adverse effects to the fetus [73].

Stated that the antimuscarinic effects of Jimson weed lead to the continuous bronchodilation to help with asthma but the release on acetylcholine can be harmful to the fetus [73].

- **Safety Concerns, Side Effects, and Precautions:**

- Exposure to the fetus while a pregnant woman using Jimson weed comes from the continuous release of acetylcholine which can result in permanent damage to fetus [73].

Should be used with caution during pregnancy [70, 73].

- Acute Jimson weed poison is seen due to potential hallucinogen affects.

Symptoms include dry mouth, extreme thirst, dry skin, pupil dilation, impaired vision, urinary retention, rapid heartbeat, confusion, restlessness, and loss of consciousness [70].

Due to inhibition of central and peripheral muscarinic neurotransmission [70].

- **Interactions with Medications:**

- Further studies have been shown in terms of interactions on Jimson weed and other medications [70].
- However, toxicology reports are used due to lethal cases of Jimson weed ingestions in polysubstance abuse [70].

Those drugs including Alcohol, Marijuana, or Cocaine.

Jojoba

- **What Is It?**

- Medicinal plant that is created into an oil [74].
- Comes from the *Simmondsia chinensis* plant that is found commonly in North and Central American deserts and has been known to be cultivated in Egypt, Chile, and Argentina [74].

- **How Does It Work on the Body?**

- It works on the body with its antioxidant properties, anti-acne, anti-psoriasis, anti-inflammatory, antipyretic, analgesic, antimicrobial and anti-hyperglycemia [74].
- Its mechanisms of action will be discussed in the next section in greater detail [74].

- **What It Is Used for?**

- Anti-inflammatory, analgesic, and antipyretic properties.

Habashy et al. conducting a study in 2005 that demonstrated reduction of edema and Prostaglandin E2 (a lipid compound that is one of the main components of inflammation) in a rat study [74, 75].

- Supports that jojoba oil is involved in the blockage of both COX2, also known as cyclooxygenase II and lipoxygenase which leads to blocking inflammation [74, 76].
- This study was further confirmed with a study involving the results of jojoba liquid wax and the treatment of diaper rashes, also known as a napkin rash. [74, 75].
 - The study involved the jojoba wax and the combination of triamcinolone acetonide, nystatin, neomycin, and gramicidin [74, 75].
 - Shown that the liquid wax was just as effective as the combination listed above and jojoba was known to have fewer side effects [74, 75].

- Anti-acne

Jojoba oil's properties as a liquid wax allow the dissolution of sebum deposits within hair follicles due to an ability to penetrate the follicles and remove the comedone which ends up clearing the skin [75, 77].

One study done by A.R. Baldwin was shown that the anti-psoriasis activity of jojoba oil is related to the keratoplastic and keratolytic effect required to treat excessive scaling of the skin [78].

- Antimicrobial

A study done by Ranzato et al. (2011) showed that the liquid wax property of jojoba has been shown to break down the solid wax coating of bacilli which along with the combination of antibiotics can treat Tubercle bacilli, leprosy bacilli, and brucelli [79].

Alcoholic extracts of jojoba have been shown to be effective against *Bacillus cereus*, *Salmonella typhimurium*, and *Candida albicans* [79, 80].

- The alkaloid, saponin, and steroid component of the jojoba root extract is believed to be the cause of activity of the pathogens listed above [79, 80].

- **Dosage:**

- No known dosage as jojoba is not taken orally [74].

- **Adverse Effects:**

- No studies have been shown to prove any adverse side effects of jojoba [74].

- **Interactions:**

- No studies have been shown to prove any significant medication interactions with jojoba oil [74].

Juniper

- **What Is It?**

- *Juniperus communis* is a shrub or small evergreen tree that is found mainly in Europe, South Asia, and North America [81].
 - Belongs to the *Cupressaceae* family [81].

- **How Does It Work in the Body, Usage, and Evidence?**

- Used as herbal medicine to treat antidiarrheal, anti-inflammatory, and antiseptic in various abdominal disorders.
 - Hepatoprotective activity

A study was done by Manvi to show that Juniper was associated with decreased levels of serum SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), total bilirubin, and alkaline phosphate after they were initially increased by CCL4 infusion in rats for 9 days [81, 82].

Decreased levels of SGPT, SGOT, ALP, and bilirubin shows protection to hepatic cells [81, 82].

- Antioxidants

Antioxidant properties were confirmed by in vivo study and created the possibility of blocking the oxidation processes in yeast cells by increasing the activity of the antioxidant enzymes [81, 83].

- Antidiabetic and antihyperlipidemic

The methanolic extract of Juniper lead to significant reduction in blood glucose levels and increased HDL levels in diabetic rats [81, 84].

- Compared to group that was just given glibenclamide.

- Analgesic activity

A study was done with the methanolic extract of Juniper.

- Showed that methanolic extract of Juniper acted peripherally and centrally for the antinociceptive activity [81, 85].

- Antibacterial

The leaf extract was shown to be effective to pathogenic multidrug-resistant *Erwinia chrysanthemi*, *Escherichia coli*, *Bacillus subtilis*, *Agrobacterium tumefaciens*, and *Xanthomonas phaseoli* [81, 86].

The methanolic extract of *J. communis* was found to be very effective as compared to standard antibiotics such as ampicillin 10 mcg and erythromycin 15 mcg [81, 86].

- **Dosage:**

- No studies have been shown the optimal dosage as experiments and studies showed varying dosages [81].

- **Adverse Reactions:**

- People with allergies with juniper essential oil or have hypersensitivity can have the following:

Dermatitis [87].

Nasal congestion [87].

Blisters [87].

- **Interactions with Medications:**

- No studies have shown that Juniper interacts with other medications, but this does not mean it is not possible. Further investigation is needed to prove or disprove any effects when interacting with other notifications [81].

Kratom

- **What Is It?**

- Kratom or Mitragyna is a tropical plant indigenous to southeast Asia and is consumed by preparing the leaves into a tea or grinding them into a powdery substance [88].

- **How Does It Work in the Body, Usage, and Evidence?**

- Kratom has similar effects of opioids including pain relief and euphoria which can cause potential addiction effects.
- Binds to the mu-opioid receptors just like other opioids with similar binding affinity.

Suggests why Kratom has the effects of regulating pain perception.

- Low dose of Kratom has been shown to be a mood booster and higher doses shown to relieve anxiety.
- Most common use of Kratom is pain relief specifically back/spine pain, fibromyalgia, migraine, rheumatoid arthritis.
- Study showed that Kratom can be used as opioids substitution.

E.g., Coffee drinkers subbing this can improve social connection.

- **Dosage:**

- Doses of 5 g of raw material are reported to exert stimulant effects [88].
- Doses between 5 and 15 g are reported to lead to relaxation and analgesic effects [88].

Higher doses reported to have more chances of more side effects.

- Effects of Kratom are generally reported 5–7 h after use and optimal effects are felt within 2–4 h [88].

- **Adverse Effects:**

- Most common side effects.

Constipation [88, 90].

Nausea [88, 90].

Vomiting [88, 90].

Stomach irritation [88, 90].

Drowsiness [88, 90].

- Dizziness [88, 91].
- Sedation [88, 91].
- Liver problems [88, 91].
- Seizure [88, 91].

- Biggest concern of Kratom is its potential for dependence and addiction in humans which have raised big concerns regarding its usage.
- A proposal that was made stated that a large amount of Kratom use can be used as an alternative for more harmful substances such as narcotics [89].

There is convincing evidence that shows Kratom has less potential for addiction and overdose than original opioids [89].

Little evidence showing that Kratom is a good substitute with the same traditional effects [89].

- Due to Kratom being an unregulated supplement, it can have numerous risks.

Reported documentation of Kratom being mixed with synthetic substances such as phenylethylamine which has resulted in death [89].

In 2018, there has been epidemiology and laboratory proof that Kratom was the source of a multi-state salmonella outbreak [89].

- Kratom mixed with other illicit substances has been linked to several organ system injuries such as

Kidney injury [88, 92].

- Acute kidney injury [88, 92].

Cardiotoxicity [88, 93].

- Arrhythmias [88, 93].

Thyroid [88, 94].

Respiratory [88, 95].

Reproductive [88, 96].

- Neonatal abstinence syndrome [88, 96, 97].

Hepatic (most common) [88, 98].

- Elevated alkaline phosphatase and bilirubin [88, 98].

Neurologic [88, 99].

- Acute brain injury, seizure, cognitive impairment [88, 99].

- Centers for Disease Control and Prevention has shown that in 2016 and 2017 that Kratom was linked to 152 deaths [89].
- Important to know that Kratom does have some therapeutic effects but can quickly cause harmful effects if not used correctly or mixed with other substances of abuse [89].

- **Interactions with Medications:**

- Kratom should be cautioned if consumed with alcohol or opioids [88].
 - Especially with benzodiazepines which can cause respiratory depression [88].
 - Combine with stimulants because Kratom has stimulant effects as well [88].
- A study shows that Kratom has Cytochrome P450 enzyme activity [88, 100].
 - Increases the likelihood of herb-drug interaction with drugs that also are associated with Cytochrome P450 activity [88, 100].
- A study shows that the alkaloid portion of Kratom is an agonist from Alpha 2 adrenergic receptors [88, 101].
 - This can result to accentuation and can lead to more dangerous side effects if mixed with sedative, hypnotic, and analgesic drugs [88, 101].
- An in vitro study showed that Kratom mixed with erythromycin, loperamide, and protease inhibitors can lead to Kratom toxicity [88, 102].

Kava Kava

- **What Is It?**

- Kava is a type of perennial shrub that belongs to the pepper family known as Piperaceae [103].
 - It has commonly been grown in regions of Micronesia, Polynesia, and Melanesia [103].
 - Consumed in its traditional form as a drink [103].

- **How Does It Work in the Body, Usage, and Evidence?**

- Known for its effects as a pain reliever, muscle relaxant and anxiety remedy, nervousness, insomnia, and anti-inflammatory [103].
 - The mechanisms of Kava Kava that cause these effects require further exploration and validation [103].
- Anti-inflammatory.
 - Kava Kava has been studied and shown to have anti-inflammatory processes by inhibiting TNF-Alpha secretion [103, 104].
- Anxiolytic.
 - Kava Kava has been shown to be used to treat generalized anxiety disorder [103].

Number of studies have shown that Kava Kava can be an alternative to benzodiazepines and selective serotonin re-uptake inhibitors for patients that have been diagnosed with mild-to-moderate anxiety [103].

- Other benefits

Kava Kava had a study done to show that it can be used to treat epilepsy [103, 105].

Studies by Stein showed that Kava Kava can reduce cravings for people with substance abuse [103, 106].

- Substances including
 - Alcohol [103, 106].
 - Tobacco [103, 106].
 - Cocaine [103, 106].
 - Heroin [103, 106].

Kava has been shown to have benefits in recognition memory tasks and enhanced accuracy and performance in visual attention and working memory task [103, 107].

Kava has been noted to improve sleep but warrants future research to prove theory [103].

- **Dosage:**

- The recommended daily dose for an adult is typically one to three capsules with a daily dose of 60–250 mg for 1–2 months to notice effects [103].
- Clinical trials have shown that Kava was efficacious within the daily dose range of 20–300 mg Kavalactones for mild-and-moderate anxiety [103].

- **Adverse Effects:**

- Reports showing that four separate instances that drivers in Iowa were unable to operate a vehicle due to sedative effects, but the amount of Kava taken was unknown [103].
- Reported cases of liver issues [103].

Elevated AST, ALT, ALP, LDH, and Bilirubin [103].

- **Interactions with Medications:**

- No known interaction with other medications has been found but that does not mean they do not exist [103].
- Further investigation is needed [103].

Khella Baldi

- **What Is It?**

- Also known as Ammi Visnaga [108].
- An herb indigenous to the Mediterranean region of the North Africa, Asia, and Europe [108].

- **How Does It Work in the Body, Usage, and Evidence?**

- It has been known to treat renal colic and coronary insufficiency [108].
- Its flavonoid content is the main ingredient for its antioxidant properties [108].
- Studies have shown its use in the treatment of mild obstruction of the respiratory tract in asthma or spastic bronchitis and post op removal of kidney stones [108].
- It has also been used to dilate bronchial, urinary, and blood vessels without affecting blood pressure [108].
- Infusion of the aerial parts have been used to treat headaches [108].
- In its use in kidney disorders, it is commonly coupled with Khellin and Visnadin which are major properties of Khella Baldi [108].

These have been shown to prevent renal epithelial cell damage caused by oxalate and calcium oxalate monohydrate crystals. It achieves this through increasing urinary pH and citrate concentration thus preventing oxalate formation [108–113].

- In antispasmodic and vasodilating effects.

Contains properties that inhibits the contractile responses that mediate by Ca entry through L-type Ca channels and at high concentrations along with interfering with other sites involved with vascular smooth muscle contraction [108, 115–120].

Can treat angina pectoris due to peripheral and coronary vasodilator according to several research studies [108, 114].

Vasodilating effects are attributed to Khellin and Visnadin which have calcium antagonistic properties [108, 114].

- Calcium is used for vasoconstriction.
- Hair loss.

In a study, topical Khella Baldi has been used to increase in arterial and arteriolar activity which increased microcirculatory flow [108, 121].

- **Dosage:**
 - Daily recommended doses range from 0.05 to 0.15 g [108].
- **Adverse Effects:**
 - Advised to be avoided during pregnancy [108].
 - Also advised that people receiving Khella treatment are not exposed to direct sunlight [108].

- **Interactions:**

- No studies have shown any adverse effects with Khella but more studies have to be done in order to make this conclusion [108].

Lecithin

- **What Is It and How Does It Work in the Body?**

- Lecithin is a mixture comprised of choline, choline esters, fatty acids, glycerol, glycolipids, triglycerides, phosphoric acid, and phospholipids. It is a compound that is found in animals and vegetables. Some examples include red meat, eggs, peanuts, and oranges. In the body, it was found that lecithin, specifically in athletes can help reduce choline levels in the plasma that increase during physical stress [122]. There is also some evidence that it can help in certain conditions due to its properties of phosphatidylcholine and lipids although its exact mechanism is not yet fully understood. For example, in CNS disorders, phosphatidylcholine is a precursor for acetylcholine and higher levels can result in improved memory [123].

- **What Is It Used for and at What Dosage?**

- Lecithin can be used for athletic performance, CNS disorders, contact lenses, diabetes, GI conditions, lactation, menopause, and muscle atrophy. In patients with bipolar disorder, a dose of 10 mg three times daily was seen to decrease hallucinations, delusions, and improved speech [124]. In memory disorders, studies have been performed to measure if high doses of 20–25 g per day of lecithin result in better outcomes in memory disorders [125]. In neurologic disorders with acetylcholine deficiency, studies have been performed with doses from 25 g per day to 50–60 g per day [126].

- **Evidence for or Against Its Different Uses (Broken Down by Evidence for Each Use):**

- For Alzheimer patients, it was found that there may be a window in which lecithin can help [125], however in a multicenter study, where tacrine and lecithin were used, there was no improvement in mental status [127]. In one study, ten patients with Friedrich ataxia improved [128]. However, in a Cochrane review, there was no difference between placebo and lecithin in management of antipsychotic induced tardive dyskinesia [129]. In contact lenses, there was a study done to evaluate the effects of ocular lipid-based supplements on ocular comfort. There was no correlation between ocular comfort and lipid layers [129]. In a study looking at the dietary intake of phosphatidylcholine on type 2 diabetes, there was an associated lower risk of type II diabetes development in men [130]. Lecithin has anti-inflammatory and antioxidant properties as it can function as a protective component of colonic

mucus that can increase the intestinal hydrophobic barrier. This is essential in ulcerative colitis patients who have a loss in intestinal integrity. There is very limited evidence in lecithin uses for hypercholesterolemia, lactation, liver disease, menopause, and muscle atrophy. However, there is some evidence to show that supplementing lecithin can influence bile secretion and decrease cardiovascular risk [131].

- **Safety Concerns, Side Effects, and Precautions:**

- Generally, there are not many safety concerns with lecithin when used in moderation. However, in large doses of more than 25 g/day, there are short-term side effects of gastrointestinal stress, sweating, salivation, or anorexia [132].

- **Interactions with Medications:**

- Interactions are not well studied or documented yet in the literature.

Licorice

- **What Is It and How Does It Work in the Body?**

- Licorice, or *Glycyrrhiza glabra*, is comprised of triterpenoids, polyphenols, and polysaccharides. It works in the body through its anti-inflammatory and antiviral effects. Some studies have found that in animal studies, components of licorice can clear immune complexes thus decreasing inflammation [133]. In terms of antiviral properties, licorice is used to inhibit the virus from binding to the host membrane and replicating. Some studies have observed licorice-induced interferon production through T-cells [134].

- **What Is It Used for and at What Dosage?**

- Licorice can be used for cardiac use, diabetes, and endocrine uses. For cardiac use, effects are seen at 50–200 g/day [135].
- Licorice extract syrup was used in patients with Parkinson's Disease at a dose of 136 mg twice daily [136]. In some women, licorice has been used in conjunction with spironolactone in the treatment of polycystic ovarian syndrome [137]. For ulcer gastritis, or nonalcoholic fatty liver disease, licorice root has been used at a dose of 760 mg to 15 g [138].

- **Evidence for or Against Its Different Uses (Broken Down by Evidence for Each Use):**

- For blood pressure, licorice has been seen to increase blood pressure without changes in heart rate [135]. It was observed that of the 30 of the 39 patients that completed the trial of patients with Parkinson's Disease there was significant improvement of total disease, motor, daily activities, tremor, and rigidity

[136]. For hot flashes, patients taking 1140 mg/day noted a significant reduction in hot flashes [139]. For metabolic effects, licorice has been shown to reduce weight [135].

- **Safety Concerns, Side Effects, and Precautions:**

- When licorice is consumed at normal consumption levels, few side effects are observed. For example, if consumed in large doses, can cause hypertension. At high doses, vasospasm of the optic nerve blood vessels has been observed [140]. Hypersensitivity reactions have been noted as well [134]. Licorice can also have effect of exacerbating heart failure and should be used with caution in patients on anticoagulation [141].

- **Interactions with Medications:**

- Licorice has several interactions with other medications where it can increase the toxic effects of certain agents. For example, licorice can enhance the effects of anticoagulants and increase bleeding. Bleeding can also occur with some NSAIDs and salicylates [142]. Licorice can also increase the effect of loop and thiazide diuretics [143].

Lingonberry

- **What Is It and How Does It Work in the Body?**

- Lingonberry is from the berry family and it is found in Central Europe, Russia, and Canada. Lingonberry is classified as a “superfruit” as it is rich in antioxidants and polyphenols. In terms of how it works in the body, the lingonberry can decrease oxidants in the body, induce cell apoptosis and cancer cell proliferation, decrease cytokines, and decrease markers of inflammation [144].

- **What Is It Used for and at What Dosage?**

- Lingonberry is used for its antioxidant properties, anticancer activity, neuroprotection, anti-obesity, and anti-inflammatory properties. For antioxidant benefit, studies have shown that fresh and dried lingonberry consumed throughout the whole year can significantly reduce oxidants. One study found that dried lingonberry has greater antioxidant ability than its fresh counterpart [145]. At different doses, lingonberry can have different uses. At small doses of 1–5 mg/mL, lingonberry can decrease oxidative stress and increase adiponectin [144]. At medium doses of freeze-dried lingonberry for 13 weeks, for example, it can decrease body fat and hepatic lipid and ALT levels [146]. In terms of neuroprotection, lingonberry extract of 1 mL can protect cells from injury [147].

- **Evidence for or Against Its Different Uses (Broken Down by evidence for Each Use):**

- In its main use as an antioxidant, several studies have been performed to measure this. Drozdz et al. found that blueberries exhibited higher antioxidant activity.
 - However, the authors concluded that both would be a good source of supplementation [145]. In animal models, it has been found that lingonberries can reduce tumor number and size [148]. It has been seen however, consumption of the lingonberry is more helpful if consumed for longer as part of a lifestyle instead of for a limited time [144].
- **Safety Concerns, Side Effects, and Precautions:**
 - Studies on Lingonberry have not been performed on pregnant individuals and thus should be avoided. Due to high tannins, lingonberry may cause nausea and vomiting in some individuals [149].
 - **Interactions with Medications:**
 - Currently, there is no evidence of studies performed on interactions with other medications.

Liverwort

- **What Is It and How Does It Work in the Body?**
 - Liverwort is also known as agrimony and works in the body through a hepatoprotective and antioxidant mechanism. In terms of hepatoprotection, it is shown in animal data to increase levels of a TLR4 receptor and protein expression to induce nitric oxide synthase and COX2. As a result, it is likely able to suppress oxidative stress [150]. In a clinical trial performed in Korea, 80 adults with elevated ALT levels were given liverwort extract. Compared to placebo, those adults had reduction in their ALT levels [151]. In a clinical trial with 19 volunteers where liverwort was added to hot tea, there was significant elevation of plasma total antioxidant capacity [152].
- **What Is It Used for and at What Dosage?**
 - In terms of use, it is used for flavoring and a soothing tea for performers and speakers. Although it has been clinically investigated in small groups, there is no indication yet for liverwort. Dosing of liverwort is about 200 mL of boiled water with 1 g of dried liverwort. This should be consumed twice a day for about 1 month [152].
- **Evidence for or Against Its Different Uses (Broken Down by Evidence for Each Use):**
 - In terms of uses, liverwort can be used for analgesia, infection, antioxidant, cancer, cardioprotective, diabetes, and hepatoprotection. In animal models,

liverwort extract was seen to improve analgesia as effectively as gabapentin [153]. In the use of fighting infection, in animal models, liverwort extract was able to show antibacterial activity against *E. coli* [154] as well as antiviral activity as it interfered with viral entry into the cell [155]. For the use of anti-oxidant and cancer use, there is some clinical data to suggest that liverwort can increase the antioxidant level in the body [152]. In terms of cardiac protection, in animal models, it has been seen that liverwort can prolong clotting time [156]. In terms of diabetes, liverwort was studied in animal models showed significant improvement in insulin levels and insulin resistance after 16 weeks [157]. Lastly, in terms of hepatoprotection, liverwort was seen to reduce ALT levels [151].

- **Safety Concerns, Side Effects, and Precautions:**

- There have been reports that liverwort can produce photodermatitis [158].

- **Interactions with Medications:**

- Interactions are not well documented yet in the literature.

Lobelia Inflata

- **What Is It and How Does It Work in the Body?**

- *Lobelia inflata* is a plant that grows in Canada and the northern United States. In the body, it is used for tobacco cessation. In terms of mechanism, lobeline has affinity to nicotinic acetylcholine receptors [159].

- **What Is It Used for and at What Dosage?**

- *Lobelia inflata* has been used for smoking cessation, asthma, and bronchitis. In terms of dosage, it has been administered as an expectorant from 100 mg of dry herb up to three times a day. In history, lobelia was used like tobacco leaves and was smoked for respiratory illnesses. It was also used for nausea and emesis [160]. In 1993, it was banned over the counter for smoking cessation by the FDA [161].

- **Evidence for or Against Its Different Uses (Broken Down by evidence for Each Use):**

- There is clinical data for the use of Lobelia for tobacco cessation, CNS effects, and respiratory effects. For tobacco cessation, results have been controversial as some studies have shown lobeline to be effective, but a meta-analysis found that all previous studies could not adequately prove this [162]. Thus, the FDA removed lobeline products from its list. In terms of CNS effects, a study was performed measuring the effect of lobeline, methylphenidate, and placebo on cohort of individuals with ADHD. It found that there was no difference with

lobeline; however, the sample size was limited [163]. There is also some evidence to show lobeline can be used for heroin abuse [164]. Lastly, in terms of respiratory effects, positive effects were seen on pulmonary receptors using bolus doses [165].

- **Safety Concerns, Side Effects, and Precautions:**

- There is safety concern of the dosage of the supplement. A dose of 1 g of the plant is toxic and 4 g of the plant is fatal [158].

- **Interactions with Medications:**

- Interactions of lobelia with other medications or supplements are not well documented.

Lutein

- **What Is It and How Does It Work in the Body?**

- Lutein is a xanthophyll carotenoid that works as an antioxidant and blue light filter. In the body, it functions to protect ocular tissues [166]. In animal studies, it inhibits monocyte-mediated inflammation and protects against macular degeneration [167].

- **What Is It Used For and at What Dosage?**

- In terms of use, although with limited data, lutein can potentially be used for age-related macular degeneration and cataracts. There is possible use for cancer and cardiovascular health. For dosing, 5 mg daily or 10–20 mg daily for 3–6 months has been studied in clinical trials [168].

- **Evidence for or Against Its Different Uses (broken down by evidence for Each Use):**

- In terms of use, lutein can be used for eye health and cancer. One study performed in China observed 121 patients who supplemented their diet with 20 mg per day of lutein. It found that there was significant improvement in the central macular pigment optical density [169]. In a meta-analysis of six studies, researchers found a significant correlation of lutein reducing the risk of early age-related macular degeneration [168]. Evidence also shows some association between lutein and age-related cataracts; however, the results are mixed. For example, one meta-analysis shows lutein significantly reduced the risk of cataracts [170]. This contrasts with another meta-analysis which found that lutein and zeaxanthin had a significant reduction in nuclear cataracts but not cortical or subscapular [171]. There was no difference found between lutein supplementation and retinitis pigmentosa [172]. Likewise, there was no

correlation between lutein and its protection of retinopathy of prematurity [173]. There is still limited to no clinical trials of lutein and cancer.

- **Safety Concerns, Side Effects, and Precautions:**

- Generally, there are no safety concerns of lutein in the body.

- **Interactions with Medications:**

- There are no studied interactions with medications. However, beta-carotene and lutein may compete for absorption and cause lower levels of lutein [174].

Lysine

- **What Is It and How Does It Work in the Body?**

- Lysine is an amino acid that is found in fish, eggs, meat, and legumes. Lysine in the body works to antagonize herpes simplex virus growth [175]. It also works to build collagen for bone growth. It can increase the growth of osteoblasts as well [176].

- **What Is It Used for and at What Dosage?**

- Lysine is used for protein production. Its catabolism occurs in the liver and then is transported to the muscle for use. Clinically, lysine has been shown to prevent and treat herpes simplex virus. There is also some new evidence to suggest lysine can aid in stress, hypertension, muscle strength, and diabetes. For oral dosing, lysine is given from 3 to 6 g for up to 1 year [175].

- **Evidence for or Against Its Different Uses (Broken Down by Evidence for Each Use):**

- Lysine has been used in several studies for the treatment of herpes infections or cold sores. In one study, patients were given 500 mg daily of lysine for prevention and 1000 mg every 6 h upon prodrome development. In this study, only 1 out of 28 subjects did not see a benefit [177]. However, there are contrasting studies which show no benefit. For example, in a study of 31 patients with herpes simplex, there was no reduction of episodes with 750 mg daily of lysine [178].

- **Safety Concerns, Side Effects, and Precautions:**

- Possible side effects of lysine include abdominal pain, diarrhea, and acid reflux [179]. Very high doses are thought to be safe in patients due to fast activation of its use in the liver [180]. However, due to interactions with other medications or in patients with poor blood circulation, lysine may have a nephrotoxic effect [181]. Thus, lysine should be used with caution in patients with ischemia or preexisting renal disease [178].

- **Interactions with Medications:**

- Lysine is seen to interact with calcium supplements and aminoglycosides. Calcium with lysine supplementation can result in increased calcium absorption and decrease of calcium elimination. Aminoglycosides may increase toxicity of lysine [182].

References

Sources for Hawthorn

1. Memorial Sloan Kettering Cancer Center. Hawthorn. 2022. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/hawthorn>. Accessed 26 Apr 2022.
2. Pfaf.org. Crataegus Species—The Hawthorns. 2022. <https://pfaf.org/user/cmsspage.aspx?pageid=59>. Accessed 26 Apr 2022.
3. Chang Q, Zuo Z, Harrison F, Chow M. Hawthorn. J Clin Pharmacol. 2002;42(6):605–12.
4. The Pharmacopoeia Commission of PRC. Pharmacopoeia of the People's Republic of China, vol. 1. English ed. Beijing: Chemical Industry Press; 1997.
5. Leung AY, Foster S. Encyclopedia of common natural ingredients: used in food, drugs, and cosmetics. 2nd ed. New York, NY: John Wiley; 1996.
6. Rigeltsky J, Sweet B. Hawthorn: pharmacology and therapeutic uses. Am J Health Syst Pharm. 2002;59(5):417–22.
7. Nazhand A, Lucarini M, Durazzo A, Zaccardelli M, Cristarella S, Souto S, Silva A, Severino P, Souto E, Santini A. Hawthorn (*Crataegus* spp.): an updated overview on its beneficial properties. Forests. 2020;11(5):564.
8. Trexler SE, Nguyen E, Gromek SM, Balunas MJ, Baker WL. Electrocardiographic effects of hawthorn (*Crataegus oxyacantha*) in healthy volunteers: A randomized controlled trial. Phytother Res. 2018;32(8):1642–1646. <https://doi.org/10.1002/ptr.6094>. Epub 2018 Apr 19. PMID: 29672935.
9. Webmd.com. Hawthorn: overview, uses, side effects, precautions, interactions, dosing and reviews. 2022. <https://www.webmd.com/vitamins/ai/ingredientmono-527/hawthorn>.

Sources for Hazelnut

10. Secretariat. *Corylus avellana*—EUFORGEN European forest genetic resources programme. [Euforgen.org](https://www.euforgen.org/species/corylus-avellana/). 2022. <https://www.euforgen.org/species/corylus-avellana/>.
11. Full report (all nutrients): 12120, nuts, hazelnuts or filberts. USDA Food Data Central. 2015.
12. Webmd.com. Hazelnut: Overview, uses, side effects, precautions, interactions, dosing and reviews. 2022. <https://www.webmd.com/vitamins/ai/ingredientmono-865/hazelnut>.
13. Medicinenet.com. 2022. <https://www.medicinenet.com/hazelnut/supplements-vitamins.htm>.
14. Mollica A, Zengin G, Stefanucci A, Ferrante C, Menghini L, Orlando G, Brunetti L, Locatelli M, D'Immito M, Novellino E, Wakeel O, Ogundeleji M, Onaolapo A, Onaolapo O. Nutraceutical potential of *Corylus avellana* daily supplements for obesity and related dysmetabolism. J Funct Foods. 2018;47:562–74.

Sources for Hemp Seed/Oil

15. WebMD. Health benefits of hemp seed oil. 2022. <https://www.webmd.com/diet/health-benefits-hemp-seed-oil>.

16. Ostapeczuk K, Apori S, Estrada G, Tian F. Hemp growth factors and extraction methods effect on antimicrobial activity of hemp seed oil: a systematic review. *Separations*. 2021;8(10):183.
17. Aluko RE. Chapter 7—Hemp seed (*Cannabis sativa L.*) proteins: composition, structure, enzymatic modification, and functional or bioactive properties. In: Sustainable protein sources. San Diego, CA: Academic Press; 2017. p. 121–32.
18. Verywell Health. What is hemp? 2022. <https://www.verywellhealth.com/hemp-benefits-side-effects-dosage-and-interactions-4767355>.
19. Cho KS, Lim YR, Lee K, Lee J, Lee JH, Lee IS. Terpenes from forests and human health. *Toxicol Res*. 2017;33(2):97–106. <https://doi.org/10.5487/TR.2017.33.2.097>.
20. Callaway J, Schwab U, Harvima I, Halonen P, Mykkänen O, Hyvönen P, Järvinen T. Efficacy of dietary hempseed oil in patients with atopic dermatitis. *J Dermatolog Treat*. 2005;16(2):87–94. <https://doi.org/10.1080/09546630510035832>. PMID: 16019622.

Sources for Horny Goat Weed

21. Efloras.org. Epimedium in Flora of China @ efloras.org. http://www.efloras.org/florataxon.aspx?flora_id=2&taxon_id=111847.
22. Memorial Sloan Kettering Cancer Center. Epimedium. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/epimedium>.
23. Healthline. Does horny goat weed work for ED? <https://www.healthline.com/health/erectile-dysfunction/horny-goat-weed#what-is-it>.
24. Shindel A, Xin Z, Lin G, Fandel T, Huang Y, Banie L, Breyer B, Garcia M, Lin C, Lue T. Erectogenic and neurotrophic effects of icariin, a purified extract of horny goat weed (*Epimedium* spp.) in vitro and in vivo. *J Sex Med*. 2010;7(4):1518–28.
25. Ma H, He X, Yang Y, Li M, Hao D, Jia Z. The genus Epimedium: an ethnopharmacological and phytochemical review. *J Ethnopharmacol*. 2011;134(3):519–41.
26. Partin J, Pushkin Y. Tachyarrhythmia and hypomania with horny goat weed. *Psychosomatics*. 2004;45(6):536–7. <https://doi.org/10.1176/appi.psy.45.6.536>.
27. Yang L, Lu D, Guo J, Meng X, Zhang G, Wang F. Icariin from *Epimedium brevicornum maxim* promotes the biosynthesis of estrogen by aromatase (CYP19). *J Ethnopharmacol*. 2013;145(3):715–21.

Sources for HMB

28. Memorial Sloan Kettering Cancer Center. HMB. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/hmb>.
29. Asghari Hanjani N, Farsi F, Sepidarkish M, Omidi A, Ardehali S, Akbari-Fakhrabadi M, Heshmati J. Effect of supplementation with a combination of L-arginine, L-glutamine, and hydroxy methyl butyrate on cachexia: a systematic review. *J Food Biochem*. 2018;42(6):e12636.
30. Healthline. Hydroxymethylbutyrate (HMB): Benefits, downsides, and more. <https://www.healthline.com/nutrition/hmb#safety-dosage-and-recommendations>.
31. Webmd.com. Hydroxymethylbutyrate (HMB): Overview, uses, side effects, precautions, interactions, dosing and reviews. <https://www.webmd.com/vitamins/ai/ingredientmono-45/hydroxymethylbutyrate-hmb>.
32. Asjodi F, Izadi A. The Effects of 8 Weeks Beta-Hydroxy-Beta-Methylbutyrate (HMB) Supplementation on Body Composition, Inflammatory Response and Muscle Damage After Eccentric Exercise in Untrained Males. *Progr Nutr*. 2019;21(1-S):184–190.

Sources for I3C

33. Webmd.com. Indole-3-carbinol: Overview, uses, side effects, precautions, interactions, dosing and reviews. <https://www.webmd.com/vitamins/ai/ingredientmono-1027/indole-3-carbinol>.

34. Memorial Sloan Kettering Cancer Center. Indole-3-carbinol. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/indole-3-carbinol>.
35. Reed G. A phase I study of indole-3-carbinol in women: tolerability and effects. *Cancer Epidemiol Biomarkers Prevent.* 2005;14(8):1953–60.
36. Weng J, Tsai C, Kulp S, Chen C. Indole-3-carbinol as a chemopreventive and anti-cancer agent. *Cancer Lett.* 2008;262(2):153–63.
37. Katz E, Nisani S, Chamovitz D. Indole-3-carbinol: a plant hormone combatting cancer. *F1000Res.* 2018;7:689.

Sources for Inosine

38. Srinivasan S, Torres A, Ribas de Pouplana L. Inosine in biology and disease. *Genes.* 2021;12(4):600.
39. Webmd.com. Inosine: Overview, uses, side effects, precautions, interactions, dosing and reviews. 2022. <https://www.webmd.com/vitamins/ai/ingredientmono-704/inosine>.
40. Kerksick C, Wilborn C, Roberts M, Smith-Ryan A, Kleiner S, Jäger R, Collins R, Cooke M, Davis J, Galvan E, Greenwood M, Lowery L, Wildman R, Antonio J, Kreider R. ISSN exercise and sports nutrition review update: research and recommendations. *J Int Soc Sports Nutr.* 2018;15(1):38.
41. Chen P, Goldberg D, Kolb B, Langer M, Benowitz L. Inosine induces axonal rewiring and improves behavioral outcome after stroke. *Proc Natl Acad Sci.* 2002;99(13):9031–6.

Sources for Inositol Nicotinate

42. Go.drugbank.com. Inositol nicotinate: Uses, interactions, mechanism of action | DrugBank Online. <https://go.drugbank.com/drugs/DB08949>.
43. Webmd.com. Inositol nicotinate: Overview, uses, side effects, precautions, interactions, dosing and reviews. <https://www.webmd.com/vitamins/ai/ingredientmono-742/inositol-nicotinate>.
44. Memorial Sloan Kettering Cancer Center. Niacin. <https://www.mskcc.org/cancer-care/patient-education/niacin>.
45. Rxlist.com. https://www.rxlist.com/inositol_nicotinate/supplements.htm#UsesAndEffectiveness.
46. Pope JE. Raynaud's phenomenon (primary). *BMJ Clin Evid.* 2008;2008:1119. Published 2008 Dec 16

Sources for Ipriflavone

47. Civitelli R. In vitro and in vivo effects of ipriflavone on bone formation and bone biomechanics. *Calcif Tissue Int.* 1997;61(S1):S12–4.
48. Pubchem.ncbi.nlm.nih.gov. Ipriflavone. <https://pubchem.ncbi.nlm.nih.gov/compound/ipriflavone>.
49. Isteroids.com. Ipriflavone. <https://www.isteroids.com/bodybuilding/Ipriflavone.html#:~:text=Ipriflavone%20is%20believed%20to%20one%20of%20the%20most,body%20It%20does%20not%20come%20with%20any%20side-effects>.
50. Webmd.com. Ipriflavone: Overview, Uses, side effects, precautions, interactions, dosing and reviews. <https://www.webmd.com/vitamins/ai/ingredientmono-310/ipriflavone>.
51. Hu Q, Long C, Wu D, You X, Ran L, Xu J, Klineberg EO, Huang S, Chen J, Ning N. The efficacy and safety of ipriflavone in postmenopausal women with osteopenia or osteoporosis: a systematic review and meta-analysis. *Pharmacol Res.* 2020;159:104860.
52. Sansai K, Na Takuathung M, Khatsri R, Teekachunhatean S, Hanprasertpong N, Koonrungsesomboon N. Effects of isoflavone interventions on bone mineral density in post-

menopausal women: a systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int.* 2020;31(10):1853–64.

Sources for Iodine

53. Ods.od.nih.gov. Office of dietary supplements-iodine. <https://ods.od.nih.gov/factsheets/Iodine-Consumer/>.
54. Bioscience Notes. Synthesis of thyroid hormones—bioscience notes. <https://bioscience-notes.com/synthesis-f-thyroid-hormones/>.
55. Memorial Sloan Kettering Cancer Center. Potassium iodide and iodine. <https://www.mskcc.org/cancer-care/patient-education/potassium-iodide-and-iodine-01>.
56. Webmd.com. Iodine: Overview, uses, side effects, precautions, interactions, dosing and reviews. <https://www.webmd.com/vitamins/ai/ingredientmono-35/iodine>.
57. Dineva M, Fishpool H, Rayman M, Mendis J, Bath S. Systematic review and meta-analysis of the effects of iodine supplementation on thyroid function and child neurodevelopment in mildly-to-moderately iodine-deficient pregnant women. *Am J Clin Nutr.* 2020;112:389–412.
58. Velasco I, Bath SC, Rayman MP. Iodine as Essential Nutrient during the First 1000 Days of Life. *Nutrients* 2018;10:290. <https://doi.org/10.3390/nu10030290>.

Sources for Iron

59. Ods.od.nih.gov. Office of dietary supplements—iron. <https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/>.
60. Kenneth R, Bridges M. Hemoglobin synthesis. [Sickle.bwh.harvard.edu](https://sickle.bwh.harvard.edu/hbsynthesis.html). <https://sickle.bwh.harvard.edu/hbsynthesis.html>.
61. Webmd.com. Iron: Overview, uses, side effects, precautions, interactions, dosing and reviews. <https://www.webmd.com/vitamins/ai/ingredientmono-912/iron>.
62. Camaschella C. Iron deficiency. *Blood*. 2019;133(1):30–9.
63. Stoffel N, von Siebenthal H, Moretti D, Zimmermann M. Oral iron supplementation in iron-deficient women: how much and how often? *Mol Asp Med.* 2020;75:100865.
64. Campbell N. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med.* 1992;117(12):1010.

Sources for Java Tea

65. Orthosiphon Stamineus (Java Tea). <http://umpir.ump.edu.my/id/eprint/22482/1/Gimbun%202019.pdf>. Accessed 1 Oct 2022.
66. Yuliana ND, Khatib A, Link-Struensee AMR, Ijzerman AP, Rungkat-Zakaria F, Choi YH, Verpoorte R. Adenosine A1 receptor binding activity of methoxy flavonoids from Orthosiphon Stamineus. *Planta Med.* 2009;75:132–5.
67. Zhong YS, Yu CH, Ying HZ, Wang ZY, Cai HF. Prophylactic effects of Orthosiphon Stamineus Benth extracts on experimental induction of calcium oxalate nephrolithiasis in rats. *J Ethnopharmacol.* 2012;144:761–7.
68. Yam MF, Ang LF, Salman IM, Ameer OZ, Lim V, Ong LM, Ahmad M, Asmawi MZ, Basir R. Orthosiphon stamineus leaf extract protects against ethanol-induced gastropathy in rats. *J Med Food.* 2009;12:1089–97.
69. Adam Y, Somchit MN, Sulaiman MR, Nasaruddin AA, Zuraini A, Bustamam AA, Zakaria ZA. Diuretic properties of orthosiphon stamineus Benth. *J Ethnopharmacol.* 2009;124:154–8.

Sources for Jimson Weed

70. Kit C. Jimson weed poisoning—A case report. *Perm J.* 2002;6:28–30. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6220643/#b2-permj-6-4-28>. Accessed 1 Oct 2022

71. Soni P, et al. Pharmacological properties of *Datura Stramonium L.* as a potential medicinal tree: An overview. *Asian Pac J Trop Biomed.* 2012;2:1002–8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3621465/#b17>. Accessed 10 Oct 2022
72. Information Packaging Unlimited. Jimson weed. http://www.infopackaging.com/IPUweb/On-Line_Services/adic/jweed.htm. Accessed 23 Sept 2002.
73. Pretorius E, Marx J. *Datura stramonium* in asthma treatment and possible effects on prenatal development. *Environ Toxicol Pharm.* 2006;21(3):331–7.

Sources for Jojoba

74. Gad HA, et al. Jojoba oil: An updated comprehensive review on chemistry, pharmaceutical uses and toxicity. *Polymers (Basel).* 2021;13(11):1711. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8197201/#B11-polymers-13-01711>. Accessed 10 Oct 2022
75. Pazyar N, Yaghoobi R, Ghassemi MR, Kazerouni A, Rafeie E, Jamshydian N. Jojoba in dermatology: a succinct review. *G Ital Dermatol Venereol.* 2013;148:687–91.
76. Abdel-Mageed WM, Bayoumi SA, Salama AA, Salem-Bekhit MM, Abd-Alrahman SH, Sayed HM. Antioxidant lipoxygenase inhibitors from the leaf extracts of *Simmondsia chinensis*. *Asian Pac J Trop Med.* 2014;7:S521–6.
77. Miwa TK. Structural determination and uses of jojoba oil. *J Am Oil Chem Soc.* 1984;61:407.
78. Baldwin AR, American Oil Chemists' Society. Seventh International Conference on Jojoba and Its Uses: Proceedings. Champaign, IL: American Oil Chemists' Society; 1988. p. 453p.
79. Ranzato E, Martinotti S, Burlando B. Wound healing properties of jojoba liquid wax: an in vitro study. *J Ethnopharmacol.* 2011;134:443–9.
80. Baccouch N, Ben SH, Belhadj S, Hentati O, Abdennabi R, Gharsallah N, Elfeki A, Ayedi M, Allouche N. Chemical characterization and biological activities of *Simmondsia chinensis* (Link) C. K. Schneid seeds oil. *Cell Mol Biol.* 2018;64:11–6.

Sources for Juniper

81. Bais S, et al. A phytopharmacological review on a medicinal plant: *Juniperus communis*. *Int Sch Res Notices.* 2014;2014:634723. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4897106/>. Accessed 12 Oct 2022
82. Manvi, Garg G. P. Screening and evaluation of pharmacognostic, phytochemical and hepatoprotective activity of *J. communis* L. stems. *Int J Pharma Bio Sci.* 2010.
83. Hoferl M, Stoilova I, Schmidt E, et al. Chemical composition and antioxidant properties of Juniper Berry (*J. communis* L.) Essential oil. Action of the essential oil on the antioxidant protection of *Saccharomyces cerevisiae* model organism. *Antioxidants.* 2014;3:81–98.
84. Banerjee S, Singh H, Chatterjee TK. Evaluation of anti-diabetic and anti-hyperlipidemic potential of methanolic extract of *Juniperus Communis* (L.) in streptozotocininduced diabetic rats. *Int J Pharm Bio Sci.* 2013;4:P10–7.
85. Banerjee S, Mukherjee A, Chatterjee TK. Evaluation of analgesic activities of methanolic extract of medicinal plant *Juniperus communis* Linn. International. *J Pharm Pharm Sci.* 2012;547–50.
86. Sati SC, Joshi S. Antibacterial potential of leaf extracts of *Juniperus communis* L. from Kumaun Himalaya. *Afr J Microbiol Res.* 2010;4(12):1291–4.
87. Raina R, et al. Potential of *Juniperus communis* L as a nutraceutical in human and veterinary medicine. *Heliyon.* 2019;5:e02376. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6726717/>. Accessed 12 Oct 2022

Sources for Kratom

88. Swogger MT, et al. Understanding Kratom use: a guide for healthcare providers. *Front Pharmacol.* 2022;13:801855. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8924421/>. Accessed 12 Oct 12 2022
89. Eastlack SC, et al. Kratom–pharmacology, clinical implication, and outlook: a comprehensive review. *Pain Ther.* 2020;9:55–69. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7203303/>. October 12, 2022
90. Grundmann O. Patterns of Kratom use and health impact in the US—results from an online survey. *Drug Alcohol Depend.* 2017;176:63–70.
91. Swogger MT, Walsh Z. Kratom use and mental health: a systematic review. *Drug Alcohol Depend.* 2018;183:134–40.
92. Ilmie MU, Jaafer H, Mansor SM, Abdullah JM. Subchronic toxicity study of standardized methanolic extract of *Mitragyna speciosa* Korth in Sprague-Dawley rats. *Front Neurosci.* 2015;9:189.
93. Lu J, Wei H, Wu J, Jamil MFA, Tan ML, Adenan MI, et al. Evaluation of the cardiotoxicity of mitragynine and its analogues using human induced pluripotent stem cell-derived cardiomyocytes. *PLoS One.* 2014;9:e115648.
94. Sheleg SV, Collins GB. A coincidence of addiction to “Kratom” and severe primary hypothyroidism. *J Addict Med.* 2011;5(4):300–1.
95. Pathak V, Hahn C, Cabellon M, Aris R. Adult respiratory distress syndrome secondary to the use of herbal drug Kratom. *Am J Respir Crit Care Med.* 2014;189:A6492.
96. Murthy P, Clark D. An unusual cause for neonatal abstinence syndrome. *Paediatr Child Health.* 2019;24:12–4.
97. Davidson L, Rawat M, Stojanovski S, Chandrasekharan P. Natural drugs, not so natural effects: neonatal abstinence syndrome secondary to “Kratom”. *J Neonatal Perinatal Med.* 2019;12:109–12.
98. Fernandes CT, Iqbal U, Tighe SP, Ahmed A. Kratom-induced cholestatic liver injury and its conservative management. *J Investig Med High Impact Case Rep.* 2019;7:232470961983613.
99. Burke D, Shearer A, Van Cott A. Two cases of provoked seizure associated with Kratom Ingestion (P4.5–030). *Neurology.* 2019;92:P4–5.
100. Hanapi NA, Ismail S, Mansor SM. Inhibitory effect of mitragynine on human cytochrome P450 enzyme activities. *Pharm Res.* 2013;5(4):241–6.
101. Prozialeck WC, Jivan JK, Andurkar SV. Pharmacology of Kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. *J Am Osteopath Assoc.* 2012;112(12):792–9.
102. Rusli N, Amanah A, Kaur G, Adenan MI, Sulaiman SF, Wahab HA, et al. The inhibitory effects of mitragynine on P-glycoprotein in vitro. *Naunyn Schmiedeberg's Arch Pharmacol.* 2019;392(4):481–96.

Sources for Kava Kava

103. Bian T, et al. Kava as a clinical nutrient: promises and challenges. *Nutrients.* 2020;12(10):3044. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7600512/>. Accessed 12 Oct 2022
104. Huck O, Han X, Mulhall H, Gumenchuk I, Cai B, Panek J, Iyer R, Amar S. Identification of a Kavain analog with efficient anti-inflammatory effects. *Sci Rep.* 2019;9:12940.
105. Cairney S, Maruff P, Clough AR. The neurobehavioural effects of kava. *Aust N Z J Psychiatry.* 2002;36:657–62.
106. Steiner GG. Kava as an anticonvulsant: preliminary data. *Pac Health Dialog.* 2001;8:335–9.
107. Münte TF, Heinze HJ, Matzke M, Steitz J. Effects of oxazepam and an extract of kava roots (*piper methysticum*) on event-related potentials in a word recognition task. *Neuropsychobiology.* 2004;27:46–53.

Sources for Khella

108. Khalil N, et al. AMMI Visnaga L., a potential medicinal plant: a review. *Molecules*. 2020;25(2):301. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7024292/>. Accessed 14 Oct 2022
109. Vanachayangkul P. Ammi visnaga L. for the Prevention of Urolithiasis. Ph.D. Thesis. University of Florida; Gainesville, FL; 2008.
110. Vanachayangkul P, Byer K, Khan S, Butterweck V. An aqueous extract of Ammi visnaga fruits and its constituents khellin and visnagin prevent cell damage caused by oxalate in renal epithelial cells. *Phytomedicine*. 2010;17:653–8.
111. Charafi S, Kzaiber F, Hafid A, Berkani M, Oussama A. Study of Ammi visnaga Lam on oxalocalcic crystallization. *Glob J Tradit Med Sys*. 2012;1:7–12.
112. Nagal A, Singla RK. Herbal resources with antiurolithiatic effects: a review. *Indo Glob J Pharm Sci*. 2013;3:6–14.
113. Nirumand MC, Hajialyani M, Rahimi R, Farzaei MH, Zingue S, Nabavi SM, Bishayee A. Dietary plants for the prevention and management of kidney stones: preclinical and clinical evidence and molecular mechanisms. *Int J Mol Sci*.
114. Balandrin MF, Kinghorn AD, Farnsworth NR. Human medicinal agents from plants. In: Plant-derived natural products in drug discovery and development, vol. 534. Washington, DC: American Chemical Society; 1993. p. 2–12.
115. Rauwald HW, Brehm O, Odenthal KP. The involvement of a Ca²⁺ channel blocking mode of action in the pharmacology of Ammi visnaga fruits. *Planta Med*. 1994;60:101–5.
116. Duarte J, Vallejo I, Perez-Vizcaino F, Jimenez R, Zarzuelo A, Tamargo J. Effects of visnadin on rat isolated vascular smooth muscles. *Planta Med*. 1997;63:233–6.
117. Venugopala KN, Rashmi V, Odhav B. Review on natural coumarin lead compounds for their pharmacological activity. *BioMed Res Inter*. 2013;2013:1–14.
118. Ubeda A, Tejerina T, Tamargo J, Villar A. Effects of khellin on contractile responses and 45Ca²⁺ movements in rat isolated aorta. *J Pharm Pharmacol*. 1991;43:46–8.
119. Campos-Toimil M, Orallo F, Santana L, Uriarte E. Synthesis and vasorelaxant activity of new coumarin and furocoumarin derivatives. *Bioorg Med Chem Lett*. 2002;12:783–6.
120. Tripathi Y, Pandey A. Bioprospecting of phytodiversity for new therapeutic products: trends, potential and challenges. *Org Med Chem*. 2017;2:1–7.
121. Curri SB, Bombardelli E. Pharmaceutical compositions having activity on the cutaneous microcirculation. 5,176,919. US patent. 1 May 1993.

Sources for Lecithin, Licorice, Lingonberry, Liverwort, Lobelia inflata, Lutein, and Lysine

122. Von Allworden HN, Horn S, Kahl J, Feldheim W. The influence of lecithin on plasma choline concentrations in triathletes and adolescent runners during exercise. *Eur J Appl Physiol Occup Physiol*. 1993;67:87–91.
123. Pringsheim T, Doja A, Gorman D, McKinlay D, Day L, Billinghurst L, Carroll A, Dion Y, Luscombe S, Steeves T, Sandor P. Canadian guidelines for the evidence-based treatment of tic disorders: pharmacotherapy. *Can J Psychiatr*. 2012;57:133–43.
124. Cohen BM, Lipinski JF, Altesman RI. Lecithin in the treatment of mania: double-blind, placebo-controlled trials. *Am J Psychiatry*. 1982;139:1162–4.
125. Levy R. Tacrine and lecithin in Alzheimer's disease. Patient heterogeneity explains varied response. *BMJ*. 1994;308:1506. author reply 1507
126. Pentland B, Martyn CN, Steer CR, Christie JE. Lecithin treatment in Friedreich's ataxia. *Br Med J (Clin Res Ed)*. 1981;282:1197–8.

127. Chatellier G, Lacomblez L. Tacrine (tetrahydroaminoacridine; tha) and lecithin in senile dementia of the alzheimer type: a multicentre trial. *Groupe français d'étude de la tetrahydroaminoacridine.* BMJ. 1990;300:495–9.
128. Melancon SB, Dallaire L, Potier M, Vanasse M, Marois P, Geoffroy G, Barbeau A. Oral lecithin and linoleic acid in friedreich's ataxia: I. Design of the study, material and methods. *Can J Neurol Sci.* 1982;9:151–4.
129. Rohit A, Willcox MD, Stapleton F. Lipid supplements and clinical aspects of tear film in habitual lens wearers. *Optom Vis Sci.* 2017;94:174–82.
130. Virtanen JK, Tuomainen TP, Voutilainen S. Dietary intake of choline and phosphatidylcholine and risk of type 2 diabetes in men: the Kuopio ischaemic heart disease risk factor study. *Eur J Nutr.* 2020;59:3857–61.
131. Leblanc MJ, Brunet S, Bouchard G, Lamireau T, Yousef IM, Gavino V, Levy E, Tuchweber B. Effects of dietary soybean lecithin on plasma lipid transport and hepatic cholesterol metabolism in rats. *J Nutr Biochem.* 2003;14:40–8.
132. Potter M, Moses A, Wozniak J. Alternative treatments in pediatric bipolar disorder. *Child Adolesc Psychiatr Clin N Am.* 2009;18:483–514, xi
133. Chen M, Zhu J, Kang J, Lai X, Gao Y, Gan H, Yang F. Exploration in the mechanism of action of licorice by network pharmacology. *Molecules.* 2019;24:2959.
134. Isbrucker RA, Burdock GA. Risk and safety assessment on the consumption of licorice root (*glycyrrhiza sp.*), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. *Regul Toxicol Pharmacol.* 2006;46:167–92.
135. Sigurjonsdottir HA, Wallerstedt S. Licorice—much more than candy. *Lakartidningen.* 2015;112:DC49.
136. Petramfar P, Hajari F, Yousefi G, Azadi S, Hamed A. Efficacy of oral administration of licorice as an adjunct therapy on improving the symptoms of patients with Parkinson's disease, a randomized double blinded clinical trial. *J Ethnopharmacol.* 2020;247:112226.
137. Armanini D, Nacamulli D, Francini-Pesenti F, Battaglin G, Ragazzi E, Fiore C. Glycyrrhetic acid, the active principle of licorice, can reduce the thickness of subcutaneous thigh fat through topical application. *Steroids.* 2005;70:538–42.
138. Hajighamohammadi AA, Zargar A, Oveisip S, Samimi R, Reisian S. To evaluate of the effect of adding licorice to the standard treatment regimen of helicobacter pylori. *Braz J Infect Dis.* 2016;20:534–8.
139. Menati L, Khaleghinezhad K, Tadayon M, Siahpoosh A. Evaluation of contextual and demographic factors on licorice effects on reducing hot flashes in postmenopause women. *Health Care Women Int.* 2014;35:87–99.
140. Santaella RM, Fraunfelder FW. Ocular adverse effects associated with systemic medications : recognition and management. *Drugs.* 2007;67:75–93.
141. Page RL 2nd, O'bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, Spencer AP, Trupp RJ, Lindenfeld J, American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Drugs that may cause or exacerbate heart failure: a scientific statement from the American heart association. *Circulation.* 2016;134:e32–69.
142. Stanger MJ, Thompson LA, Young AJ, Lieberman HR. Anticoagulant activity of select dietary supplements. *Nutr Rev.* 2012;70:107–17.
143. Hukkanen J, Ukkola O, Savolainen MJ. Effects of low-dose liquorice alone or in combination with hydrochlorothiazide on the plasma potassium in healthy volunteers. *Blood Press.* 2009;18:192–5.
144. Kowalska K. Lingonberry (*vaccinium vitis-idaea l.*) fruit as a source of bioactive compounds with health-promoting effects-a review. *Int J Mol Sci.* 2021;22:5126.

145. Drozdz P, Seiene V, Wojcik J, Pyrzynska K. Evaluation of bioactive compounds, minerals and antioxidant activity of lingonberry (*vaccinium vitis-idaea L.*). *Fruits Molecules*. 2017;23:53.
146. Heyman L, Axling U, Blanco N, Sternier O, Holm C, Berger K. Evaluation of beneficial metabolic effects of berries in high-fat fed c57bl/6j mice. *J Nutr Metab*. 2014;2014:403041.
147. Hossain MZ, Shea E, Daneshtalab M, Weber JT. Chemical analysis of extracts from new-foundland berries and potential neuroprotective effects. *Antioxidants (basel)*. 2016;5:36.
148. Misikangas M, Pajari AM, Paivarinta E, Oikarinen SI, Rajakangas J, Marttinen M, Tanayama H, Torronen R, Mutanen M. Three nordic berries inhibit intestinal tumorigenesis in multiple intestinal neoplasia/+ mice by modulating beta-catenin signaling in the tumor and transcription in the mucosa. *J Nutr*. 2007;137:2285–90.
149. Brendler T, Gruenwald J, Ulbricht C, Basch E, Natural Standard Research Collaboration. Devil's claw (*harpagophytum procumbens dc*): an evidence-based systematic review by the natural standard research collaboration. *J Herb Pharmacother*. 2006;6:89–126.
150. Yoon SJ, Koh EJ, Kim CS, Zee OP, Kwak JH, Jeong WJ, Kim JH, Lee SM. *Agrimonia eupatoria* protects against chronic ethanol-induced liver injury in rats. *Food Chem Toxicol*. 2012;50:2335–41.
151. Cho YM, Kwon JE, Lee M, Lea Y, Jeon DY, Kim HJ, Kang SC. *Agrimonia eupatoria l.* (agrimony) extract alters liver health in subjects with elevated alanine transaminase levels: a controlled, randomized, and double-blind trial. *J Med Food*. 2018;21:282–8.
152. Ivanova D, Vankova D, Nashar M. *Agrimonia eupatoria* tea consumption in relation to markers of inflammation, oxidative status and lipid metabolism in healthy subjects. *Arch Physiol Biochem*. 2013;119:32–7.
153. Lee KH, Rhee KH. Anti-nociceptive effect of *agrimonia eupatoria* extract on a cisplatin-induced neuropathic model. *Afr J Tradit Complement Altern Med*. 2016;13:139–44.
154. McMurray RL, Ball MEE, Tunney MM, Corcionivoschi N, Situ C. Antibacterial activity of four plant extracts extracted from traditional chinese medicinal plants against *listeria monocytogenes*, *escherichia coli*, and *salmonella enterica* subsp. *Enterica serovar enteritidis*. *Microorganisms*. 2020;8:962.
155. Lee YG, Kang KW, Hong W, Kim YH, Oh JT, Park DW, Ko M, Bai YF, Seo YJ, Lee SM, Kim H, Kang SC. Potent antiviral activity of *agrimonia pilosa*, *galla rhois*, and their components against sars-cov-2. *Bioorg Med Chem*. 2021;45:116329.
156. Fei X, Yuan W, Jiang L, Wang H. Opposite effects of *agrimonia pilosa ledeb* aqueous extracts on blood coagulation function. *Ann Transl Med*. 2017;5:157.
157. Jang HH, Nam SY, Kim MJ, Kim JB, Choi JS, Kim HR, Lee YM. *Agrimonia pilosa ledeb*. Aqueous extract improves impaired glucose tolerance in high-fat diet-fed rats by decreasing the inflammatory response. *BMC Complement Altern Med*. 2017;17:442.
158. USDA. Plants database. 2021. Accessed 3 Oct 2022.
159. Damaj MI, Patrick GS, Creasy KR, Martin BR. Pharmacology of lobeline, a nicotinic receptor ligand. *J Pharmacol Exp Ther*. 1997;282:410–9.
160. Bolyard JL. Medicinal plants and home remedies of appalachia. Springfield, IL: Thomas; 1981.
161. FDA. Drug products containing active ingredients offered over the counter (otc) for use as a smoking deterrent. FDA website. 2019. Accessed 3 Oct 2022.
162. Glover ED, Rath JM, Sharma E, Glover PN, Lafin M, Tonnesen P, Repsher L, Quiring J. A multicenter phase 3 trial of lobeline sulfate for smoking cessation. *Am J Health Behav*. 2010;34:101–9.
163. Martin CA, Nuzzo PA, Ranseen JD, Kleven MS, Guenthner G, Williams Y, Walsh SL, Dwoskin LP. Lobeline Effects on Cognitive Performance in Adult ADHD. *J Atten Disord*. 2018;22(14):1361–1366. <https://doi.org/10.1177/1087054713497791>. Epub 2013 Aug 21. PMID: 23966351; PMCID: PMC4062608
164. Hart N, Rocha A, Miller DK, Nation JR. Dose-dependent attenuation of heroin self-administration with lobeline. *J Psychopharmacol*. 2010;24:51–5.

165. Anand A, Roy A, Bhargava B, Raj H, Barde PB, Vijayan VK. Early symptom-relief after valvulotomy in mitral stenosis indicates role of lobeline-sensitive intrapulmonary receptors. *Respir Physiol Neurobiol.* 2009;169:297–302.
166. Granado F, Olmedilla B, Blanco I. Nutritional and clinical relevance of lutein in human health. *Br J Nutr.* 2003;90:487–502.
167. Trumbo PR, Ellwood KC. Lutein and zeaxanthin intakes and risk of age-related macular degeneration and cataracts: an evaluation using the food and drug administration's evidence-based review system for health claims. *Am J Clin Nutr.* 2006;84:971–4.
168. Ma L, Lin XM. Effects of lutein and zeaxanthin on aspects of eye health. *J Sci Food Agric.* 2010;90:2–12.
169. Yao Y, Qiu QH, Wu XW, Cai ZY, Xu S, Liang XQ. Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. *Nutrition.* 2013;29:958–64.
170. Cui YH, Jing CX, Pan HW. Association of blood antioxidants and vitamins with risk of age-related cataract: a meta-analysis of observational studies. *Am J Clin Nutr.* 2013;98:778–86.
171. Liu XH, Yu RB, Liu R, Hao ZX, Han CC, Zhu ZH, Ma L. Association between lutein and zeaxanthin status and the risk of cataract: a meta-analysis. *Nutrients.* 2014;6:452–65.
172. Adackapara CA, Sunness JS, Dibernardo CW, Melia BM, Dagnelie G. Prevalence of cystoid macular edema and stability in oct retinal thickness in eyes with retinitis pigmentosa during a 48-week lutein trial. *Retina.* 2008;28:103–10.
173. Hammond BR Jr. Possible role for dietary lutein and zeaxanthin in visual development. *Nutr Rev.* 2008;66:695–702.
174. Van Den Berg H, Van Vliet T. Effect of simultaneous, single oral doses of beta-carotene with lutein or lycopene on the beta-carotene and retinyl ester responses in the triacylglycerol-rich lipoprotein fraction of men. *Am J Clin Nutr.* 1998;68:82–9.
175. Griffith RS, Delong DC, Nelson JD. Relation of arginine-lysine antagonism to herpes simplex growth in tissue culture. *Cancer Chemotherapy.* 1981;27:209–13.
176. Torricelli P, Fini M, Giavaresi G, Giardino R, Gnudi S, Nicolini A, Carpi A. L-arginine and l-lysine stimulation on cultured human osteoblasts. *Biomed Pharmacother.* 2002;56:492–7.
177. Wright EF. Clinical effectiveness of lysine in treating recurrent aphthous ulcers and herpes labialis. *Gen Dent.* 1994;42:40–2; quiz 51–2.
178. Simon CA, Van Melle GD, Ramelet AA. Failure of lysine in frequently recurrent herpes simplex infection. *Arch Dermatol.* 1985;121:167–8.
179. Kalogeropoulou D, Lafave L, Schweim K, Gannon MC, Nuttall FQ. Lysine ingestion markedly attenuates the glucose response to ingested glucose without a change in insulin response. *Am J Clin Nutr.* 2009;90:314–20.
180. Flodin NW. The metabolic roles, pharmacology, and toxicology of lysine. *J Am Coll Nutr.* 1997;16:7–21.
181. Lo JC, Chertow GM, Rennke H, Seifter JL. Fanconi's syndrome and tubulointerstitial nephritis in association with l-lysine ingestion. *Am J Kidney Dis.* 1996;28:614–7.
182. Tomblin FA Jr, Lucas KH. Lysine for management of herpes labialis. *Am J Health Syst Pharm.* 2001;58(298–300):304.

Chapter 4

Maca–Pyridoxine (Vitamin B6)



Alana Weisstuch

Maca

- **What is it?**
 - Maca is a herbaceous plant [1].
- **How does it work in the body?**
 - Some studies have shown that maca has a hormonal effect on post-menopausal women and healthy adult males [2, 3]. When taken, maca can stimulate luteinizing hormone, inhibit the production of follicle-stimulating hormone, and allow for the production of androgen. This process can in turn, improve sexual function [1].
- **What is it used for?**
 - While more research is needed, maca can be used to improve stamina and sexual functioning in post-menopausal women. Further research is still needed for the claims of treating infertility [1].
- **Precautions/side effects:**
 - Maca should not be used in those with hormone-sensitive cancers. Side effects can include disruption in menstrual cycles, mood, sleep, and GI upset [1].
- **Evidence for and against:**

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- One systematic review by Shin et al. concluded that more research is needed to determine the exact effectiveness of maca on the improvement of sexual function. Two of the randomized control trials studied did show a positive significant effect on sexual dysfunction; however, two additional studies did not show any clinically significant effect [1, 2].
- A meta-analysis studied the effect of maca on sexual function. Of the studies, three main groups of subjects were included: post-menopausal women, healthy men, men with erectile dysfunction and a small group of male athletes. It was concluded that the current data for supplementation of maca is insufficient. Further research is needed to clinically support the prescription of maca supplementation for sexual function [4].

- **Dosage:**

- The recommended dosage of maca is pending more research. However, one double blind randomized study showed a significant improvement in sexual dysfunction when taking 3 g/day [2, 3].

- **Adverse effects:**

- No comprehensive studies have shown definitive adverse side effects of maca supplementation [1, 3].

- **Interactions:**

- There are no known significant medication interactions with maca supplementation [5].

Magnesium

- **What is it?**

- Magnesium is a chemical element which has many different functions within the body. Magnesium is a cofactor for more than 300 enzyme reactions [6].

- **What is it used for?**

- Magnesium can be used to reduce asthma symptoms, help prevent cancer, and improve CAD, DM, depression, fatigue, HTN, leg cramps, migraines, osteoporosis, and premenstrual syndrome [6].

- **How does it work in the body?**

- Magnesium can help reduce mineral deposits into arteries. Magnesium can increase the activity of TRPM7 receptors which can then increase the effect of anticalcification proteins [6].

- Magnesium is an essential component for the conversion of Vitamin D to its active form. This conversion allows for optimal calcium absorption, metabolism, and normal parathyroid hormone function [6].
- Magnesium can have an effect on blood pressure through its functions as a calcium channel blocker by decreasing vascular resistance, and by changing vascular tone and reactivity [6].
- Magnesium can decrease the rigidness of arteries in those with CAD [6].
- For those with diabetes, magnesium can act as a cofactor on the metabolism of insulin and glucose [6].
- Magnesium can act as an anti-inflammatory agent by controlling the activation of NF- κ B activation and the production of cytokin [6].
- Magnesium can be used as a laxative by its ability to absorb water in the intestines [6].
- Magnesium can play a role in cancer prevention through its role of maintaining genetic stability, regulating cell proliferation, protecting against insulin resistance, oxidative stress, and inflammation. On the contrary, low levels of magnesium have been shown to inhibit the growth of tumors. Overall, more research is needed.

- **Evidence for and against:**

- Magnesium has been shown to have a positive effect on preventing osteoporosis [7]. Supplementation was associated with decreased fractures and increased bone density [7]. It is noted that exceedingly high and low levels have shown to be harmful to bone health [7].
- Magnesium may have a positive effect on depression or mood as it is essential for the conversion of tryptophan to serotonin [7].
- Magnesium can be used as a sleep aid, as it acts as an antagonist on NMDA and inversely acts as an agonist on GABA [7].
- One randomized double blind placebo controlled study showed magnesium supplementation stimulates insulin production [8].
- A case control study showed that those who had a diet rich in magnesium had a lower likelihood of colorectal tumors [9].
- Those who took magnesium for 1 year along with medical treatment for heart failure had improved life expectancy and improvement in side effects [10].
- A meta-analysis conducted in 2016 concluded that magnesium supplementation of 300 mg for 1 month may reduce blood pressure in those with hypertension, however, further research is needed [11].
- A review conducted in 2002 studied pregnant women with leg cramps. Those who supplemented magnesium had the best outcome of reduction in leg cramps when compared to calcium, sodium chloride, or multivitamins [12].
- Adults with low intake of magnesium may be at increased risk for asthma. A randomized control trial showed improvement in asthma symptoms in those supplemented with magnesium [13].
- A systematic review by Whelan showed no significant improvement of PMS symptoms with magnesium supplementation [14].

- One double blind placebo controlled study showed that magnesium sulfate supplementation had a positive effect on migraines [15].

- **Interactions with medications:**

- When aminoglycosides are taken with magnesium, it can increase the risk of causing neuromuscular weakness and/or paralysis [16].
- Magnesium may reduce the ability of the body to properly absorb certain types of antibiotics (quinolone, tetracycline, and nitrofurantoin). It is recommended to leave at least an hour between medications [16].
- Magnesium can cause dizziness, nausea, or fluid retention when taken with calcium channel blockers [16].
- Antacids contain magnesium hydroxide which can increase absorption of medications used to regulate blood sugar [16].
- Magnesium can hinder absorption of fluoroquinolones, when taken together. Leaving at least 4 h between taking the two, can decrease the risk of poor absorption [16].
- When magnesium and labetalol are taken together, it could slow heart rate or reduce heart function [16].
- When magnesium and levomethadyl are taken together, there is risk for QT prolongation [16].
- Magnesium can hinder the absorption of these tiludronate and alendronate [16].

- **Dosage:**

- The RDAs for adult males and females are listed below [17]:

Males, 19–30 years of age: 400 mg daily.

Females, 19–30 years of age: 310 mg daily.

Males, 31 years of age and over: 420 mg daily.

Females, 31 years of age and over: 320 mg daily.

- In various studies, the following dosages have been shown to be beneficial [18]:

Relieving asthma symptoms (~350–450 mg).

Migraines (360–600 mg/day).

HTN (>480 mg/day).

- **Adverse reactions:**

- Magnesium can cause GI distress (such as nausea or diarrhea), abdominal pain, or bone pain [6].

- **Precautions/safety concern:**

- Magnesium and calcium compete for absorption. When supplementing with magnesium, it is important to check calcium levels in order to minimize risk of calcium deficiency [16].

Magnolia

- **What is it?**

- Magnolia is an herb, traditionally used in Chinese medicine. The flower and the bark of the herb exhibit different functions. The bark is mainly used to relieve symptoms of anxiety, depression, or improve diabetes and the flower is used for congestion or sinus headaches [19].

- **How it works in the body?**

- Magnolol and honokiol are the active compounds of Magnolia, they can possibly reduce inflammation [20].

- **Evidence for and against:**

- *DM*: More research in humans is crucial to prove the clinical effect of magnolia on diabetes. In mice studies, magnolia may have an effect on regulating crucial transporters of insulin production which then decreases blood glucose levels [21, 22].
 - *Depression*: In rats, the active compounds of magnolia bark, have been shown to regulate corticosterone levels and platelet adenylyl cyclase which are both markers of depression [23].
 - *Anxiety*: In mice, honokiol may stimulate GABA-A receptors which can decrease anxiety [24].
 - *Cancer*: Magnolia bark has been shown to decrease/inhibit many pathways of cancer cell expression via binding to receptors/regulatory proteins [20].
 - *Congestion/headaches*: The flower of magnolia may be used for relieving symptoms of congestion or sinus headaches [19].

- **Interactions with medications:**

- Honokiol may inhibit the action of the following drugs by inhibiting or altering crucial enzymes [20].

CYP450 substrates.
UDP-glucuronosyltransferases.
P-Glycoprotein substrates.

- Because magnolol can show antiplatelet activities, it can increase the risk of bleeding when taking antiplatelet agents [20].
 - Lab studies showed that magnolia bark extract can be used as an anti-diabetic agent by lowering blood glucose levels [20].
 - Magnolia bark extract and honokiol may increase the effects of benzodiazepines [20].

- **Safety concerns, side effects, and precautions:**

- Magnolia can cause contact dermatitis [20].

- Magnolia should not be taken with sleep, anxiety, diabetic medications, or blood thinners as it can increase the effects [20].

- **Dosage:**

- Dosage of the Magnolia bark extract varies from 200 to 800 mg/day [19].

Manganese

- **What is it?**

- Manganese is a trace mineral that is found in small quantities throughout the body. Magnesium is mostly found in bones and the main vital organs (kidneys, pancreas, and liver) [25].

- **How does it work in the body?**

- Manganese plays a role in many bodily functions such as formation (bones, blood clotting factors, sex hormones, connective tissue), metabolism (fat, carbohydrates), absorption (calcium), and regulation (blood sugar). It is also imperative for the functioning of the brain and nerves. Lastly, manganese helps in the process of neutralizing free radicals as it is a component of the antioxidant enzyme superoxide dismutase (SOD) [25].

- **What is it used for?**

- Manganese can be used as an antiepileptic, help decrease symptoms of osteoporosis, increase levels of SOD, and decrease PMS symptoms [25].

- **Evidence for and against:**

- *Osteoporosis*: A study showed that Mn can possibly decrease bone loss for post-menopausal women (in conjunction with An, Cu, and Ca) [25]. No significant clinical evidence that manganese can prevent osteoporosis [25].
 - *Arthritis*: More research is needed to study the relationship between the production of SOD and manganese supplementation [25].
 - *PMS*: One study showed that patients with PMS had lower levels of manganese in their blood [26].
 - *DM*: Some studies show that people with diabetes have low levels of Mn [27]. It is unclear if having diabetes lowers Mn, or if low levels in blood allow for the development of diabetes [27].
 - *Epilepsy*: Some studies show that people with seizures have low levels of Mn. It is unclear if having seizures lowers Mn, or if low levels in blood allow for the development of seizures [25].

- **Safety concerns, side effects, and precautions:**

- Higher manganese supplementation, requires more calcium and phosphorus ingestion as they all work together in the body [25].
- When supplementing manganese orally, side effects are rare. Toxicity can occur if an individual is routinely exposed to manganese vapors or in those receiving intravenous nutrition (containing Mn) for an extended period of time [25].

Toxicity symptoms include: hallucinations, appetite loss, headaches, uncontrolled muscle movements, extreme irritability, and leg cramps or muscle stiffness [25].

- **Interactions with medications:**

- When taking Haloperidol with Mn in individuals with liver disease, hallucinations, and behavioral disturbances may occur. Antipsychotics could worsen side effects of Mn supplementation [25].
- Some blood pressure medications may decrease serum manganese levels [25].
- Antacids or laxatives containing magnesium can lessen the effectiveness of manganese supplementation. It may be beneficial to separate intake of magnesium and manganese by ~1–2 h [25].
- Certain antibiotics and manganese can interfere with each other's absorption (i.e., tetracycline and quinolone). It may be beneficial to separate intake of the antibiotic and manganese by ~1–2 h [25].

- **Dosage:**

- Manganese supplementation should not exceed 10 mg/day. The AI for men older than 19 is 2.3 mg and for women older than 19 is 1.8 mg [25].

Mangosteen

- **What is it?**

- Mangosteen is a tropical plant mainly found in Southeast Asia [28].

- **What is it used for?**

- In traditional eastern medicine, mangosteen is used to heal wounds, treat diarrhea, and improve skin infections [28]. Mangosteen has also been shown to reduce inflammation, stop the growth of some cancer cells, decrease damage of LDL, and decrease infections (bacterial, fungal) [28].

- **How it works in the body?**

- Mangosteen may reduce inflammation and damage of LDL.

- **Safety concerns, side effects, and precautions:**

- Mangosteen can cause significant lactic acidosis ingestion and exacerbate colitis (in mice) [29, 30].
- **Interactions with medications:**
 - Mangosteen can act as an antioxidant and interfere with chemotherapy [28]. Could also interact with Cytochrome P450 substrates [28].
- **Evidence for or against its different uses:**
 - Mangosteen contains xanthones alpha, beta-mangostins, and garcinone which can hinder the development of mycobacterium tuberculosis [31].
 - Limited research exists on the effect of mangosteen in humans. One animal study may reduce inflammation for asthma [32].
 - In vitro, mangosteen may weaken enzymes and LDL production which can reduce damage of LDL [33]. It is important to note that further studies on human subjects are crucial in order to make a clinical claim on the effectiveness of mangosteen on cholesterol.
 - In animal subjects, isogarcinol, a compound of mangosteen, may exhibit anti-inflammatory effects [34].
 - Mangosteen xanthones may act as a chemoprotective agent against cancer cells [28].
 - In a randomized, double blind, placebo control clinical trial completed in 2015, mangosteen was seen to have antioxidant and anti-inflammatory effects [35].

Medium Chain Triglycerides (MCT)

- **What is it?**
 - MCTs are made of three fatty acid chains (6–12 carbons long) which are attached to a glycerol particle. MCTs are readily available for absorption into the GI tract and bloodstream [36, 37].
- **What is it used for?**
 - MCT is utilized for the management of GI disorders (malabsorptive disorders—pancreatic insufficiency, chyle leaks, short bowel syndrome). MCT has also been shown to reduce CAD, epilepsy, Alzheimer's disease, and obesity [37].
- **How it works in the body?**
 - The digestion and absorption of MCTs is a faster process when compared to long chain triglycerides. MCT does not stimulate CCK and is absorbed through passive diffusion. MCT attaches to albumin and travels from the GI

tract into the portal system. Following this step, no further changes of the MCT model are required [37].

- **Evidence for and against:**

- A review conducted in 2016 does not show enough evidence to support that MCT oil decreases the risk of cardiovascular risk [38].
- Further research is needed on a large scale in order to prove the effect of MCT oils on Alzheimer's disease [39].
- A randomized control trial concluded that an MCT-rich diet can have the same effect as a ketogenic diet on epilepsy [40].
- Intake of MCTs has a greater effect on reducing body weight when compared to long chain triglycerides [41].

- **Safety concerns, side effects, and precautions:**

- When taking large amounts of MCT oil, GI distress can occur (bloating, diarrhea, cramping, gas).
- When cooking with MCT, the temperature should be <150 °C /302 °F. This allows for a reduction in oxidation and therefore, savors the taste of the food [37].
- When administering MCT oil through a feeding tube, it is important to flush the tube with water before and after [37].
- MCTs do not contain essential fatty acids; therefore, another source of essential fatty acids should be provided to the patient in order to prevent deficiency [37].

- **Dosage:**

- One tablespoon/15 mL of MCT oil = 14 g fat +115 kcal.
- Recommended maximum dose for improving GI disorders: 50–100 g/day (equivalent to ~4–7 tablespoons/60–100 mL/day). MCT supplementation should be slowly advanced to the maximum dose [37].

Melatonin

- **What is it?**

- Melatonin is a hormone that helps control the sleep cycle [42].

- **What is it used for?**

- The main use of melatonin is used to help symptoms of insomnia. It may also be effective for seasonal affective disorder, migraines, and reduce negative side effects of chemotherapy [43]. Melatonin has also been shown to reduce the risk of certain cancers (prostate, breast), act as a cardioprotective agent,

decrease chronic pain, and to reduce symptoms of irritable bowel syndrome, epilepsy, and sunburns [42, 43].

- **How does it work in the body?**

- Melatonin is produced by the pineal gland. The secretion of melatonin is regulated by the body's circadian rhythm. When there is sunlight, less melatonin is produced and when there is darkness, more melatonin is produced [42, 43].

- **Safety concerns, side effects, and precautions:**

- **Side effects:** Melatonin can cause headaches, drowsiness, trouble sleeping, disruptions in sleep patterns, nightmares, confusion/AMS, fast HR, red in face, itching, stomach cramps, low body temperature, dizziness, decreased libido, breast enlargement in men (gynecomastia), and reduced sperm count [42].
 - Melatonin is not recommended for women who are pregnant and/or nursing or those struggling with depression [42].

- **Possible interactions:**

- Could decrease the effects of antidepressants however further studies needed on humans to confirm this [43].
 - Birth control could raise melatonin levels in the body. Additional supplementation of melatonin could result in too high of melatonin buildup [43].
 - Melatonin can decrease the effectiveness of blood pressure medications or corticosteroids [43].
 - When taken in combination with anticoagulants, there is higher chance of bleeding [43].

- **Dose:**

- The typical adult dose of melatonin is 1–5 mg. Doses of 1 mg has been shown to be just as effective as higher doses [44].

- **Evidence for or against its different uses:**

- *Insomnia/sleep patterns:* A review showed individuals (<18 years old) with sleep-onset insomnia and ADHD melatonin was effective in treating insomnia [45]. A study of middle aged adults found that a prolonged release of melatonin can positively affect one's sleep schedule [46]. Melatonin can also be a useful agent to help combat jet-lag [47]. The majority of the studies included in a systematic review, found that upon arrival to the destination, it is best to take the melatonin close to the time of sleep [46].
 - *Seasonal affective disorder:* More clinical research is needed to prove the clinical effect of melatonin on seasonal affective disorder [48].
 - *Migraines/chronic pain:* A randomized control trial concluded that melatonin does not significantly help with migraine prevention [49].
 - *Reduce negative side effects of chemotherapy:* A randomized control trial was conducted to evaluate the effectiveness of melatonin supplementation on

chemotherapy side effects. One hundred subjects were randomized to either receive chemotherapy alone or chemotherapy in conjunction with melatonin. The subjects receiving melatonin had better outcomes such as longer survival rate and less chemotherapy side effects [50].

- *Cancers:* Melatonin has been shown to slow or stop the spread of breast cancer cells, prostate cancers, colon cancer, and slow tumor growth [51].
- *Irritable bowel syndrome:* Melatonin has been shown to decrease IBS-related symptoms in IBS patients [45, 52].
- *Epilepsy:* Broad and detailed research is still needed on the effects of melatonin on epilepsy. Research is split on if melatonin helps or hinders those with epilepsy [43].
- *Sunburns:* Sunburn ointments with infusion of melatonin may help heal sunburns, however, further research is needed [43].

Methionine

- **What is it?**

- Methionine is a key amino acid needed for proper growth and maturation. It helps with metabolism and stress resistance by acting as a precursor for the pathways [53].

- **How does it work in the body?**

- *Methionine cycle:* Methionine and ATP produce S-adenosyl methionine (SAM). SAM acts as a methyl donor to molecules allowing for the production of S-adenosylhomocysteine (SAH). It is important that there are low levels of SAH in the cells and, therefore, S-adenosylhomocysteine hydrolase (SAHH/AHCY) breaks it apart. The breakdown of SAH forms adenosine and L-homocysteine. Homocysteine can then be remethylated to form methionine. Adequate functioning of the methionine cycle allows for proper growth and development [53].
- *Transsulfuration pathway:* Cysteine can be produced in the liver through the transsulfuration pathway by using the by-product of the methionine cycle, homocysteine. Cysteine is used for the production of certain proteins. An important by-product of this pathway is H₂S which has many important functions. H₂S can act as an antioxidant agent and helps to control inflammation, insulin release, neural communication, and muscle relaxation [53].
- *Salvage cycle:* Polyamines are produced from the regeneration of methionine from SAM. As one ages, polyamine levels are lower [53].

- **Dosage:**

- Methionine can be used for adults to increase acid in urine [54]:

Capsules: ~200 mg 3–4×/day.

Tablets: 500 mg 3–4×/day.

- **What is it used for?**

- Methionine can be used for the development and maintenance of lean body mass [55].

- **Safety concerns, side effects, and precautions:**

- Methionine is a precursor for homocysteine; therefore, excessive supplementation can lead to hyperhomocysteinemia which can put one at an increased risk for cardiovascular disease [55].

- **Medication interactions:**

- Methionine can decrease the effectiveness of levodopa; therefore, high doses of methionine should be avoided when taking the medication. If taken together, closely monitor for worsening clinical presentation and adjust dose as necessary [56].

- **Evidence for or against its different uses:**

- Human studies are limited on the effects of methionine supplementation. Most studies involving various animals are inconclusive on the effects of methionine supplementation. One study conducted on poultry concluded that the supplementation of methionine improved growth [57].

Milk Thistle

- **What is it?**

- Milk thistle is a plant, part of the asteraceae family. This herb primarily grows in places that are dry and sunny. The seed of milk thistle contains a chemical called silymarin, a flavonoid, which is the primary ingredient responsible for its medicinal effect. Milk thistle functions as an antioxidant and anti-inflammatory agent [58].

- **What is it used for [58]?**

- Milk thistle can be used to help treat alcohol or drug-induced liver damage, and viral hepatitis [58, 59].
 - Milk thistle can be used to reverse the poisonous effects of a death cap mushroom [58, 59].
 - The silymarin ingredient can be protective against cancer by preventing cell growth and decreasing the flow of blood to tumors [58, 59].

- **How does it work in the body?**

- Silymarin-phosphatidylcholine is a complex of silymarin that facilitates the attachment of the supplement to the cell membrane, allowing for better absorption than standard milk thistle. Once the complex attaches to the cell membrane, it can prevent toxins from entering the cell [58].

- **Safety concerns, side effects, and precautions:**

- **Side effects:** Milk thistle can cause GI disturbances and rashes [58].
- **Precautions/concerns:** Pregnant or breastfeeding women, individuals with hormone-related cancers, or with allergies to ragweed, chrysanthemums, marigolds, chamomile, yarrow, or daisies, should not use milk thistle [58].

- **Possible interactions:**

- Given milk thistle's action in the liver, it may interfere with drug metabolism of antipsychotics, phenytoin, halothane, birth control pills and/or hormone replacement therapy [58].

Milk thistle may interfere with allergy drugs, statins, anti-anxiety drugs, anticoagulants, and some cancer drugs [58].

- **Evidence for or against its different uses:**

- *Alcoholic or hepatitis-induced liver disease:* A systematic review including 13 randomized clinical trials, concluded that milk thistle supplementation does not significantly affect the clinical complications of histology of liver disease. However, there was significance in reduction of liver-related mortality [60].
- *Mushroom poisoning:* When given intravenously, Silibinin, a component of milk thistle, can help reduce the poisonous effects of the amanita mushroom. It does so by competing with the uptake at the liver [61].
- *Viral hepatitis:* A systematic review was conducted to assess the effect of milk thistle's chemical compound, silymarin, on individuals with hepatitis B and C. It was found that silymarin can lower levels of transaminase in the blood; however, there is no evidence of the effect on viral load or the liver [62].
- *Cancer:* A review concluded that milk thistle can be used for cancer prevention. In vitro and vivo studies have shown that silymarin can act as a chemoprotective agent, facilitate apoptosis in cancer cells, and potentially act as an anti-inflammatory agent. Overall, milk thistle may be useful to use as an adjunct therapy with chemotherapy [63].

- **Dosage:**

- Silymarin can be taken via capsules, tablets, tinctures, or intravenously. When taking silymarin for hepatoprotection a dosage of 420 mg three times a day for 6–8 weeks is recommended. When supplementing for maintenance, the recommended dosage is 280 mg/day. The recommended dosage for mushroom poisoning is 33 mg/kg/day for ~81.67 h via intravenous solution [64].

Myrtle

- **What is it?**
 - Myrtle is a plant most often found in Mediterranean regions. The berries, leaves, flowers, and essential oils of plants have been used in traditional medicines [65].
- **What is it used for?**
 - The myrtle plant can be taken for its antioxidant, anti-inflammatory, and antimicrobial effects. Additionally, it can be used to help treat GI disturbances (ulcers, diarrhea, reflux) and decrease hyperglycemia in diabetics. Although more studies are needed, myrtle plants can offer cardiovascular protection [65].
- **How does it work in the body?**
 - It is unknown how myrtle reacts in the human body.
- **Evidence:**
 - Evidence is extremely limited in the human population.

Antioxidant: Myrtle as an antioxidant has been studied in fish. A study conducted in 2017 concluded myrtle was found to produce higher levels of ghrelin (increasing appetite), improve lipid metabolism, and act as an antioxidant agent [66].

Anti-inflammatory: Myrtle has been found to exhibit anti-inflammatory effects; however, current studies are primarily assessing mice [67, 68].

Antimicrobial: Myrtle extracts have been shown to exhibit antibacterial effects by making the cell more permeable and allowing the contents inside the cell to leak out and elicit change. In one study, the extracts if myrtle, stopped the growth of Gram-positive bacteria, however, no effects were found for Gram-negative bacteria [69].

GI: Myrtle has also been found to have promising effects on gastrointestinal diseases, specifically in rats. The gastrointestinal benefits are thought to be related to myrtle's antioxidant effects [65].

DM: A study from 2019, assessed the effects of myrtle berry extract on diabetic rats. After ingestion, levels of hyperglycemia reduced [65].
- **Dosage:**
 - Recommended dosage in humans is not well enough studied to provide recommendations.
- **Interactions:**
 - No well-studied medication interactions.

N-Acetyl-L-Cysteine

- **What is it?**

- Cysteine is an amino acid. The supplemental form taken is *N*-acetyl-L-cysteine (NAC) which the body breaks down into cysteine [70].

- **How does it work in the body?**

- After the body breaks down *N*-acetyl-L cysteine to make cysteine, it further breaks down into glutathione which functions as an antioxidant [70].

- **What is it used for?**

- The main use is to help prevent kidney and liver damage in acetaminophen overdose patients. NAC is typically given intravenously after an acetaminophen overdose [70, 71].
 - When NAC is combined with nitroglycerin, it can reduce chest pain, heart attacks, or death [70].
 - NAC has also shown effectiveness in increasing glutathione levels for those with HIV/AIDS [70].
 - While further research is needed, NAC may reduce flare-ups in those with COPD [70].

- **Dosage:**

- The dosage varies depending on health conditions but seems to have conclusive recommendations for acetaminophen overdose.

Acetaminophen poisoning [72]:

- 20 h protocol via IV: First administer 150 mg/kg for 15–60 min and then decrease the dose to 50 mg/kg for the 4 h. For the last 16 h, increase the dosage to 100 mg/kg. Overall this provides a total of 300 mg/kg for ~20 h.
 - 72 h protocol orally: First provide a loading dose of 140 mg/kg and then provide 70 mg/kg every 4 h.

- **Evidence for or against its different uses:**

- *Acetaminophen overdose*: A review from 2008, studied the pathophysiology, clinical manifestation, and management of acute acetaminophen toxicity. In a case involving a middle aged woman suffering from acetaminophen overdose, NAC was found to possibly improve liver failure [72].
 - *Angina*: A randomized control study evaluated the effects of nitroglycerin and NAC on individuals suffering from angina. Although there was a large percentage of side effects, primarily headaches, it was found that when taking nitroglycerin and NAC together, reductions in angina can occur [73].
 - *HIV/AIDS*: A commonality between HIV patients is glutathione deficiency, and it has been theorized that NAC supplementation can be used to replete

glutathione. A randomized, double blind placebo controlled trial by Rosa et al. studied the supplementation of *N*-acetylcysteine in HIV patients and concluded that glutathione was successfully replete in those given *N*-acetylcysteine [74].

- COPD: A meta-analysis completed in 2009 concluded that NAC supplementation can significantly reduce the risk of COPD exacerbation. It is important to proceed with caution when choosing NAC supplementation over traditional inhaled corticosteroids as further research is needed [75].

- **Safety concerns/side effects/precautions:**

- Toxic forms of cysteine are D-cysteine, D-cystine and 5-methyl cysteine which should all be avoided [70].
- Homocysteine levels could become elevated with NAC supplementation. It is important to check homocysteine levels when supplementing NAC as high levels of homocysteine have been linked to heart disease [70].
- NAC can cause nausea, vomiting, and diarrhea [70].

- **Interactions with medication:**

- *N*-Acetyl cysteine has been shown to increase the effects of some medications, such as immunosuppressants, nitroglycerin, oxiconazole, and isosorbide [70].
- *N*-Acetyl cysteine may lessen the effects of activated charcoal [70].
- When taking NAC with nitroglycerin, it can lead to severe headaches [70].

Niacin

- **What is it?**

- Niacin (Vitamin B3) is a water-soluble vitamin. It plays a role in the breakdown and metabolism of proteins, fatty acids, and carbohydrates [76].

- **How does it work in the body?**

- Niacin is essential in the conversion of carbohydrates to glucose [77]. It also aids in the production of sex and stress hormones [77].

- **What is it used for?**

- Niacin can be used to lower LDL and triglycerides [77]. When supplementing niacin, research has shown that those with heart disease may have slowed progression of atherosclerosis and lower risk for heart attack or stroke [77].
- Niacin may raise blood sugar but have positive effects on the amount of fat in the blood; therefore, more research is needed on niacin supplementation for diabetics [77]. Niacin is associated with lower risk of cataracts and Alzheimer's

disease [77]. Although more research is needed, applying topical niacin can possibly improve skin conditions [77].

- **Dosage:**

- RDA: 16 mg/day in adult males 14 years and older. 14 mg/day for females 14 years and older [77].
- Multiple resources show variable doses between 1 and 3 g/day can be effective on lowering lipids for adults [76, 78, 79].
- For high levels of LDL, 3000 mg/day of niacin supplementation has shown effectiveness [76, 78].
- With regular release niacin, it is recommended to start at 350 mg once daily with dinner and increase every week until therapeutic dose is reached [79]. For extended release, it is recommended to start at 500 mg × 4 weeks (taken at night time) and adjust by 500 mg or less every 4 weeks to a max of 2000 mg/day [79].
- Pellagra treatment for pediatrics: regular release 50–300 mg/day for 3–4 weeks [79].
- Excessive intake is excreted by the kidneys, no toxicity levels have been found [76].

- **Evidence for or against its different uses:**

- *Skin:* A randomized, double blind control trial studied the effects of topical niacin on facial photoaging. The 50 adults included in this study, applied 5% niacinamide twice daily for 12 weeks. At the end of 12 weeks, there were significant improvements in facial appearance [80].
- *CVD:* Research has shown that niacin is one of the most useful agents to help manage dyslipidemia. The coronary drug project demonstrated that niacin supplementation had similar effects to statins for reduction in cardiovascular disease and mortality [81]. In a 3-year trial, treatment of coronary disease with simvastatin and niacin showed clinical and measurable benefits [82]. A review and meta-analysis of randomized controlled trials concluded that niacin improves endothelial function [83].
- *DM:* A randomized control trial looked at the effect of niacin on lipid profiles and glycemic control in individuals with diabetes. Niacin usage showed significant improvements in HDL-C and LDL-C. Glucose levels were modestly increased. This study concluded that niacin can be safely used for patients with diabetes [84].

- **Safety concerns/side effects:**

- Niacin supplementation can lead to flushing, pruritus, paresthesias, and nausea [76, 78, 79].
- Niacin supplementation is contraindicated in adults with significant liver dysfunction/disease, stomach ulcers, or kidney disease [79, 81]. Therefore, caution should be taken when supplementing niacin in those with excessive alcohol intake [79].

- **Interactions with medications:**

- Niacin should not be taken with antibiotic tetracycline as it interferes with the absorption of the drug [77].
- Niacin may enhance some anticoagulants, resulting in a greater risk of bleeding [77].
- Niacin can enhance blood pressure medications, resulting in lower blood pressure levels [77].
- Diabetics taking niacin should monitor blood sugar levels as it can be increased [77].
- Aspirin can be used as an agent to decrease niacin flush [77].
- Alcohol can increase side effects when taken with niacin (flushing, hepatotoxicity) [85].
- Bile acid sequestrants should be taken separately from niacin as they may decrease absorption [85].
- Niacin should be avoided with use of simvastatin due to risk of rhabdomyolysis [85].

Omega-6 Fatty Acids

- **What is it?**

- Omega-6 fatty acids are essential polyunsaturated fatty acids. Most of the omega-6 consumed is linolenic acid (LA; commonly found in vegetable oils) which is when converted to gamma-linolenic acid (GLA) in the body. Common sources of GLA can be found in various oils [86].

- **How does it work in the body?**

- After ingestion, LA is converted into gamma-linolenic acid (GLA). GLA is broken down to arachidonic acid (AA). GLA has been shown to decrease inflammation [86].

- **What is it used for?**

- Omega-6 fatty acids have a wide range of therapeutic effects. It has been found beneficial for the following: rheumatoid arthritis (RA), allergies, ADHD, breast cancer, eczema, high blood pressure, menopausal symptoms, breast pain, osteoporosis, and PMS [86].

- **Dosage:**

- The average diet provides sufficient omega-6 [86].

- **Evidence for or against its different uses:**

- *RA:* A review looking at the effectiveness of herbal therapies on RA found that studies involving GLA showed improvements in clinical outcomes.

Nonetheless, more research is needed to identify the dosage and duration of treatment [87].

- **Allergies:** Contrary to prior epidemiological studies, a systematic review and meta-analysis from 2009 did not find benefits of supplementing omega 3 and 6 oils for preventing allergic diseases [88].
- **ADHD:** Individuals with ADHD exhibit fatty acid abnormalities which could possibly be affecting their behaviors. Supplementing fatty acids is found to be safe; however, more research is needed to identify the potential benefits on presentations of ADHD [89].
- **Breast cancer:** It has been suggested that GLA can modulate steroid hormone receptors and therefore benefit individuals with breast cancer. A study from 2000, provided GLA and tamoxifen or tamoxifen to 38 women with breast cancer. The women that were treated with GLA and tamoxifen showed a quicker clinical change. This study concludes that GLA can be used adjunctively with tamoxifen for individuals with breast cancer [90].
- **Eczema:** A meta-analysis looking at unconventional therapeutic approaches for atopic eczema. This analysis did not find convincing evidence on the efficacy of GLA supplementation on atopic eczema [91].
- **Breast pain:** A meta-analysis looking at management of mastalgia, included studies assessing the effects of evening primrose oil (EPO). There was no significant advantage of EPO supplementation for management of mastalgia when compared to the placebo [92].
- **Osteoporosis:** A study looked at older women over the course of 3 years with osteoporosis. The women who used EPA and GLA supplements were found to have less bone loss than the placebo group [86].
- **PMS:** Most studies did not show significant relief of PMS when supplementing with GLA [86].

- **Safety concerns/side effects/precautions:**

- **Precautions:** Individuals with a history of seizures should not take omega-6 as it may exacerbate symptoms. Pregnant individuals should not take certain GLAs as it can result in early labor. Ingesting GLA doses greater than 3000 mg/day can lead to inflammation [86].
- **Side effects:** One may develop headaches and GI disturbances when taking EPO. GLA can possibly decrease blood pressure [86].

- **Interactions with medications:**

- Niacin should be avoided with use of a number of medications. For example, niacin supplementation can increase bleeding in those taking blood thinners. Additionally, when linolenic acid breaks down into gamma-linolenic acid it can increase effects of ceftazidime (antibiotic) as well as increase the effect of chemotherapies [86].

Omega-3 Fatty Acids

- **What is it?**

- Omega-3 fatty acids are long chain polyunsaturated fatty acids. Most common dietary sources include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Good sources of ALA include flaxseeds and walnuts. EPA and DHA are found in fish [93].

- **How does it work in the body?**

- The body does not produce omega-3 fatty acids; therefore, it is important to ensure adequate consumption through the diet [94]. In the body, omega-3 fats are incorporated with cell membranes and modulate the function of cell receptors [95]. DHA and EPA lower triglycerides by reducing hepatic production of VLDL (very low density lipoproteins) [96].

- **What is it used for?**

- Omega 3 FA can be used to prevent cardiovascular disease by specifically lowering triglyceride levels and blood pressure [93, 96]. Omega-3 fatty acids can also be used in treatments for RA, depression, bipolar disorder, schizophrenia, ADHD, cognitive decline, inflammatory bowel disease (IBD), asthma, some cancers and macular degeneration [94].

- **Dosage:**

- Supplementing 3–4 g/day of omega 3 FA has been proven to be very effective for lowering triglycerides. A dosage of <1 g/day may have little effect [93, 96].

- **Evidence for or against its different uses:**

- *Cardiovascular disease:* Eating a diet rich in unsaturated fats has been proven to lower the risk of cardiovascular disease, specifically improving HDL levels and decreasing LDL/triglycerides. This can be done by following a Mediterranean diet [97].
- *RA:* One study looked at the effects of fish oil for the side effects of rheumatoid arthritis. A statistical improvement was seen in the group taking fish oil on both pain and strength after 12 weeks of supplementation. Of note, best improvements were seen in those supplements with fish and olive oil [98].
- *Depression:* While it has been speculated that fish oil could have a positive effect on depression, significant research has been unable to prove this as a fact [99, 100].
- *Bipolar disorder:* A randomized double blind placebo controlled study was conducted to assess the benefits of supplementing ethyl-EPA for depressive moods in bipolar individuals. After significant improvements were found, the study concluded that ethyl-EPA can be used adjunctly with bipolar medications as an effective treatment [101].

- *Schizophrenia*: A review from 2006 found that using omega 3 fatty acids as a form of the treatment for schizophrenics remain inconclusive [102].
- *ADHD*: Studies on diet changes with ADHD are common; however, more research on the exact effect of omega-3 supplementation requires further research [103].
- *Macular degeneration*: A prospective study from 2001 showed an inverse relationship between those who had four or more serving of fish/week with age-related macular degeneration [102].
- *Cognitive decline/dementia*: A well-known association between cognitive decline and dementia has been studied through epidemiological studies. These studies have concluded that omega 3 consumption has a positive effect on the treatment or prevention of cognitive decline; however, more clinical trials are needed [104].
- *IBD*: Omega-3 fatty acids are found to help gastrointestinal disorders due to their anti-inflammatory effects. Epidemiologic studies found that with ingestion of omega 3 fatty acids, there was a decrease in inflammatory bowel disease in eskimos. Results of a review looking at the effects of omega-3 fatty acids on inflammatory bowel diseases were controversial [105].
- *Asthma*: It is difficult to study the effects of fish oil on asthma due to the many other factors in the environment that could exacerbate asthma. A study completed in 2000 conducted in a controlled hospital environment, exhibited less symptoms when supplementing with fish oil [106].
- *Cancers*: One study focused on the risk of prostate cancer and fatty fish consumption. Six-thousand male participants over a 30-year time frame were included in the study. Of those who ate no fatty fish were at a much higher risk of prostate cancer when compared to those who did [107].

- **Safety concerns/side effects/precautions:**

- Side effect of fish oil include GI upset such as nausea or diarrhea [93, 94].
- Omega 3 should be avoided in those with fish allergies [96].
- When supplementing with omega 3, patients with altered liver function may exhibit increased ALT levels [96].

- **Interactions with medications:**

- Omega-3 fatty acid supplementation can increase blood sugars, diabetic patients may need to increase insulin dosage [94].
- If an individual is on cyclosporin following a transplant, omega-3 fatty acid supplementation may reduce medication side effects, such as elevated blood pressure [94].
- Omega 3 can increase antiplatelet effects of antiplatelet agents and may also increase anticoagulant effects of anticoagulants [96].

Oolong Tea

- **What is it?**

- Oolong tea is a traditional Chinese tea that is produced in Southern China. It is made from the *Camellia sinensis* tea plant through partial fermentation [108].

- **How does it work in the body?**

- The exact mechanism of how oolong tea acts in the body is unknown.

- **What is it used for?**

- There are limited human studies on the beneficial health effects of oolong tea. As a traditional use, oolong tea has been thought to burn body fat or increase metabolism effects. Some studies have focused on oolong tea's relationship with diabetes on whether it lowers blood glucose levels. Oolong tea can also be used to increase energy due to its caffeine content.

Diabetes: Multiple studies have focused on the effect that oolong tea plays on diabetes. One study conducted in 2011 focused on the long-term consumption of oolong tea. They concluded a positive association between prolonged oolong tea consumption and diabetes risk [109]. On the contrary, other studies found that after consuming oolong tea, glycemic levels were decreased. However, it is important to note that these studies did not focus on the long-term consumption of oolong tea [110, 111].

Metabolism/fat burning: A study conducted in 2003 looked at the resting energy expenditure of participants before and after consuming oolong tea when compared to those consuming water. It was suggested oolong tea had a positive effect on metabolism [112].

- **Dosage:**

- There is no exact dosage for oolong tea. With consuming 5300 mL of oolong tea for short periods of time, a positive effect on burning fat has been shown [111].

- **Safety concerns/side effects/precautions:**

- Just like any caffeine containing beverage, oolong tea should be avoided with other stimulants and should not be taken before bed.

- **Interactions with medications:**

- Unknown.

Pancrelipase

- **What is it?**

- Pancrelipase is a digestive enzyme supplement which contains proteases, lipase, and amylase [113].

- **What is it used for?**

- It is used in patients with any kind of pancreatic insufficiency such as chronic pancreatitis, postsurgical pancreatic insufficiency, pancreatic cancer, cystic fibrosis, or Crohn's disease [113].

- **How does it work in the body?**

- The basic environment of the duodenum activates pancrelipase and allows for digestion. Lipase, protease, and amylase work to break down fats, protein, and sugars [113].

- **Evidence:**

- Pancrelipase is FDA approved. It has been studied for efficiency in clinical trials and verified as a safe and effective options for those with pancreatic insufficiency [113, 114]. One study conducted in 2021 showed significant improvement of stool frequency or other symptoms associated with malabsorption after 1 week of receiving pancrelipase [115]. Another study conducted in 2000 focused on patients with cystic fibrosis, they found that enteric-coated, delayed-release pancrelipase were successful in decreasing the amount of fat found in stool [116].

- **Safety concerns/side effects/precautions:**

- Most common side effects of pancrelipase are GI upset such as changes in bowel movements, vomiting, altered blood glucose levels, feelings of dizziness, or sore throat/cough [114].
 - High doses of pancrelipase could increase chances of fibrosing colonopathy [114].
 - Pancrelipase should not be chewed or crushed as it could irritate the inside of the mouth [114].

- **Interactions with medications:**

- There are known contraindications for pancrelipase [114].

- **Dosage:**

- Adults should start with 500 lipase units/kg of weight and buildup to a maximum of 2500 lipase units per meal [113, 114]. For higher doses give <10,000 lipase units/kg of body weight per day or <4000 lipase units/g of fat ingested per day [114].

Pancreatin

- **What is it?**
 - Pancreatin is a digestive enzyme supplement which contains trypsin, amylase, and lipase [117]. Pancreatin can improve fat absorption [117].
- **What is it used for?**
 - Pancreatin is used for pancreatic insufficiency in those with impaired pancreatic function such as those with diabetes, pancreatic cancer, chronic pancreatitis, or cystic fibrosis [117].
- **How does it work in the body?**
 - Pancreatin supplementation functions as an exogenous enzyme in lieu of the endogenous enzymes in those with pancreatic insufficiency. In order for proper passage through the digestive tract [117, 118].
- **Dosage:**
 - The dosage of pancreatin depends on severity of the pancreatic insufficiency. The dosage is also tailored to the patient's age, weight, and genotype. Research shows that in order to appropriately reduce steatorrhea, there should be a minimum dose of 25,000–500,000 IU of lipase/meal and 10,000 IU for snacks [117, 119].
- **Evidence:**
 - All FDA approved forms of exogenous enzyme replacement therapies have been proved successful through clinical trials [117].
 - Objective pancreatic function tests are not as reliable as liver function tests, and it is therefore important to note that the efficacy of the drug is based on subjective improvement of symptoms [119].
 - One study conducted in 2013, studied enteric-coated pancreatin replacement for 1 year in those with chronic pancreatitis. They concluded pancreatin showed significant improvement in symptoms of malabsorption [120].
 - There is evidence to support the use of both enteric-coated and unprotected forms of pancreatin on fat digestion; however, further research is needed for confirmation. Most forms of the available enzymes are enterically coated [119, 121].
- **Safety concerns/side effects/precautions:**
 - Inflammatory colonic stenosis can occur with high dose ingestion of pancreatin [119].
 - Pancreatin should be avoided in those who are pregnant or breastfeeding as the effects are unknown [118].
- **Interactions with medications:**

- Pancreatin may potentially decrease the absorption of iron and folic acid. Therefore, the administration should be separated [122].
- Taking antacids separately from pancreatin, can improve the efficiency of the drug. Therefore, one should wait at least 1 h between consuming antacids and pancreatin [118, 121].

Pantethine

- **What is it?**

- Pantethine is made in the body from pantothenic acid (Vitamin B5). It functions as an important precursor for Coenzyme A which assists carbohydrate and lipid metabolism in the body [123, 124].

- **How it works in the body?**

- Pantethine and cysteamine work together to inhibit acetyl-coenzyme (CoA) carboxylase and HMG-CoA reductase. This inhibitory effect increases Coenzyme A within the cells and therefore alters lipoprotein metabolism. The exact mechanisms for how pantethine lowers cholesterol is still unknown [124].

- **What is it used for?**

- When pantethine is taken as a supplement, it can help to lower cholesterol, triglycerides and reduce risk of cardiovascular disease. It has also been theorized that pantethine could act as a neuroprotective agent or have a positive effect on Alzheimer's [124].

- **Evidence for or against its different uses:**

- *Cholesterol/triglycerides/cardiovascular disease:* A study conducted in 2011 followed 120 subjects who are at low to medium risk of cardiovascular disease. One group supplemented with 600 mg pantethine per day for 8 weeks and then increased to 900 mg/day for another 8 weeks. The other group received placebo pills. All subjects followed a similar diet. Those in the experimental group had a significant lowering of triglycerides and LDL. More research on a grand scale is needed to confirm this [123].
 - *Alzheimer's:* Studies on the neurological and cognitive effect of pantethine requires further research on human subjects before becoming a recommended line of therapy for brain function [124].
 - *Fatty liver:* Small trials have shown positive effects on fatty liver with 6 months of pantethine supplementation [125]. This goes hand in hand with its effects of triglycerides and cholesterol. Larger clinical trials are needed [125].

- **Medication interactions:**

- No drug interactions listed.

- **Dosage:**

- Clinical trials have seen therapeutic effects with 600–900 mg/day.

- **Safety concerns/side effects/precautions:**

- Pantethine is known to be a fragile supplement; it must be kept refrigerated to prevent breakdown [124].
 - Pantethine can cause diarrhea and elevated liver enzymes [124].

Pantothenic Acid (Vitamin B5)

- **What is it?**

- Pantothenic acid is an essential water-soluble vitamin found in both food and colonic bacteria [126].

- **How does it work in the body?**

- Vitamin B5 is essential to break down carbohydrates into glucose. Pantothenic acid helps produce red blood cells, and both sex and stress-related hormones [127].

- **What is it used for?**

- Limited research has shown that Vitamin B5 may be used to reduce elevated cholesterol and triglyceride levels [127]. Additionally, although more research is needed, Vitamin B5 can aid in wound healing [127].

- **Evidence:**

- *Cholesterol and triglycerides:* A review completed in 2006, concluded that the supplementation of pantethine may act as a triglyceride or cholesterol lowering agent; however, further research is needed for confirmation [127, 128].

- *Wound healing:* Limited research has shown that when Vitamin B5 is combined with Vitamin C, it may help optimize wound healing of surgical wounds [129].

- **Dosage:**

- Measured by AI not RDA [127, 130]. For adults >19 years, 5 mg is the AI [127]. Therapeutic dosage of supplementation can range from 600 to 900 mg/day [128].

- **Safety concerns, side effects, precautions:**

- No known safety concerns/side effects.

- **Interactions with medications:**

- The timing of Vitamin B5 and tetracycline should be separated as B5 can interfere with the absorption of the antibiotic [127].
- Vitamin B5 should not be taken with cholinesterase inhibitors as it could increase the effects of the medication [127].

Peppermint Oil

- **What is it?**

- Peppermint is a member of the mint family. It is a cross between watermint and spearmint [131].

- **How does it work in the body?**

- Peppermint allows for the muscles in the stomach to relax which can then better the passage of bile, and thereby increase the flow of food through the stomach. This process aids in reducing indigestion, flatulence, and bloating [132].
 - A key active component of peppermint, menthol, can break up mucus and help with congestion [132].

- **What is it used for?**

- Enteric-coated peppermint capsules can be beneficial to lessen side effects for patients suffering from IBS. In other words, supplementation can be beneficial for those experiencing stomach pain, flatus, bloating, or irregular bowel movements. Peppermint oil relieves these symptoms as it can “reduce stimulated motor activity” [133].
 - Peppermint oil can be used to relieve the itching or burning on the skin from hives and/or poison ivy [132].
 - Peppermint oil can be used as a decongestant and expectorant with ointment or rubs [132].
 - Peppermint oil can also be used as a treatment for nausea [132].

- **Dosage:**

- There is no clear dosage for peppermint oil; however, multiple studies have shown improvement in IBS symptoms with the following dosages [134]:

200 mg 3x daily for 1 month [134].

187 mg 3–4 times daily for 1 month [134].

225 mg 2x daily for 1 month [134].

- **Evidence for or against its different uses:**

- *IBS*: A systematic review and meta-analysis was conducted in 2018 that looked at the use of peppermint oil with the treatment of irritable bowel syndrome. Four trials compared the use of peppermint oil with a placebo for the

treatment of symptoms associated with IBS. It was concluded that peppermint oil was more effective than the placebo in relieving IBS symptoms [134].

- *Nausea:* A pretest and post-test research study by Lane et al. studied the effect of peppermint spirits/aromatherapy (combination of peppermint and aromatic ethyl alcohol base) on nausea. Participants rated their levels of nausea and it was found that peppermint aromatherapy can be an effective addition to the treatment of nausea [135].

- **Safety concerns/side effects/precautions:**

- Peppermint oil should be avoided in those with GERD as it can relax the lower esophageal sphincter and allow for acid to flow back into the stomach which can worsen GERD symptoms [132]. If the non-enteric-coated capsules are ingested, this may lead to heartburn [132].
- Pure menthol is poisonous and large doses of peppermint oil can be dangerous [132].

- **Interactions with medication**

- Peppermint oil should be avoided when taking cyclosporine, as it can slow the breakdown in the body [132].
- Antacids should be taken separately (~2 h). With less stomach acid, the peppermint capsules could dissolve in the stomach instead of the intestines. As a result, the peppermint would have a lessened effect [132].
- Other interactions with peppermint and medications have only been proven in test tube or animal studies. Further research before providing actual claims is needed [132].

Phosphorus

- **What is it?**

- Phosphorus is the second most abundant mineral in the body. Majority is stored in the bones and teeth [136].

- **How does it work in the body?**

- Phosphorus works together with calcium to build strong bones and teeth. It also aids in filtering waste in the kidneys and is essential to produce DNA and RNA [136].

- **What is it used for?**

- Phosphorus supplementation can be beneficial to treat hypophosphatemia, osteoporosis, hypercalcemia, and possibly lower blood pressure [136].

- **Evidence:**

- *Osteoporosis and hypercalcemia:* A study evaluated the relationship of calcium and phosphorus and its prevention of osteoporosis. If calcium intake increases, it is important to also increase phosphorus intake. If calcium levels are higher than phosphorus, there can be a decrease in phosphorus absorption. When treating osteoporosis, it is important to take calcium and phosphorus in conjunction with one another [137].
- *Blood pressure:* Research has found that sodium restriction is not the only way to help treat hypertension. In other words, managing other minerals is just as important in the treatment of hypertension. The International Study of Macro- and Micro-Nutrients on blood pressure published in 2008, the results showed possible lower blood pressure in those with increased phosphorus intake. However, it is important to remember that this difference may be due to the fact that those with higher phosphorus intakes follow a healthier diet and have increased mineral intake from whole foods [138].

- **Dosage:**

- The RDA for adults >19 years is 700 mg.

- **Safety concerns/side effects/precautions:**

- Too much phosphorus can cause diarrhea and calcification of organs and soft tissue. This can interfere with the body's ability to use iron, calcium, magnesium, and zinc [136].
- If there are higher phosphorus levels than calcium in the body, the body will use calcium stored in the bones. This can lead to osteoporosis and gum/teeth problems [136].
- Phosphorus should be checked in alcoholics or those who frequently drink alcohol. Alcohol can drain phosphorus from the bones and lead to hypophosphatemia [136].

- **Interactions with medications:**

- A number of medications may decrease the amount of phosphorus in the body and therefore supplementation would be considered. Medications that may lower phosphorus in the body include antacids, anticonvulsants, bile acid sequestrants, high doses of insulin, ACE inhibitors, cyclosporine, cardiac glycosides, heparin, and NSAIDs [136].
- Supplementing phosphorus while taking potassium supplements or medications that increase potassium (i.e., potassium sparing diuretics) could lead to hyperkalemia [136].

Potassium

- **What is it?**
 - Potassium is an essential mineral needed for cells to function [139].
- **How does it work in the body?**
 - Potassium has multiple functions in the body. Potassium acts as an electrolyte and balances the amount of water inside cells. Additionally, it is crucial for skeletal and smooth muscle contraction which is critical to maintaining normal function of the heart, muscular and digestive systems [139].
- **What is it used for?**
 - One obvious use for potassium supplementation is to treat hypokalemia which could be caused by excessive losses (i.e., vomiting, diarrhea), malnutrition, or malabsorption [140]. Other less common uses for potassium supplementation include, the prevention of osteoporosis in older women, attempt to lower blood pressure, and decrease risk of stroke [139].
- **Dosage:**
 - Adequate intake for adults >19 years old is 4700 mg/day [139].
- **Evidence:**
 - *Hypertension:* Hypertension has traditionally been managed with the intake of salt, however, for the best management recent research has shifted its focus to the replacement of other minerals, such as potassium [141, 142]. A systematic review published in 2006 looked at six randomized controlled trials. The review found that there was no significant effect on hypertension with potassium supplementation [143].
 - *Osteoporosis:* A cohort study was done to assess the effects of long-term potassium ingestion on bone mineral density in elderly women. It was found that higher intakes of potassium can possibly decrease the risk of osteoporosis [144].
 - *Risk of stroke:* A meta-analysis conducted in 2011 looked into ten independent prospective studies. They concluded a statistically significant decrease in risk of stroke in those that were supplemented with potassium [145].
- **Safety concerns/side effects/precautions:**
 - Potassium supplementation could lead to GI upset such as diarrhea or nausea, muscle weakness, slowed or irregular heart rate [139].
 - Potassium supplementation should be given to people with kidney disease.
 - Avoid potassium supplementation in those taking medications that can raise serum potassium such as potassium sparing diuretics, Bactrim, Septra, and ACE inhibitors [139].

- **Interactions with medications:**

- Several medications increase the risk of hyperkalemia and therefore potassium supplementation should be avoided. These medications include ACE inhibitors, angiotensin receptor blockers, potassium sparing diuretics, and indomethacin [139].

Pyridoxine (Vitamin B6)

- **What is it?**

- Pyridoxine is a water-soluble vitamin. The active form is pyridoxal 5'-phosphate [146].

- **How does it work in the body?**

- Pyridoxine plays an important role in maintaining the nervous system as it helps with normal brain and nerve function [147]. It also aids in the production of antibodies and red blood cells [147]. Pyridoxal phosphate is essential for gluconeogenesis during the transamination and decarboxylation of amino acids and acts as a cofactor to convert homocysteine to cysteine [146].

- **What is it used for?**

- Vitamin B6 deficiency is not common; however, it could occur in those with alcoholism, and liver or kidney disease [147]. Supplementation is used to ensure normal nerve function, produce hemoglobin and antibodies, and keep blood sugars within normal limits [147]. Although research is pending, vitamin B6 can also be used to reduce nausea during pregnancy and reduce the risk of age-related macular degeneration (AMD) [147].

- **Dosage:**

- The optimal dose is not well studied [148]. RDA is 1.3 mg/day for adults [147].

- **Evidence:**

- *Diabetes:* Pyridoxine supplementation has been shown to be effective in lowering blood glucose in those with gestational diabetes [149].
- *Nausea during pregnancy:* A review of randomized control trials looks at the different ways to treat nausea and vomiting in pregnant women. Supplementing 30 mg of pyridoxine, was found to be a useful tool in reducing nausea [150].
- *AMD:* A randomized control study including more than 5000 women, concluded that supplementing 50 mg of vitamin B6, 1000 µg of vitamin B12, and 2500 µg of folic acid can lower the risk of AMD [151].
- *Pain relief/improve fine motor skills:* When combined with thiamine and cobalamin, pyridoxine has been shown to improve fine motor skills [152]. The triple supplementation of pyridoxine, thiamin, and cobalamin has also been shown to relieve pain in diabetic patients [153].

- *Heart disease:* Elevated homocysteine levels have been linked to an elevated risk of CVD. Supplementing folic acid, pyridoxine, and cobalamin may lower homocysteine levels; however, research is not definitive on this [148, 154].
- **Safety concerns/side effects/precautions:**
 - Excessive intake of pyridoxine could impair coordination or sensory function [147]. Other risks include dizziness, nausea, or a numbing feeling to hands/feet [146].
- **Interactions with medication:**
 - Be sure to separate the timing of certain antibiotics (tetracycline) with pyridoxine supplementation, as B6 could limit the efficiency of the antibiotic [155].
 - Do not supplement with phenytoin or Levodopa as B6 could limit the potency of the medications [155].

References

Sources for Maca

1. Maca. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/maca>. Accessed 15 Jan 2021.
2. Dording CM, Fisher L, Papakostas G, et al. A double-blind, randomized, pilot dose-finding study of Maca Root (*L. meyenii*) for the management of SSRI-induced sexual dysfunction. *CNS Neurosci Ther*. 2008;14(3):182–91. <https://doi.org/10.1111/j.1755-5949.2008.00052.x>.
3. Shin B-C, Lee MS, Yang EJ, Lim H-S, Ernst E. Maca (*L. meyenii*) for improving sexual function: a systematic review. *BMC Complement Altern Med*. 2010;10(1):44. <https://doi.org/10.1186/1472-6882-10-44>.
4. Corazza O, Martinotti G, Santacroce R, et al. Sexual enhancement products for sale online: raising awareness of the psychoactive effects of yohimbine, maca, Horny goat weed, and Ginkgo biloba. *Biomed Res Int*. 2014;2014:1–13. <https://doi.org/10.1155/2014/841798>.
5. UpToDate. https://www.uptodate.com/drug-interactions/?source=responsive_home#di-analyze. Accessed 15 Jan 2021.

Sources for Magnesium

6. Magnesium. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/magnesium>. Accessed 16 Jan 2022.
7. Schwalfenberg GK, Genuis SJ. The importance of magnesium in clinical healthcare. *Scientifica*. 2017;2017:1–14. <https://doi.org/10.1155/2017/4179326>.
8. Mooren FC, Krüger K, Völker K, Golf SW, Wadepuhl M, Kraus A. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects—a double-blind, placebo-controlled, randomized trial. *Diabetes Obes Metab*. 2011;13(3):281–4. <https://doi.org/10.1111/j.1463-1326.2010.01332.x>.

9. Wark PA, Lau R, Norat T, Kampman E. Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis. *Am J Clin Nutr.* 2012;96(3):622–31. <https://doi.org/10.3945/ajcn.111.030924>.
10. Stepniewska K, Martynow AI. Magnesium orotate in severe congestive heart failure (Mach). *Int J Cardiol.* 2009;131(2):293–5. <https://doi.org/10.1016/j.ijcard.2007.11.022>.
11. Zhang X, Li Y, Del Gobbo LC, et al. Effects of magnesium supplementation on blood pressure. *Hypertension.* 2016;68(2):324–33. <https://doi.org/10.1161/hypertensionaha.116.07664>.
12. Young G, Jewell D. Interventions for leg cramps in pregnancy. *Cochrane Database Syst Rev.* 2002; <https://doi.org/10.1002/14651858.cd000121>.
13. Kazaks AG, Uriu-Adams JY, Albertson TE, Shenoy SF, Stern JS. Effect of oral magnesium supplementation on measures of airway resistance and subjective assessment of asthma control and quality of life in men and women with mild to moderate asthma: a randomized placebo controlled trial. *J Asthma.* 2010;47(1):83–92. <https://doi.org/10.3109/02770900903331127>.
14. Whelan AM, Jurgens TM, Naylor H. Herbs, vitamins and minerals in the treatment of pre-menstrual syndrome: a systematic review. *Can J Clin Pharmacol.* 2009;16(3):e407–29.
15. Bigal ME, Bordini CA, Tepper SJ, Speciali JG. Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study. *Cephalalgia.* 2002;22(5):345–53. <https://doi.org/10.1046/j.1468-2982.2002.00364.x>.
16. Magnesium. Mount Sinai Health System. <https://www.mountsinai.org/health-library/supplement/magnesium>. Accessed 16 Jan 2022.
17. Office of dietary supplements—magnesium. NIH Office of Dietary Supplements. <https://ods.od.nih.gov/factsheets/Magnesium-healthProfessional/>. Accessed 16 Jan 2022.
18. Beckstrand RL, Pickens JS. Beneficial effects of magnesium supplementation. *J Evid Based Complementary Altern Med.* 2011;16(3):181–9. <https://doi.org/10.1177/2156587211401746>.

Sources for Magnolia

19. Poivre M, Duez P. Biological activity and toxicity of the Chinese herb *Magnolia officinalis* Rehder & E. Wilson (Houpo) and its constituents. *J Zhejiang Univ Sci B.* 2017;18(3):194–214. <https://doi.org/10.1631/jzus.B1600299>.
20. *Magnolia officinalis*. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/magnolia-officinalis>. Accessed 18 Jan 2022.
21. Sun J, Wang Y, Fu X, et al. *Magnolia officinalis* extract contains potent inhibitors against PTP1B and attenuates hyperglycemia in db/db mice. *Biomed Res Int.* 2015;2015:139451. <https://doi.org/10.1155/2015/139451>.
22. Choi SS, Cha BY, Lee YS, et al. Magnolol enhances adipocyte differentiation and glucose uptake in 3T3-L1 cells. *Life Sci.* 2009;84(25–26):908–14. <https://doi.org/10.1016/j.lfs.2009.04.001>.
23. Xu Q, Yi LT, Pan Y, et al. Antidepressant-like effects of the mixture of honokiol and magnolol from the barks of *Magnolia officinalis* in stressed rodents. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(3):715–25. <https://doi.org/10.1016/j.pnpbp.2007.11.020>.
24. Kuribara H, Kishi E, Maruyama Y. Does dihydrohonokiol, a potent anxiolytic compound, result in the development of benzodiazepine-like side effects? *J Pharm Pharmacol.* 2000;52(8):1017–22. <https://doi.org/10.1211/0022357001774741>.

Sources for Manganese

25. Magnolia officinalis. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/magnolia-officinalis>. Accessed 18 Jan 2022.
26. Shamberger RJ. Calcium, magnesium, and other elements in the red blood cells and hair of normals and patients with premenstrual syndrome. *Biol Trace Elem Res.* 2003;94(2):123–9. <https://doi.org/10.1385/BTER:94:2:123>.
27. Ekmekcioglu C, Prohaska C, Pomazal K, Steffan I, Schernthaner G, Marktl W. Concentrations of seven trace elements in different hematological matrices in patients with type 2 diabetes as compared to healthy controls. *Biol Trace Elem Res.* 2001;79(3):205–19. <https://doi.org/10.1385/BTER:79:3:205>.

Sources for Mangosteen

28. Mangosteen. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/mangosteen>. Accessed 20 Jan 2022.
29. Wong LP, Klemmer PJ. Severe lactic acidosis associated with juice of the mangosteen fruit *Garcinia mangostana*. *Am J Kidney Dis.* 2008;51(5):829–33. <https://doi.org/10.1053/j.ajkd.2007.12.043>.
30. Gutierrez-Orozco F, Thomas-Ahner JM, Berman-Booty LD, et al. Dietary α-mangostin, a xanthone from mangosteen fruit, exacerbates experimental colitis and promotes dysbiosis in mice. *Mol Nutr Food Res.* 2014;58(6):1226–38. <https://doi.org/10.1002/mnfr.201300771>.
31. Suksamrarn S, Suwannapoch N, Phakhodee W, et al. Antimycobacterial activity of prenylated xanthones from the fruits of *Garcinia mangostana*. *Chem Pharm Bull (Tokyo)*. 2003;51(7):857–9. <https://doi.org/10.1248/cpb.51.857>.
32. Jang HY, Kwon OK, Oh SR, Lee HK, Ahn KS, Chin YW. Mangosteen xanthones mitigate ovalbumin-induced airway inflammation in a mouse model of asthma. *Food Chem Toxicol.* 2012;50(11):4042–50. <https://doi.org/10.1016/j.fct.2012.08.037>.
33. Quan X, Wang Y, Ma X, et al. α-Mangostin induces apoptosis and suppresses differentiation of 3T3-L1 cells via inhibiting fatty acid synthase. *PLoS One.* 2012;7(3):e33376. <https://doi.org/10.1371/journal.pone.0033376>.
34. Fu Y, Zhou H, Wang M, Cen J, Wei Q. Immune regulation and anti-inflammatory effects of isogarcinol extracted from *Garcinia mangostana* L. against collagen-induced arthritis. *J Agric Food Chem.* 2014;62(18):4127–34. <https://doi.org/10.1021/jf405790q>.
35. Xie Z, Sintara M, Chang T, Ou B. Daily consumption of a mangosteen-based drink improves in vivo antioxidant and anti-inflammatory biomarkers in healthy adults: a randomized, double-blind, placebo-controlled clinical trial. *Food Sci Nutr.* 2015;3(4):342–8. <https://doi.org/10.1002/fsn3.225>.

Sources for MCTs

36. Medium chain triglycerides. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/patient-education/medium-chain-triglycerides-01>. Accessed 21 Jan 2021.
37. The use of medium-chain triglycerides med.virginia.edu. <https://med.virginia.edu/ginutrition%20/wp-content/uploads/sites/199/2014/06/Parrish-February-17.pdf>. Accessed 21 Jan 2021.
38. Eyres L, Eyres MF, Chisholm A, Brown RC. Coconut oil consumption and cardiovascular risk factors in humans. *Nutr Rev.* 2016;74(4):267–80. <https://doi.org/10.1093/nutrit/nuw002>.

39. Reger MA, Henderson ST, Hale C, et al. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol Aging*. 2004;25(3):311–4. [https://doi.org/10.1016/S0197-4580\(03\)00087-3](https://doi.org/10.1016/S0197-4580(03)00087-3).
40. Neal EG, Chaffe H, Schwartz RH, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia*. 2009;50(5):1109–17. <https://doi.org/10.1111/j.1528-1167.2008.01870.x>.
41. Mumme K, Stonehouse W. Effects of medium-chain triglycerides on weight loss and body composition: a meta-analysis of randomized controlled trials. *J Acad Nutr Diet*. 2015;115(2):249–63. <https://doi.org/10.1016/j.jand.2014.10.02>.

Sources for Melatonin

42. Melatonin. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/melatonin>. Accessed 22 Jan 2021.
43. Melatonin. Mount Sinai Health System. <https://www.mountsinai.org/health-library supplement/melatonin>. Accessed 22 Jan 2022.
44. Pharmacotherapy for insomnia in adults. UpToDate. https://www.uptodate.com/contents/pharmacotherapy-for-insomnia-in-adults?search=melatonin+dose&source=search_result&selectedTitle=1~120&usage_type=default&display_rank=1#H2582713949. Accessed 22 Jan 2021.
45. Bendz LM, Scates AC. Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. *Ann Pharmacother*. 2010;44(1):185–91. <https://doi.org/10.1345/aph.1M365>.
46. Lyseng-Williamson KA. Melatonin prolonged release: in the treatment of insomnia in patients ages >55 years. *Drugs Aging*. 2012;29(11):911–23.
47. Herxheimer A, Petrie KJ. Melatonin for preventing and treating jet lag. *Cochrane Database Syst Rev*. 2001;(1):CD001520. <https://doi.org/10.1002/14651858.CD001520>.
48. Kaminski-Hartenthaler A, Nussbaumer B, Forneris CA, et al. Melatonin and agomelatine for preventing seasonal affective disorder. *Cochrane Database Syst Rev*. 2015;2015(11):CD011271.
49. Alstadhaug KB, Odeh F, Salvesen R, Bekkelund SI. Prophylaxis of migraine with melatonin: a randomized controlled trial. *Neurology*. 2010;75(17):1527–32.
50. Lissoni P, Chilelli M, Villa S, Cerizza L, Tancini G. Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. *J Pineal Res*. 2003;35(1):12–5.
51. Srinivasan V, Spence DW, Pandi-Perumal SR, Trakht I, Cardinali DP. Therapeutic actions of melatonin in cancer: possible mechanisms. *Integr Cancer Ther*. 2008;7(3):189–203. Review.
52. Song GH, Leng H, Gwee KA, Moochhala SM, Ho KY. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomized, double blind, controlled study. *Gut*. 2005;54:1402–7.

Sources for Methionine

53. Parkhitko AA, Jouandin P, Mohr SE, Perrimon N. Methionine metabolism and methyltransferases in the regulation of aging and lifespan extension across species. *Aging Cell*. 2019;18(6):e13034. <https://doi.org/10.1111/acel.13034>.
54. Methionine (oral route) proper use. Mayo Clinic. <https://www.mayoclinic.org/drugs-supplements/methionine-oral-route/proper-use/drg-20065729>. 2022. Accessed 1 Feb 2022.

55. Lighthart-Melis GC, Engelen MP, Simbo SY, et al. Metabolic consequences of supplemented methionine in a clinical context. *J Nutr.* 2020;(Suppl_1):150, 2538S–2547S. <https://doi.org/10.1093/jn/nxaa254>.
56. Lexicomp drug interactions. UpToDate. https://www.uptodate.com/drug-interactions/?source=responsive_home#di-document. Accessed 15 Feb 2022.
57. Kalbande VH, Ravikanth K, Maini S, Rekhe DS. Methionine supplementation options in Poultry. *Int J Poult Sci.* 2009;8(6):588–91. <https://doi.org/10.3923/ijps.2009.588.591>.

Sources for Milk Thistle

58. Milk thistle. Mount Sinai Health System. <https://www.mountsinai.org/health-library/herb/milk-thistle>. Accessed 1 Feb 2022.
59. Milk thistle. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/milk-thistle>. Accessed 1 Feb 2022.
60. Rambaldi A, Jacobs BP, Iaquinto G, Giud C. Milk thistle for alcoholic and/or hepatitis B or C liver diseases—a systematic cochrane hepato-biliary group review with meta-analyses of randomized clinical trials. *Am J Gastroenterol.* 2005;100(11):2583–91. Review.
61. Vo KT, Montgomery ME, Mitchell ST, et al. Amanita phalloides mushroom poisonings—Northern California, December 2016. *MMWR Morb Mortal Wkly Rep.* 2017;66(21):549–53. <https://doi.org/10.15585/mmwr.mm6621a1>.
62. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: a systematic review. *J Viral Hepat.* 2005;12(6):559–67. Review.
63. Ramasamy K, Agarwal R. Multitargeted therapy of cancer by silymarin. *Cancer Lett.* 2008;269(2):352–62. Review.
64. Karimi G, Vahabzadeh M, Lari P, Rashedinia M, Moshiri M. “Silymarin”, a promising pharmacological agent for treatment of diseases. *Iran J Basic Med Sci.* 2011;14(4):308–17.

Sources for Myrtle

65. Giampieri F, Cianciosi D, Forbes-Hernández TY. Myrtle (*Myrtus communis* L.) berries, seeds, leaves, and essential oils: new undiscovered sources of natural compounds with promising health benefits. *Food Front.* 2020;1(3):276–95. <https://doi.org/10.1002/ff2.37>.
66. Safari R, Hoseinifar SH, Van Doan H, Dadar M. The effects of dietary myrtle (*Myrtus communis*) on skin mucus immune parameters and mRNA levels of growth, antioxidant and immune related genes in zebrafish (*Danio rerio*). *Fish Shellfish Immunol.* 2017;66:264–9. <https://doi.org/10.1016/j.fsi.2017.05.007>.
67. Al-Hindawi MK, Al-Deen IH, Nabi MH, Ismail MA. Anti-inflammatory activity of some Iraqi plants using intact rats. *J Ethnopharmacol.* 1989;26(2):163–8. [https://doi.org/10.1016/0378-8741\(89\)90063-9](https://doi.org/10.1016/0378-8741(89)90063-9).
68. Hosseinzadeh H, Khoshdel M, Ghorbani M. Antinociceptive, anti-inflammatory effects and acute toxicity of aqueous and ethanolic extracts of *Myrtus communis* L. Aerial parts in mice. *J Acupunct Meridian Stud.* 2011;4(4):242–7. <https://doi.org/10.1016/j.jams.2011.09.015>.
69. Aleksic V, Knezevic P. Antimicrobial and antioxidative activity of extracts and essential oils of *Myrtus communis* L. *Microbiol Res.* 2014;169(4):240–54. <https://doi.org/10.1016/j.micres.2013.10.003>.

Sources for *N-Acetyl-L-cysteine*

70. Cysteine. Mount Sinai Health System. <https://www.mountsinai.org/health-library/supplement/cysteine>. Accessed 2 Feb 2022.
71. N-acetylcysteine. Memorial Sloan Kettering Cancer Center. <https://www.mskcc.org/cancer-care/integrative-medicine/herbs/n-acetylcysteine>. Accessed 2 Feb 2021.
72. Acetaminophen (paracetamol) poisoning in adults: treatment. UpToDate. https://www.uptodate.com/contents/acetaminophen-paracetamol-poisoning-in-adults-treatment?search=N-Acetyl+Cysteine+dosage&source=search_result&selectedTitle=2~134&usage_type=default&display_rank=1#H6. Accessed 2 Feb 2022.
73. Ardissino D, Merlini PA, Savonitto S, et al. Effect of transdermal nitroglycerin or N-acetylcysteine, or both, in the long-term treatment of unstable angina pectoris. *J Am Coll Cardiol*. 1997;29(5):941–7.
74. De Rosa SC, Zaretsky MD, Dubs JG, et al. N-Acetylcysteine replenishes glutathione in HIV infection. *Eur J Clin Investig*. 2000;30(10):915–29.
75. Sutherland ER, Crapo JD, Bowler RP. N-Acetylcysteine and exacerbations of chronic obstructive pulmonary disease. *COPD*. 2006;3(4):195–202.

Sources for *Niacin*

76. Overview of water-soluble vitamins. UpToDate. https://www.uptodate.com/contents/overview-of-water-soluble-vitamins?search=niacin+dosage&source=search_result&selectedTitle=4~125&usage_type=default&display_rank=3#H22. Accessed 3 Feb 2022.
77. Vitamin B3 (niacin). Mount Sinai Health System. <https://www.mountsinai.org/health-library/supplement/vitamin-b3-niacin>. Accessed 5 Feb 2022.
78. Low-density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors. UpToDate. https://www.uptodate.com/contents/low-density-lipoprotein-cholesterol-lowering-with-drugs-other-than-statins-and-psk9-inhibitors?search=niacin+cholesterol&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H3691238451. Accessed 5 Feb 2022.
79. Niacin (vitamin B3): drug information. UpToDate. https://www.uptodate.com/contents/niacin-vitamin-b3-drug-information?search=niacin+cholesterol&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#F50991221. Accessed 5 Feb 2022.
80. Bissett DL, Oblong JE, Berge CA, et al. Niacinamide: a B vitamin that improves aging facial skin appearance. *Dermatologic Surg*. 2005;31:860–865; discussion 865.
81. Boden WE, Sidhu MS, Toth PP. The therapeutic role of niacin in dyslipidemia management. *J Cardiovasc Pharmacol Ther*. 2014;19(2):141–58.
82. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345(22):1583–92. <https://doi.org/10.1056/NEJMoa011090>.
83. Sahebkar A. Effect of niacin on endothelial function: a systematic review and meta-analysis of randomized controlled trials. *Vasc Med*. 2014;19(1):54–66.
84. Elam M, Hunninghake DB, Davis KB, et al. Effects of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. *Arterial Disease Multiple Intervention Trial*. *JAMA*. 2000;284:1263–70.
85. Lexicomp drug interactions. UpToDate. https://www.uptodate.com/drug-interactions/?search=niacin%2Bcholesterol&topicId=9695&source=responsive_topic#di-document. Accessed 5 Feb 2021.

Source for Omega-6 Fatty Acids

86. Omega-6 fatty acids. Mount Sinai Health System. <https://www.mountsinai.org/health-library/supplement/omega-6-fatty-acids>. Accessed 5 Feb 2022.
87. Little C, Parsons T. Herbal therapy for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2001;(1):CD002948.
88. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy. 2009;64(6):840–8. Epub 2009 Apr 7.
89. Richardson AJ, Puri BK. The potential role of fatty acids in attention-deficit/hyperactivity disorder. Prostaglandins Leukot Essent Fat Acids. 2000;63(1/2):79–87.
90. Kenny FS, Pinder SE, Ellis IO, et al. Gamma linolenic acid with tamoxifen as primary therapy in breast cancer. Int J Cancer. 2000;85:643–8.
91. Worm M, Henz BM. Novel unconventional therapeutic approaches to atopic eczema. Dermatology. 2000;201(3):191–5.
92. Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A. Evidence-based management of mastalgia: a meta-analysis of randomised trials. Breast. 2007;16(5):503–12. Epub 2007 May 16.

Sources for Omega-3 Fatty Acids

93. Fish oil: physiologic effects and administration. UpToDate. https://www.uptodate.com/contents/fish-oil-physiologic-effects-and-administration?search=omega+3+fatty+acids&sourc e=search_result&selectedTitle=2~118&usage_type=default&display_rank=1. Accessed 21 Jan 2021.
94. Omega-3 fatty acids. Mount Sinai Health System. <https://www.mountsinai.org/health-library/supplement/omega-3-fatty-acids>. Accessed 10 Jan 2021.
95. Omega-3 fatty acids: an essential contribution. The Nutrition Source. 2019. <https://www.hsph.harvard.edu/nutritionsource/what-should-you-eat/fats-and-cholesterol/types-of-fat/omega-3-fats/>. Accessed 15 Jan 2021.
96. Omega-3-acid ethyl esters (fish oil): drug information. UpToDate. https://www.uptodate.com/contents/omega-3-acid-ethyl-esters-fish-oil-drug-information?search=omega+3+supplement&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#F171384. Accessed 21 Jan 2021.
97. Balk EM, Lichtenstein AH, Chung M, et al. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006;189(1):19–30.
98. Berbert AA, Kondo CR, Almendra CL, et al. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition. 2005;21:131–6.
99. Silvers KM, Woolley CC, Hamilton FC, et al. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. Prostaglandins Leukot Essent Fat Acids. 2005;72:211–8.
100. Rocha Araujo DM, Vilarim MM, Nardi AE. What is the effectiveness of the use of polyunsaturated fatty acid omega-3 in the treatment of depression? In: Database of Abstracts of Reviews of Effects (DARE): quality-assessed Reviews [Internet]. York, UK: Centre for Reviews and Dissemination; 2010. <https://www.ncbi.nlm.nih.gov/books/NBK79352/>.
101. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br J Psychiatry. 2006;188:46–50. <https://doi.org/10.1192/bjp.188.1.46>.
102. Cho E, Hung S, Willet WC, Spiegelman D, Rimm EB, Seddon JM, et al. Prospective study of dietary fat and the risk of age-related macular degeneration. Am J Clin Nutr. 2001;73(2):209–18.

103. Richardson AJ, Puri BK. The potential role of fatty acids in attention-deficit/hyperactivity disorder. *Prostaglandins Leukot Essent Fatty Acids.* 2000;63(1–2):79–87. <https://doi.org/10.1054/plef.2000.0196>.
104. Cole GM. Omega-3 fatty acids and dementia. *Prostaglandins Leukot Essent Fat Acids.* 2009;81(2–3):213–21.
105. Belluzzi A, Boschi S, Brignola C, Munarini A, Cariani C, Miglio F. Polyunsaturated fatty acids and inflammatory bowel disease. *Am J Clin Nutr.* 2000;71(Suppl):339S–42S.
106. Nagakura T, Matsuda S, Shichijo K, Sugimoto H, Hata K. Dietary supplementation with fish oil rich in omega-3 polyunsaturated fatty acids in children with bronchial asthma. *Eur Respir J.* 2000;16(5):861–5.
107. Terry P, Lichtenstein P, Feychtung M, Ahlbom A, Wolk A. Fatty fish consumption and risk of prostate cancer. *Lancet.* 2001;357(9270):1764–6.

Sources for Oolong Tea

108. Hayat K, Iqbal H, Malik U, Bilal U, Mushtaq S. Tea and its consumption: benefits and risks. *Crit Rev Food Sci Nutr.* 2015;55(7):939–54. <https://doi.org/10.1080/10408398.2012.678949>.
109. Hayashino Y, Fukuhara S, Okamura T, Tanaka T, Ueshima H. High oolong tea consumption predicts future risk of diabetes among Japanese male workers: a prospective cohort study. *Diabet Med.* 2011;28(7):805–10. <https://doi.org/10.1111/j.1464-5491.2011.03239.x>.
110. Hosoda K, Wang MF, Liao ML, et al. Antihyperglycemic effect of oolong tea in type 2 diabetes. *Diabetes Care.* 2003;26(6):1714–8. <https://doi.org/10.2337/diacare.26.6.1714>.
111. Rumpler W, Seale J, Clevidence B, et al. Oolong tea increases metabolic rate and fat oxidation in men. *J Nutr.* 2001;131(11):2848–52. <https://doi.org/10.1093/jn/131.11.2848>.
112. Komatsu T, Nakamori M, Komatsu K, et al. Oolong tea increases energy metabolism in Japanese females. *J Med Investig.* 2003;50(3–4):170–5.

Sources for Pancrelipase

113. Venkatesh P. Pancrelipase therapy. In: StatPearls [Internet]; 2021. <https://www.ncbi.nlm.nih.gov/books/NBK534816/>. Accessed 18 Feb 2022.
114. Creon® (pancrelipase) delayed-release capsule: official website. Creon® (pancrelipase) tablets. <https://www.creon.com/how-to-take-creon>. Accessed 18 Feb 2022.
115. Barkin JA, Barkin JS. Effect of pancrelipase therapy on exocrine pancreatic insufficiency symptoms and coefficient of fat absorption associated with chronic pancreatitis. *Pancreas.* 2021;50(2):176–82. <https://doi.org/10.1097/MPA.0000000000001733>.
116. Stern RC, Eisenberg JD, Wagener JS, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. *Am J Gastroenterol.* 2000;95(8):1932–8. <https://doi.org/10.1111/j.1572-0241.2000.02244.x>.

Sources for Pancreatin

117. Ianiro G, Pecere S, Giorgio V, Gasbarrini A, Cammarota G. Digestive enzyme supplementation in gastrointestinal diseases. *Curr Drug Metab.* 2016;17(2):187–93. <https://doi.org/10.2174/138920021702160114150137>.

118. Pancreatin. St. Luke's. <https://www.stlukesonline.org/health-services/health-information/healthwise/2017/06/27/13/09/pancreatin>. Accessed 10 Feb 2022.
119. Mössner J, Keim V. Pancreatic enzyme therapy. Dtsch Arztebl Int. 2010;108(34–35):578–82. <https://doi.org/10.3238/arztebl.2011.0578>.
120. Ramesh H, Reddy N, Bhatia S, et al. A 51-week, open-label Clinical Trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013;13(2):133–9. <https://doi.org/10.1016/j.pan.2013.01.009>.
121. Kettwaroo GA, Graham DY. Rational use of pancreatic enzymes for pancreatic insufficiency and pancreatic pain. Adv Exp Med Biol. 2019;1148:323–43. https://doi.org/10.1007/978-981-13-7709-9_14.
122. Iron sulfate and pancreatin interactions. Drugs.com. <https://www.drugs.com/drug-interactions/iron-sulfate-with-pancreatin-1082-13326-1786-0.html>. Accessed 10 Feb 2022.

Pantethine

123. Rumberger JA, Napolitano J, Azumano I, Kamiya T, Evans M. Pantethine, a derivative of vitamin B(5) used as a nutritional supplement, favorably alters low-density lipoprotein cholesterol metabolism in low- to moderate-cardiovascular risk North American subjects: a triple-blinded placebo and diet-controlled investigation. Nutr Res. 2011;31(8):608–15. <https://doi.org/10.1016/j.nutres.2011.08.001>.
124. Pantethine cognitive vitality for researchers. https://www.alzdiscovery.org/uploads/cognitive_vitality_media/Pantethine-Cognitive-Vitality-For-Researchers.pdf. Accessed February 18, 2022.
125. Osono Y, Hirose N, Nakajima K, Hata Y. The effects of pantethine on fatty liver and fat distribution. Journal of Atherosclerosis and Thrombosis. 2000;7(1):55–8. <https://doi.org/10.5551/jat1994.7.55>.

Sources for Pantothenic Acid

126. Vitamin B5 (pantothenic acid): drug information. UpToDate. https://www.uptodate.com/contents/vitamin-b5-pantothenic-acid-drug-information?search=pantothenic+acid&source=panel_search_result&selectedTitle=1~28&usage_type=panel&kp_tab=drug_general&display_rank=1. Accessed 8 Feb 2022.
127. Vitamin B5 (pantothenic acid). Mount Sinai Health System. <https://www.mountsinai.org/health-library/supplement/vitamin-b5-pantothenic-acid>. Accessed 8 Feb 2022.
128. Pins JJ, Keenan JM. Dietary and nutraceutical options for managing the hypertriglyceridemic patient. Prog Cardiovasc Nurs. 2006;21(2):89–93. Review.
129. Ellinger S, Stehle P. Efficacy of vitamin supplementation in situations with wound healing disorders: results from clinical intervention studies. Curr Opin Clin Nutr Metab Care. 2009;12(6):588–95. Review.
130. Overview of water-soluble vitamins. UpToDate. https://www.uptodate.com/contents/overview-of-water-soluble-vitamins?search=pantothenic+acid&source=search_result&selectedTitle=2~28&usage_type=default&display_rank=1#H32. Accessed 8 Feb 2022.

Sources for Peppermint

131. Peppermint oil. National Center for Complementary and Integrative Health. <https://www.nccih.nih.gov/health/peppermint-oil>. Accessed 5 Feb 2022.
132. Peppermint. Mount Sinai Health System. <https://www.mountsinai.org/health-library/herb/peppermint>. Accessed 5 Feb 2022.
133. Treatment of irritable bowel syndrome in adults. UpToDate. https://www.uptodate.com/contents/treatment-of-irritable-bowel-syndrome-in-adults?search=peppermint+oil&source=search_result&selectedTitle=1~12&usage_type=default&display_rank=1. Accessed 5 Feb 2022.
134. Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ*. 2008;337:a2313. <https://doi.org/10.1136/bmj.a2313>.
135. Lane B, Cannella K, Bowen C, et al. Examination of the effectiveness of peppermint aromatherapy on nausea in women post C-section. *J Holist Nurs*. 2012;30:90–104.

Sources for Phosphorus

136. Phosphorus. Mount Sinai Health System. <https://www.mountsinai.org/health-library/supplement/phosphorus>. Accessed 2 Feb 2022.
137. Heaney RP, Nordin BE. Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. *J Am Coll Nutr*. 2002;21(3):239–44.
138. Elliott P, Kesteloot H, Appel LJ, Dyer AR, Ueshima H, Chan Q, Brown IJ, Zhao L, Stamler J, INTERMAP Cooperative Research Group. Dietary phosphorus and blood pressure: international study of macro- and micro-nutrients and blood pressure. *Hypertension*. 2008;51(3):669–75. Erratum in: *Hypertension* 2008 Apr;51(4):e32.

Sources for Potassium

139. Potassium. Mount Sinai Health System. <https://www.mountsinai.org/health-library/supplement/potassium>. Accessed 2 Feb 2022.
140. Clinical manifestations and treatment of hypokalemia in adults. UpToDate. https://www.uptodate.com/contents/clinical-manifestations-and-treatment-of-hypokalemia-in-adults?search=potassium+supplementation&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 2 Feb 2022.
141. Hermansen K. Diet, blood pressure and hypertension. *Br J Nutr*. 2000;83(Suppl 1):S113–9. <https://doi.org/10.1017/s0007114500001045>.
142. Adrogué HJ, Madias NE. The impact of sodium and potassium on hypertension risk. *Semin Nephrol*. 2014;34(3):257–72. <https://doi.org/10.1016/j.semnephrol.2014.04.003>.
143. Dickinson HO, Nicolson DJ, Campbell F, Beyer FR, Mason J. Potassium supplementation for the management of primary hypertension in adults. *Cochrane Database Syst Rev*. 2006;(3):CD004641. <https://doi.org/10.1002/14651858.CD004641.pub2>.
144. Zhu K, Devine A, Prince RL. The effects of high potassium consumption on bone mineral density in a prospective cohort study of elderly post-menopausal women. *Osteoporos Int*. 2009;20(2):335–40.
145. Larsson SC, Orsini N, Wolk A. Dietary potassium intake and risk of stroke: a dose-response meta-analysis of prospective studies. *Stroke*. 2011;42(10):2746–50.

Sources for Pyridoxine

146. Overview of water-soluble vitamins. UpToDate. https://www.uptodate.com/contents/overview-of-water-soluble-vitamins?search=pantothenic+acid&source=search_result&selectedTitle=2~28&usage_type=default&display_rank=1#H3740724926. Accessed 5 Feb 2022.
147. Vitamin B6. Mount Sinai Health System. <https://www.mountsinai.org/health-library/nutrition/vitamin-b6>. Accessed 12 Feb 2022.
148. Vitamin supplementation in disease prevention. UpToDate. https://www.uptodate.com/contents/vitamin-supplementation-in-disease-prevention?search=pyridoxine+supplement&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3#H41. Accessed 12 Feb 2022.
149. Spellacy WN, Buhi WC, Birk SA. Vitamin B6 treatment of gestational diabetes mellitus. Am J Obstet Gynecol. 1977;127(6):599–602. [https://doi.org/10.1016/0002-9378\(77\)90356-8](https://doi.org/10.1016/0002-9378(77)90356-8).
150. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2002;(1):CD000145. <https://doi.org/10.1002/14651858.CD000145>.
151. Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. Arch Intern Med. 2009;169(4):335–41. <https://doi.org/10.1001/archinternmed.2008.574>.
152. Bonke D. Influence of vitamin B1, B6, and B12 on the control of Fine Motoric movements. Nutr Neurobiol. 1986;(38):104–9. <https://doi.org/10.1159/000412604>.
153. Rizvi A, Ahmad A, Rizvi Z. Efficacy of combination of vitamin B1, B6 and B12 in management of diabetic peripheral neuropathy. Pak J Med Health Sci. 2013;7(3):801–3.
154. Booth GL, Wang EE. Preventive health care, 2000 update: screening and management of hyperhomocysteinemia for the prevention of coronary artery disease events. The Canadian Task Force on Preventive Health Care. CMAJ. 2000;163(1):21–9.
155. Complementary and alternative medicine. Possible interactions with: vitamin B6 (pyridoxine). Complementary and Alternative Medicine. St. Luke's Hospital. <https://www.stlukes-stl.com/health-content/medicine/33/000992.htm>. Accessed 8 Jan 2022.

Chapter 5

Quercetin–Syrian Rue



Michelle Gorbonosov and Lawrence Market

Quercetin

- **Gen:**
 - Quercetin belongs to a group of plant pigments called flavonoids that give fruits and vegetables their color. Flavonoids are considered to be antioxidants.
- **Mechanism of Action:**
 - Flavonoids are antioxidants, meaning they neutralize free radicals that are generally regarded as dangerous for being able to damage cell membranes and DNA, causing cell death. These flavonoids, quercetin included, can decrease the damage that free radicals cause. Quercetin can also stabilize cells that release histamine in the body and therefore can have an anti-inflammatory and anti-histamine effect.
- **Dosage:**
 - The most common dose for adults is 500 mg one a day, but some people can take up to 1000 mg a day.

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- **Precautions:**

- Generally considered safe, some side effects can include upset stomach and headache. Very high doses above 1000 mg per day, there have been reports of kidney damage as some evidence suggest that a product of quercetin can lead to a loss of protein function.

- **Interactions:**

- Quercetin may reduce the effectiveness of certain antibiotics. Quercetin may enhance the effects of blood thinners such as warfarin, clopidogrel, aspirin as well as drugs such as corticosteroids, digoxin, and medications that are metabolized by the liver.

Quince

- **Gen:**

- Quince is a small tree bearing a yellow fruit. The seed, fruit, and leaves are used as medicine, primarily for digestive disorders, diarrhea, and gastrointestinal inflammation.

- **Mechanism of Action:**

- The mechanism of quince is not fully understood but is widely believed to be an antioxidant, and it also may have a mechanism of inhibiting bacterial growth, specifically against *Helicobacter pylori* infections.

- **Dosage:**

- Not enough information is known to recommend dosages. However in a study involving 137 pregnant women, a 10 mg dose of quince syrup taken with a meal is as effective as traditional medication at relieving acid reflux symptoms.

- **Precautions:**

- There isn't enough information to know if quince is safe for medicinal use. The seeds contain cyanide, which suggests that quince seeds might not be safe.

- **Interactions:**

- Quince contains a type of soft fiber called mucilage. Mucilage can decrease the amount of medicine the body absorbs. Taking quince at the same time you take medications by mouth can decrease the effectiveness of your medication.

Red Clover

- **Gen:**
 - Red clover is a perennial herb that commonly grows wild in meadows throughout Europe and Asia and has been naturalized to grow in North America. The red flowers at the end of the branched stems are usually dried for therapeutic use.
- **Mechanism of Action:**
 - Red clover might help protect against heart disease, but studies in humans have not found strong evidence. Red clover isoflavones have been associated with an increase in HDL (good) cholesterol in pre- and postmenopausal women, but other studies show conflicting results. Red clover may also have blood-thinning properties, which keeps blood clots from forming. It appears to improve blood flow.
- **Dosage:**
 - Dose may vary from person to person, but general guidelines are as follows:
 - Dried herb (used for tea): 1–2 tsp dried flowers or flowering tops steeped in 8 oz. hot water for 1/2 h; drink 2–3 cups daily.
 - Powdered herb (available in capsules): 40–160 mg per day, or 28–85 mg of red clover isoflavones.
- **Precautions:**
 - General side effects may include headache, nausea, and rash. Red clover may increase the risk of bleeding, particularly in those people who are taking blood-thinning medications.
- **Interactions:**
 - Red clover may interfere with the body's ability to process some drugs that are broken down by liver enzymes. For that reason, you should check with your doctor before taking red clover. Red clover may increase effects of estrogen.

Red Raspberry Leaf

- **Gen:**
 - Red raspberry is a plant that is the source of a widely eaten, tasty, sweet berry. However, red raspberry fruit and leaf have also been used as medicine for centuries. Red raspberry leaf is used for gastrointestinal tract disorders, high blood pressure, fever, diabetes, and vitamin deficiency.

- **Mechanism of Action:**

- The chemicals in red raspberry might have antioxidant effects and help relax blood vessels. They might also cause muscles to contract or relax, depending on the dose and the muscle involved.

- **Dosage:**

- Traditional dosages include 5–10 mg (1–2 tsp) crushed leaf per 240 mL of water up to six times per day, or up to 12 g dry leaf.

- **Precautions:**

- Red raspberry leaf might act like estrogen. If you have any condition that might be sensitive to estrogen, don't use red raspberry leaf.

- **Interactions:**

- Insulin decreases blood sugar levels in the body. Red raspberry leaf might also decrease blood sugar levels in the body. Taking raspberry leaf along with insulin might cause blood sugar levels in the body to be too low. Monitor your blood sugar closely.

Red Sandalwood

- **Gen:**

- Red sandalwood is a tree and the wood at the center of the trunk and the bark are used as medicine. It is used most commonly for digestive tract problems and as a diuretic.

- **Mechanism of Action:**

- Red sandalwood may increase the loss of body water through urine. It may also decrease reabsorption of water in the bowels, reducing diarrhea.

- **Dosage:**

- The general safe dosage for internal consumption is 2–5 g of the red sandalwood powder.

- **Precautions:**

- Avoid use when constipated or dehydrated, as loss of water on top of these conditions may have a negative effect on health.

- **Interaction:**

- Red sandalwood might have an effect like a water pill or "diuretic." Taking red sandalwood might decrease how well the body gets rid of lithium. This

could increase the amount of lithium in the body and result in serious side effects.

Red Yeast Rice

- **Gen:**
 - Red yeast rice has been used for centuries in China as both food and medicine. It is made by fermenting a type of yeast called *Monascus purpureus* over red rice.
- **Mechanism of Action:**
 - Red yeast rice contains chemicals that are similar to prescription statin medications. One of these, called monacolin K, has the same makeup as the drug lovastatin.
- **Dosage:**
 - Most studies have used standardized extract: 600 mg, 2–4 times daily.
- **Precautions:**
 - People with liver disease, and those at risk for liver disease, should not take red yeast rice. Red yeast rice may affect the function in the same way prescription drugs to lower cholesterol can.
- **Interactions:**
 - If you take a statin, grapefruit and grapefruit juice can increase the amount of the drug in your blood. That can give you a greater chance of side effects and liver damage. Because red yeast rice may act like statins in the body, you should not drink grapefruit juice or eat grapefruit while taking red yeast rice.
 - Additionally, red yeast rice also may lower amounts of CoQ10 in the body.
 - CoQ10 is very important in heart and muscle health and in energy production.

Rhubarb

- **Gen:**
 - Rhubarb is a plant and the stalk is commonly eaten. Its root and underground stem are used make medicine. Taking a rhubarb root extract by mouth seems to improve symptoms of menopause, including hot flushes, mood, quality of life, and fatigue. Rhubarb is also used for the management of GI disorders as it has a mild laxative effect.

- **Mechanism of Action:**

- Mechanisms of action have been proposed and include inhibition of protein decomposition, accelerated reutilization of certain amino acids, reduction of the formation of free radicals, inhibition of overexpression of plasminogen activator inhibitor-1, and suppression of cytokines.

- **Dosage:**

- Dried rhubarb extract 20–50 mg/kg daily has been used in clinical trials and is a commonly accepted dosage.

- **Precautions:**

- There are chemicals in rhubarb that might harm the kidneys or increase the risk of kidney stones. Don't take rhubarb if you have a bowel obstruction, appendicitis, unexplained stomach pain, or inflammatory conditions such as Crohn disease, colitis, and irritable bowel syndrome.

- **Interactions:**

- Because rhubarb can harm kidneys, avoid taking with nephrotoxic medications. Avoid taking rhubarb with laxatives as rhubarb already has a laxative effect on the body and may cause diarrhea.

Riboflavin (Vitamin B2)

- **Gen:**

- Vitamin B2, also called riboflavin, is one of eight B vitamins. All B vitamins help the body to convert food (carbohydrates) into fuel (glucose), which is used to produce energy. These B vitamins, often referred to as B-complex vitamins, also help the body metabolize fats and protein. B-complex vitamins are necessary for a healthy liver, skin, hair, and eyes. They also help the nervous system function properly.

- **Mechanism of Action:**

- In addition to producing energy for the body, riboflavin works as an antioxidant, fighting damaging particles in the body known as free radicals. Free radicals can damage cells and DNA and may contribute to the aging process, as well as the development of a number of health conditions, such as heart disease and cancer. Antioxidants, such as riboflavin, can fight free radicals and may reduce or help prevent some of the damage they cause.

- **Dosage:**

- Daily recommendations for adults are as follows:

Men, 19 years and older: 1.3 mg (RDA).
Women, 19 years and older: 1.1 mg (RDA).
Pregnant women: 1.4 mg (RDA).
Breastfeeding women: 1.6 mg (RDA).

- Please consult a healthcare provider before giving riboflavin supplements to those 18 years of age or younger.

- **Precautions:**

- Riboflavin is generally considered safe, even at high doses. Riboflavin does not seem to cause any serious side effects. However, extremely high doses may cause itching, numbness, yellow or orange urine, or sensitivity to light.

- **Interactions:**

- Please speak to healthcare professional when taking riboflavin with anticholinergic medications, tetracyclines, tricyclic antidepressants, antipsychotic medication, thiamine diuretics, phenytoin, and doxorubicin.

Roman Chamomile

- **Gen:**

- Chamomile is one of the most popular herbs in the Western world. There are two plants known as chamomile: the more popular German chamomile and English chamomile. Both are used to calm frayed nerves, to treat stomach problems, to relieve muscle spasms, and to treat skin conditions and mild infections.

- **Mechanism of Action:**

- Roman chamomile has the characteristics of multi-target and multi-pathway in the treatment of anxiety disorder. Its possible mechanism is to intervene anxiety disorder in the process of disease development, such as neuroactive ligand–receptor interaction, serotonin synapse, and cAMP signaling pathway.

- **Dosage:**

- For adults drinking tea, pour 1 cup of boiling water over 2–3 heaping tsp (2–4 g) of dried herb, steep 10–15 min. Drink 3–4 times per day between meals.

- **Precautions:**

- Roman chamomile is considered generally safe, however has some precautions to keep in mind. Chamomile may make asthma worse, so people with asthma should not take it. Pregnant women should avoid chamomile because of the risk of miscarriage. If you are allergic to asters, daisies, chrysanthemums, or ragweed, you may also be allergic to chamomile. Drinking a lot of

highly concentrated chamomile tea may cause vomiting. Chamomile may cause drowsiness, so please do not take it while operating machinery or driving. Stop taking chamomile at least 2 weeks before surgery or dental work because of the risk of bleeding.

- **Interactions:**

- Please do not use chamomile without taking to your healthcare provider if you are also taking blood-thinning medications, sedatives, blood pressure medications, diabetes medications, birth control pills, certain antifungal drugs, or drugs that lower cholesterol.

Saccharomyces boulardii

Saccharomyces boulardii is a yeast species. In the Western world, it was discovered by a French microbiologist in 1920s who noted that certain people drinking a tea made from lychee and mangosteen did not develop cholera [1]. He isolated *Saccharomyces boulardii* from this tea. *S. boulardii* works as a probiotic; it is thought to transiently colonize the gut microbiota to minimize pathogenic microorganisms from growing and produce bioactive metabolites [2].

- **Dosage:**

- For adults, doses of 250–500 mg (about 5–10 billion colony-forming units) for up to 4 weeks. Some studies have examined up to 1000 mg for potentially up to 4 weeks [3]. In infants, doses of 50–200 mg/kg daily for up to 28 days [4]. A variety of formulations are available of *S. boulardii* but not all have been studied to be found effective.

- The main uses of *S. boulardii* include:

Diarrhea and antibiotic-induced diarrhea: In children, it has been shown to decrease acute diarrheal episodes [4]. In adults, there is conflicting evidence regarding antibiotic-induced diarrhea (AID) [4]. Some studies, including meta-analyses, have shown that it can prevent or reduce AID if started within 48 h of antibiotics while other studies show no difference between groups taking and not taking *S. boulardii* [4].

***Clostridium difficile* (*C. diff*) diarrhea:** A 2015 meta-analysis that showed *S. boulardii* reduced acute diarrheal episodes in adults and children found that it, also, reduced the occurrence of *C. diff* in children but not adults [5]. The Infectious Disease Society does not recommend the use of probiotics, including *S. boulardii*, for prevention of *C. diff* infections due to insufficiency evidence [6].

***Helicobacter pylori*:** A 2019 systematic review with a meta-analysis showed that *S. boulardii* can improve eradication rates of *H. pylori* when

used conjointly with triple therapy while also reducing gastrointestinal side effects [3]. The dosage studied was 100–1000 mg for 1–4 weeks [3].

Necrotizing enterocolitis: A 2021 systematic review with meta-analysis showed that *S. boulardii* can prevent necrotizing enterocolitis, reducing feeding intolerance and hospitalization time [7]. However, there was no effect on mortality or progression to sepsis [7].

- **Safety:**

- This is a relatively safe probiotic. Some studies report rare cases of fungemia in older adults, immunocompromised patients and adults with central venous catheters [4]. People with a yeast allergy may be allergic to this and other probiotics [4].

- **Medication Interactions:**

- A minor interaction with antifungals [4].

S-Adenosyl-L-methionine

S-Adenosyl-L-methionine (SAMe) is a compound found in the human body. It works by donating a methyl group, contributing multiple different reactions to metabolize hormones, neurotransmitters, and proteins [8]. It was discovered in Italy by Cantoni [9].

- **Dosage:**

- For adults with osteoarthritis, 400–1200 mg daily in up to three divided doses for up to 84 day has been studied [8]. One study looked at intravenous loading dose of SAMe 400 mg daily for 5 days, then switching to oral can improve symptoms as quickly as 14 days [10]. For cholestasis in liver disease, studies have looked at SAMe 500 BID orally or 1600 mg orally once a day for 2–8 weeks, or IV 800 mg daily or IV 500 mg BID for 2–3 weeks [8]. SAMe for depression has been studied at doses of total 800–1600 mg orally for 4–12 weeks and IV/IM at 200–400 mg 1–4 weeks [8]. Oral formulations should be taken with food.
 - The main uses studied include:

Osteoarthritis (knee and hip): Older studies from the 1980s and 1990s compared SAMe at doses above to placebo and other NSAIDs, showing that SAMe can be as effective as NSAIDs in improving osteoarthritis symptoms [8]. It may require up to 30 days to get the full effect of SAMe treatment. IV treatment can take 14 days to experience the full effect [8]. A Cochrane review from 2009 did say this treatment for osteoarthritis is inconclusive but more data is needed to prove this treatment is clinically effective [11].

Major depression: Studies have shown mixed results when SAMe is used alone when compared to placebo, TCAs, and escitalopram [8]. However, when used in combination with traditional treatment in patients not responding to their current treatment, it can improve remission rates [12]. IV/IM formulations have been shown to be better than placebo and as good as TCAs when used at the doses above [8].

Cholestasis: When compared to placebo, some studies stated that SAMe at the doses above can improve patient symptoms such as pruritus and fatigue as well as markers of disease including alkaline phosphatase levels [8]. Some studies were conducted looking at SAMe for intrahepatic cholestasis of pregnancy, but the results were mixed [13].

- **Safety:**

- Well tolerated at the doses above but at higher doses can cause GI distress, nausea, vomiting, sweating, and insomnia [8].

- **Medication Interactions:**

- Levodopa, Serotonergic drugs as SAMe has some serotonergic properties [8].

Sage

Sage consists of multiple plants part of the *Salvia* genus comprised have many different species. The two most common species that have been used as medicine are *Salvia officinalis* and *Salvia lavandulifolia* (Spanish sage) [14]. The leaf and oil contain compounds that are thought to have antibacterial, antiviral, antioxidant effects as well as others in in vitro and animal studies [14].

- **Dosage:**

- Sage extract has been studied from 280 to 1500 mg daily for up to 12 weeks [14]. Spanish sage essential oil has been studied at a single dose of 25–50 µL [14]. Sage can be found in creams and ointments that can be used topically.
 - The main uses studied include:

Cognition/memory: An RCT study that was published in 2021 looking at improvement in cognition used a compound called Cognivia, which combined sage polyphenols and Spanish sage terpenoids [15]. The treatment group, compared to placebo, received a single dose of 600 mg of Cognivia [15]. Memory was assessed within 2–4 h after the single dose and after 29 days. It showed there was improvement in memory after 29 days. Essential oils of sage may improve memory, but aromatherapy has not shown the same effect [14].

Hyperlipidemia (HLD): An RCT (published 2011) 500 mg of sage three times a day for 2 months can improve LDL and triglyceride levels while

increasing HDL levels [16]. However, the study did not look at long-term morbidity or mortality improvement in patients with HLD.

Menopausal symptoms: Sage seems to improve menopausal symptoms such as hot flashes and irritability; however, it does not seem to improve vaginal dryness and sexual desires [14]. Doses range from 280 mg daily for 4 weeks to 300 mg daily for 3 months [14].

- **Safety:**

- Sage is generally safe, however a few components of sage including thujone, camphor and cineol components can be toxic in large amounts [14].

- **Medication Interaction:**

- Sage may interact with anticholinergics, antihypertensives, antidiabetics, anticonvulsants, cholinergic medications, medications that interfere with the CYP450 system substrates, and estrogens [14]. Please be mindful when starting your patient on doses of Sage listed above.

Sangre de Grado

Sangre de grado (*Croton lechleri*) is a tree native to certain countries in South America. The red sap produced by the tree is used as medicine to treat certain conditions. The sap contains alkaloids, the main one being taspine, as well as proanthocyanidins [1]. Sangre de grado is thought to have multiple mechanisms including blocking sensory afferent nerves to improve pain and inhibiting chloride channels in the gastrointestinal tract to minimize sodium and water loss, improving diarrhea [1].

- **Dosage:**

- Crofelemer (FDA approved to treat HIV-related diarrhea) is dosed at 125 mg twice a day for 4 weeks [1]. For traveler's diarrhea, 125–500 mg up to four times a day for 2 days has been used [1]. For genital herpes, formulations of a sangre de grado ointment containing 15% Crofelemer used three times a day for 21 days has been studied [1].
 - The main uses for sangre de grado are listed below:

HIV-induced diarrhea: A randomized, placebo-controlled trial in 2013 showed that Crofelemer, which contains multiple proanthocyanidins, improved diarrheal episodes in HIV/AIDS patients [2]. Crofelemer has been FDA approved for this use.

Traveler's diarrhea: A product called SP-303, which contains a concentrated version of certain components of sangre de grado was studied in a randomized placebo-controlled trial in 2002 [4]. It was shown to shorten the duration of traveler's diarrhea [4].

Genital herpes: In patients with HIV/AIDs who has anogenital warts or herpes eruption, a topical form of sangre de grado was studied back in 1997 [17].

Compared to placebo, the study did show shorter time to heal compared to placebo; however, there was a small sample size. There are currently no recent studies that further evaluated the topical form.

- **Safety:**

- While the medication is safe and well-tolerated, overdose is possible. Side effects in animal studies have been shown at varying doses [1].

- **Medication Interaction:**

- No known current interactions at this time.

St. John's Wort

St. John's wort (*Hypericum perforatum*) is a yellow plant that is native to Europe and Asia and has been used there for centuries. It works mainly as a serotonin reuptake inhibitor, but can also inhibit the reuptake of dopamine and norepinephrine. It does this by activating the cytochrome P450 system, specifically CYP3A4 and monooxygenase enzymes. The main compounds in St. John's Wort that have this mechanism are hypericin and hyperforin.

- **Dosage:**

- The usual dosage for St. John's wort with 0.3% hypericin or 5% hyperforin is 300 mg orally BID or TID (total daily dose of 600–900 mg) or topically.
 - The main uses for St. John's wort are listed below:

Depression: St. John's wort works similarly to SSRIs with the mechanism for the treatment of depression. Meta-analysis and individual trials have compared St. John's wort to placebo as well as other anti-depressant medications. It has shown to improve depression symptoms for patients. Some studies mentioned that some participants tolerated St. John's wort better than SSRIs. However, other studies have shown that it was no more effective than placebo. Severe forms of depression should not be treated with St. John's wort.

Somatoform disorders: There is some data that St. John's wort can be used to improve symptoms of somatoform disorders compared to placebo. However, some of the studies did not follow patients for a prolonged period of time and did not include data on adverse side effects.

St. John's wort may be beneficial with symptoms relating to premenstrual cravings, cramping and irritability, menopausal symptoms such as hot

flashes, seasonal affective disorder, obsessive compulsive disorder, and eczema

- **Safety Concerns:**

- The most concerning safety concerns are regarding the interactions St. John's wort has with other commonly used medications (as discussed below). Common side effects reported if St. John's wort is taken alone include dizziness, anxiety, fatigue, diarrhea, photosensitivity, and dry mouth. It is contraindicated in pregnancy and lactation.

- **Interactions:**

- St. John's wort interacts with many common prescription medications due to its proposed mechanism of action. It can reduce the effectiveness of the medications listed below:
 - Allergy medications: Loratadine, Fexofenadine, Cetirizine; Antidepressants: SSRIs, TCAs, MAO inhibitors, Nefazodone; Birth control pills, Clopidogrel, Coumadin, Cyclosporine, Digoxin, HIV medications including protease inhibitors and non-nucleoside reverse transcriptase inhibitors; Immunosuppressant medications such as Adalimumab (Humira), Statins, Triptans, Warfarin.

Sorrel

Sorrel is a perennial plant that grows in Europe and Asia. The main ingredients in Sorrel are tannins, which are bitter compounds, along with proanthocyanidins and Flavan-3-ols [18]. The mechanism behind how sorrel may treat rhinosinusitis is by dehydrating cells and reducing secretions [18]. Other possible actions sorrel may have include anticarcinogenic, antimicrobial, and anti-platelet, but these were mostly in vitro studies [18].

- **Dosage:**

- Studies have looked at sorrel when used in combination with other products including Elderflower and Gentian root [18]. The dosage of sorrel in these combinations was 36 mg TID for up to 14 days [18].
 - The main use of sorrel is for:

Rhinosinusitis: A product named Sinupret, which is a combination of multiple herbs including sorrel, was compared to placebo to see if symptoms of rhinosinusitis improved [19]. However, these patients also may have taken antibiotics and decongestants. Other studies did show symptoms improvement as well [18]. One study looked at Sinupret in combination with Nasonex and it showed symptoms improvement [20]. Since

sorrel has not been studied on its own, it is unclear which compound is improving rhinosinusitis symptoms.

- **Safety:**

- Sorrel is general safe but patients can overdose on the plant if ingesting more than 15–30 g though lower doses may be fatal as well [18]. Oxalic acid is the compound that can cause overdose [18]. In 1989, a patient did fatally overdose on sorrel soup [21].

- **Medication Interactions:**

- Anticoagulants, Allegra, Calcium, Iron, and Zinc [18].

Spearmint

Spearmint is a mint plant that grows in Europe, Asia, and the United States. It is used as a flavoring in the food industry.

- **Dosage:**

- Doses varied in studies but included two cups of pure spearmint tea, 900 mg daily of spearmint. Duration varied as well from weeks to months.
 - The main use for spearmint includes:

Cognition: When compared to placebo, spearmint may improve mood and working memory in older adults with age-associated memory problems [22]. However, there are conflicting studies that show that spearmint gum does not improve cognition. In healthy adults, attention may improve when taking spearmint but not memory [22].

IBS: A small study looked at improvement in abdominal pain in patients with IBS after taking 30 drops of a combined solution containing spearmint, coriander, and lemon balm along with psyllium or loperamide [23]. While scores improved, it was not clear if it was the individual products or the combination that improved symptoms.

Hirsutism: There are some studies that concluded that spearmint for the dosing and duration above may improve hirsutism. One randomized-control trial showed that people with PCOS perceived their hirsutism improved with improvement in testosterone levels [24]. The duration of tracked patients over 30 days and had patients report a subjective assessment of their hirsutism [24]. However, objectively it seemed that the amount of hair was actually not reduced [24].

Osteoarthritis: A study in 2014 did show that spearmint may improve pain in osteoarthritic patients [25]. However, the study did not have a control group to compare and based the scores on subjective pain scoring.

- **Safety:**

- The dosage used in foods is safe for adults, children, and pregnant patients. However, doses at higher doses may not be safe.

- **Medication Interactions:**

- Spearmint may interact with drugs that can cause liver damage or CNS depression [26].

Saw Palmetto

Saw palmetto (*Serenoa repens*) is a small palm tree native to the United States that has been used to treat issues related to male and female reproductive organs. The part of the plant that is considered active would be the free fatty acids and sterols. Its proposed mechanism of action is that it inhibits 5-alpha-reductase; this decreased the conversion of testosterone to DHT. Some studies suggest that it may decrease inflammation by minimizing prostaglandin and leukotriene production.

- **Dosage:**

- The dosage of saw palmetto used in studies is 160 mg twice a day or 320 mg once a day of which 80–90% should contain the volatile oil. Limited data is available for use in children and during pregnancy.
 - The main uses of saw palmetto are discussed below:

Benign prostate hyperplasia (BPH): The most common use of saw palmetto is to treat the symptoms of BPH including diminished stream, post-void dribbling, overflow incontinence, and urinary retention. A meta-analysis initially published in 2002 showed that saw palmetto compared to placebo did improve the symptoms of BPH as measured by the International Prostate Symptom Score. However, an update to the meta-analysis published in 2009 that included nine new trials showed that it did not improve symptoms compared to placebo. In 2012, two other new long-term trials included in the meta-analysis supported the second conclusion that saw palmetto compared to placebo did not improve symptoms.

Alopecia: A systematic review published in 2020 did show some evidence that saw palmetto may benefit patients with androgenic alopecia and telogen effluvium.

Some other limited data does show that saw palmetto can promote urination and show anti-inflammatory effects, but there is insufficient data to support its clinical use.

- **Safety:**

- Saw palmetto is thought to be safe. Its main side effects are mild but include gastrointestinal distress, headaches, rhinitis, and fatigue. Saw palmetto does not falsely lower PSA levels. Some case reports have reported hot flashes in

young girls, acute pancreatitis, liver damage, coagulopathy, and prolonged bleeding time.

- **Medication Interactions:**

- Saw palmetto can inhibit the CYP 450 system so it can potentially interact with Warfarin, Clopidogrel, and aspirin. It is recommended to not use simultaneously with finasteride.

Syrian Rue

Syrian rue (*Peganum harmala*) is a white flower shrub that grows in the Mediterranean regions. The parts of the plant that are thought to be medicinal include the beta-carboline and quinazoline alkaloids (harmine, harmaline, and tetrahydroharmine). It has been used as a stimulant, a sedative while also containing hallucinogenic properties. It is thought to have many mechanisms in the body, most importantly it can inhibit monoamine oxidase, act as an anticholinergic, antispasmodic, antihistaminic, and antiadrenergic. It may have some antineoplastic properties. It is most likely unsafe in pregnancy and breastfeeding.

- **Dosage:**

- More clinical trials need to be completed to determine if a safe oral dose can be used. A topical dose of four drops three times a day for 4 weeks has been studied in knee pain/osteoarthritic patients as detailed below.
 - The main uses for Syrian rue include:

Anti-hypertensive: In vitro studies have shown that Syrian rue can cause vasorelaxant effects on vessels, lowering blood pressure. However, there are no available randomized-control trials that support the in vitro studies.

Osteoarthritis: In a 2015 randomized controlled trial, 54 participants (27 in treatment, 27 in control) with knee pain rubbed four drops of Syrian rue three times a day on their knees for 4 weeks or olive oil. The study showed decrease in pain and function difficulty when compared to placebo.

Some limited data is available that shows improvement in anti-depressant symptoms, amenorrhea, rheumatoid arthritis, and Parkinson's disease.

- **Safety:**

- Possibly safe when used topically. The safety when used orally is unclear and has been shown to be a strong hallucinogenic. It may cause hypertension, tachycardia, and tachypnea at high doses.

- **Medication Interactions:**

- Medication interactions include CYP 450 2D6 and 3A4 substrates, serotonergic drugs, anticholinergic and cholinergic drugs, dopamine agonists, hepatotoxic drugs, and caffeine as seen in in vitro and animal studies.

References

1. <https://naturalmedicines-therapeuticresearch-com.proxy.libraries.rutgers.edu/databases/food,-herbs-supplements/professional.aspx?productid=504>.
2. Wightman EL, Jackson PA, Spittlehouse B, Heffernan T, Guillemet D, Kennedy DO. The acute and chronic cognitive effects of a sage extract: a randomized, placebo controlled study in healthy humans. *Nutrients*. 2021;13(1):218. <https://doi.org/10.3390/nu13010218>.
3. Natural medicine database. <https://naturalmedicines.therapeuticresearch.com/databases.aspx>.
4. Kianbakht S, Abasi B, Perham M, Hashem Dabaghian F. Antihyperlipidemic effects of *Salvia officinalis* L. leaf extract in patients with hyperlipidemia: a randomized double-blind placebo-controlled clinical trial. *Phytother Res*. 2011;25(12):1849–53. <https://doi.org/10.1002/ptr.3506>.
5. McFarland LV. Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients. *World J Gastroenterol*. 2010;16(18):2202–22. <https://doi.org/10.3748/wjg.v16.i18.2202>.
6. <https://ods.od.nih.gov/factsheets/Probiotics-HealthProfessional/>.
7. Szajewska H, Kolodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea. *Aliment Pharmacol Ther*. 2015;42(7):793–801. <https://doi.org/10.1111/apt.13344>.
8. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):e1–e48. <https://doi.org/10.1093/cid/cix1085>.
9. Zhou BG, Chen LX, Li B, Wan LY, Ai YW. *Saccharomyces boulardii* as an adjuvant therapy for *Helicobacter pylori* eradication: a systematic review and meta-analysis with trial sequential analysis. *Helicobacter*. 2019;24(5):e12651. <https://doi.org/10.1111/hel.12651>.
10. Gao X, Wang Y, Shi L, Feng W, Yi K. Effect and safety of *Saccharomyces boulardii* for neonatal necrotizing enterocolitis in pre-term infants: a systematic review and meta-analysis. *J Trop Pediatr*. 2021;67(3):fmaa022. <https://doi.org/10.1093/tropej/fmaa022>.
11. <https://pubmed-ncbi-nlm-nih-gov.proxy.libraries.rutgers.edu/8064733/>.
12. <https://naturalmedicines-therapeuticresearch-com.proxy.libraries.rutgers.edu/databases/food,-herbs-supplements/professional.aspx?productid=786>.
13. Cantoni CJ. The nature of the active methyl donor formed enzymatically from L-methionine and adenosine triphosphate. *J Am Chem Soc*. 1952;74(11):2942–3.
14. Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-Adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *Am J Psychiatry*. 2010;167(8):942–8.
15. <https://www.nccih.nih.gov/health/sadenosylmethionine-same-in-depth>.
16. Rutjes AW, Nüesch E, Reichenbach S, Jüni P. S-Adenosylmethionine for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*. 2009;2009(4):CD007321. <https://doi.org/10.1002/14651858.CD007321.pub2>.
17. <https://naturalmedicines-therapeuticresearch-com.proxy.libraries.rutgers.edu/databases/food,-herbs-supplements/professional.aspx?productid=755>.

18. Macarthur RD, Hawkins TN, Brown SJ, et al. Efficacy and safety of crofelemer for noninfectious diarrhea in HIV-seropositive individuals (ADVENT trial): a randomized, double-blind, placebo-controlled, two-stage study. *HIV Clin Trials.* 2013;14(6):261–73. <https://doi.org/10.1310/hct1406-261>.
19. DiCesare D, DuPont HL, Mathewson JJ, et al. A double blind, randomized, placebo-controlled study of SP-303 (Provir) in the symptomatic treatment of acute diarrhea among travelers to Jamaica and Mexico. *Am J Gastroenterol.* 2002;97(10):2585–8. <https://doi.org/10.1111/j.1572-0241.2002.06027.x>.
20. Orozco-Topete R, Sierra-Madero J, Cano-Dominguez C, et al. Safety and efficacy of Virend for topical treatment of genital and anal herpes simplex lesions in patients with AIDS. *Antivir Res.* 1997;35(2):91–103. [https://doi.org/10.1016/s0166-3542\(97\)00015-6](https://doi.org/10.1016/s0166-3542(97)00015-6).
21. Peterson B, Nguyen H. St. John's wort. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2022. <https://www.ncbi.nlm.nih.gov/books/NBK557465/>.
22. <https://www.mayoclinic.org/drugs-supplements-st-johns-wort/art-20362212>.
23. <https://www.nccih.nih.gov/health/st-johns-wort-and-depression-in-depth>.
24. <https://www.mountsinai.org/health-library/herb/st-johns-wort>.
25. <https://pubmed.ncbi.nlm.nih.gov/33961968/>.
26. <https://naturalmedicines-therapeuticresearch-com.proxy.libraries.rutgers.edu/databases/food,-herbs-supplements/professional.aspx?productid=718>.

Chapter 6

Tamarind–*Vitex agnus-castus*



David Shukhman and Paul Bernstein

Tamarind

Tamarind is a tree which is used for constipation, liver and gallbladder problems, and stomach disorders. It is also used to treat colds and fever. Women sometimes use tamarind to treat pregnancy-related nausea. It is sometimes given to children to treat intestinal worms. An extract of tamarind seeds is used in eye drops for dry eyes.

Tamarind contains ingredients that may contain laxative effects and some activity against certain fungi and bacteria. Specifically for dry eyes, it contains a chemical similar to mucin that is normally found in the eye (mucin helps protect and wet the surface of the cornea).

- **Dosage:**

- The appropriate dose of tamarind depends on several factors such as the user's age, health, and several other conditions. At this time, there is not enough scientific information to determine an appropriate range of doses for tamarind.

- **Evidence:**

- More evidence is needed to rate the effectiveness of tamarind for these uses.

- **Precautions:**

- Tamarind is likely safe when used in food amounts. Caution in those with a history of diabetes or hypoglycemia as tamarind might lower blood sugar levels. There is a concern that it might interfere with blood sugar control.

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- **Interactions:**

- Taking tamarind with aspirin or Ibuprofen might increase how much aspirin/ibuprofen the body absorbs. This could increase the amount of aspirin in the body and might increase the chance of aspirin side effects.

Taurine

Taurine (2-aminoethanesulfonic acid) is an amino acid present in many tissues of mammals. It plays an important role in heart, muscle, and nervous system functioning. Taurine is obtained through diet by eating meat, dairy, and seafood products. It can also be made in the body from the amino acid cysteine.

Vegetarians may have lower plasma levels of taurine due to reduced intake of meats.

- **Mechanism of Action:**

- Taurine can be synthesized in the body by cysteine sulfenic acid decarboxylase. It circulates in free form and is not incorporated into proteins.
 - Taurine binds with cholesterol to form bile acid and protects the liver from alcohol-induced steatosis and lipid peroxidation. With respect to skeletal muscle, taurine facilitates Ca^{2+} -dependent excitation-contraction processes, helps regulate cellular volume, and assists in antioxidant defense from stress responses. It also serves as a neurotransmitter and crosses the blood-brain barrier by transporters.
 - Taurine reduces glutamate excitotoxicity through regulation of calcium ions and mitochondrial energy metabolism.

- **Dosage:**

- For congestive heart failure: 2–6 g of taurine per day in two or three divided doses.
 - Hepatitis: 4 g of taurine three times daily for 6 weeks.
 - Nausea and vomiting due to chemotherapy: 2 g of taurine daily for 6 months has been used.
 - Muscle soreness after exercise: 2 g of taurine three times daily after meals before exercise and continued 3 days after exercise.

- **Evidence:**

- In vitro and in vivo, taurine demonstrated neuroprotective effects, reduced diabetic-induced nephropathy, and improved glycemic control. In animal models, chronic taurine intake reversed muscle dysfunction and atrophy and decreased oxidative stress, and maternal taurine ingestion conferred protection against offspring developing adult hypertension.

- In humans, consumption of taurine-rich foods has been associated with lower cardiovascular risk. Evidence on whether taurine can improve exercise performance is mixed and although taurine increased skeletal muscle in rodents, these results have not been duplicated in humans.
- Taurine has been associated with some adverse effects in animal models including increased infection risk, delayed learning and memory, and when coadministered with ethanol, drastic reductions in blood glucose resulting in death. In humans, adverse reactions have been reported from excessive ingestion of energy drinks with taurine and caffeine, and in combination with alcohol.

- **Precautions:**

- Excessive taurine intake combined with alcohol and/or caffeine has caused severe adverse effects, including death. One case study showed acute kidney injury in a 7-year-old boy who ingested large quantities of both alcohol and an energy drink containing taurine and caffeine. One case study showed Tachycardia with death in a 28-year-old-man after drinking three cans of an energy drink containing caffeine and taurine among other ingredients.

- **Interactions:**

- Caution to those taking antihypertensive medications as Taurine may increase the blood-pressure lowering effects of these drugs.

Tea Tree Oil

Tea tree oil is the essential oil distilled from *Melaleuca alternifolia*, a plant native to Australia. It has been used in traditional medicine for its antiseptic and anti-inflammatory properties to treat various skin conditions and infections. It is also a popular ingredient in skin and hair products.

- **Mechanism of Action:**

- Terpinen-4-ol, a major constituent of tea tree oil, exhibited antimicrobial activity against *Candida albicans*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Terpin-4-ol, alpha-terpineol, and alpha-pinene also had antimicrobial effects against *Staphylococcus epidermidis* and *Propionibacterium acnes*. Terpinen-4-ol suppressed inflammatory mediator production by activating human monocytes. A tea tree oil concentrate prevented influenza virus from entering the host cells by disturbing the normal viral membrane fusion procedure. Other in vitro studies indicate that tea tree oil has weak estrogenic and antiandrogenic properties that may alter the estrogen and androgen signaling pathways. At the same time, the notion that tea tree oil has hormone-modulating properties has been challenged, and further confirmatory research is needed. Skin irritation following use of tea tree oil is

due to its auto-oxidation and formation of epoxide intermediates via arene-epoxidation reactions catalyzed by human cytochrome P450 enzymes.

- **Dosage:**

- The recommended dose for acne is: Apply 5% gel to affected areas daily. The recommended dose for nail fungus (Onychomycosis) is: Apply 100% solution twice daily for 6 months.
- The recommended dose for athlete's foot is: Apply 10% cream topically twice a day for 1 month OR apply 25% or 50% solution twice a day for 1 month.
- Tea tree oil 100% solution can be applied to cuts, scrapes, burns, abrasions, insect bites, and stings.

- **Evidence:**

- In vitro studies suggest wide-spectrum antimicrobial, antiviral, antiprotozoal, anti-inflammatory and antiproliferative properties. Animal studies also suggest cytotoxic effects.
- Preliminary studies in humans suggest various topical tea tree oil formulations may help treat acne, athlete's foot, fungal nail infections, histamine-induced skin inflammation, warts, cold sores, chalazia, and dermatitis. However, additional studies are needed to confirm under what conditions topical applications may be effective.

- **Precautions:**

- Tea tree oil should not be taken orally, as severe side effects have occurred. Side effects of tea tree oil may be local irritation and inflammation at the application area.

- **Interactions:**

- None well documented.

Terminalia

The bark of *Terminalia arjuna* has been used in India for more than 3000 years, primarily as a heart remedy. An Indian physician named Vaghbhatta has been credited as the first to use this product for heart conditions in the seventh century

A.D. People today use *T. arjuna* for disorders of the heart and blood vessels (cardiovascular disease), including heart disease and related chest pain, high blood pressure, and high cholesterol. It is also used as "a water pill," and for earaches, dysentery, sexually transmitted diseases (STDs), diseases of the urinary tract, and to increase sexual desire. Its useful phytoconstituents are: Triterpenoids, β -sitosterol, flavonoids, and glycosides.

- **Mechanism of Action:**

- Triterpenoids and flavonoids are considered to be responsible for its beneficial antioxidant cardiovascular properties. The drug has shown promising effect on ischemic cardiomyopathy. Bark stem of *T. arjuna* possesses diuretic, inotropic, and chronotropic properties. The inotropic effect is considered to be mediated through the high concentration of Ca⁺⁺ present in the plant.

- **Dosage:**

- Clinical studies have been conducted in cardiovascular disorders using *T. arjuna* bark extract at doses of 500 mg every 8 h for up to 3 months. Dosages for other *Terminalia* species have not been clinically defined.

- **Evidence:**

- In a recent study the anti-ischemic effect of bark powder was evaluated in 30 patients of stable angina/post-infarct angina (500 mg tds). The authors observed that the mean anginal frequency decreased significantly, along with a significant decrease in systolic blood pressure (SBP), improvement in ECG changes, and reduction in plasma cortisol and serum cholesterol levels.

- **Precautions:**

- Mild side effects like nausea, gastritis, headache, body ache, constipation, and insomnia have been reported. No hematological, renal, or metabolic toxicity has been reported even after more than 24 months of its administration. However, high amounts of the plant extract should not be consumed, as it may induce hepatotoxicity as well as hypothyroidism.

- **Interactions:**

- Not much data is available to comment on the effect of *T. arjuna* on cytochrome P450 (CYP450) enzyme. Results from a recent *in vitro* study indicate that *T. arjuna* extracts contain constituents that can potently inhibit the activity of CYP1A

Theacrine

Theacrine (1,3,7,9-tetramethyluric acid) is a naturally occurring chemical that is similar to caffeine. It is found in different types of tea and coffee, as well as in the seeds of the Herrania and Theocrama plant species. It is also found in the tea plant *Camellia assamica* var. *kucha*, which has been used traditionally to prolong life and cure the common cold. People take theacrine by mouth for aging, the common cold, fatigue, and mental performance. Theacrine is also added to pre-workout supplements promoted for improving athletic performance.

- **Mechanism of Action:**

- Theacrine seems to affect the brain similar to caffeine. Like caffeine, theacrine stimulates the central nervous system at higher doses and decreases central nervous system activity at lower doses. But unlike caffeine, theacrine does not seem to affect blood pressure. Theacrine might also lessen liver damage caused by stress and reduce pain and swelling.

- **Dosage:**

- The appropriate dose of theacrine depends on several factors such as the user's age, health, and several other conditions. Theacrine has demonstrated clinical safety and non-habituating effects in healthy humans over 8 weeks of daily use at up to 300 mg/day. However, at this time there is not enough scientific information to determine an appropriate range of doses for theacrine.

- **Evidence:**

- Evidence shows findings that support clinical safety and non-habituating neuro-energetic effects of Theacrine as seen in the TeaCrine™ study.

- **Precautions:**

- Taken in notably low doses, theacrine could potentially carry a sedative effect on a human body. This is also a notable side effect of caffeine, which has also been suggested to sedate people when consumed in a very small dosage.

- **Interactions:**

- Data from combination studies shows that the coadministration of caffeine and theacrine produces a significant pharmacokinetic interaction, resulting in enhanced theacrine exposure.

Theaflavin

Theaflavin (TF) is a chemical in black tea that is formed from fermentation of green tea. It is the primary red pigments in black tea that possess several health benefits, including fat-reducing and glucose-lowering capabilities and lifestyle-related disease prevention related to anti-obesity, anticancer, anti-atherosclerotic, anti-inflammatory, antiviral, antibacterial, anti-osteoporotic, and anti-dental caries properties.

- **Mechanism of Action:**

- Enzymes such as polyphenol oxidase and peroxidase are present in tea plant leaves, which, for non-fermented tea, are either steamed, boiled, microwaved, or electrically heated to inactivate endogenous oxidases. Black tea leaves are tea leaves in which green tea catechins are oxidized by endogenous polyphenol oxidase or peroxidase during the fermentation process.

- **Dosage:**

- In the only clinical trial available, a theaflavin-enriched green tea extract (375 mg) providing 75 mg of theaflavin reduced LDL and total cholesterol in 12 weeks. Still, there's not enough clinical data to establish a safe and effective dosage for a general population.

- **Evidence:**

- Theaflavins (TFs) are only present in low concentration in black tea. Several meta-analyses have shown that the consumption of black tea results in significant primary prevention of cardiovascular diseases by decreasing plasma low-density lipoprotein cholesterol levels and blood pressure as well as inversely related to BMI. Zhao et al. reported that black tea extract inhibited the growth of *P. gingivalis* (a bacteria found in the oral cavity). It has been reported that older women who drink tea exhibit higher Bone Mineral Density measurements than women who do not drink tea. Based on animal and cellular research, tea polyphenols (mainly EGCG and theaflavins) may play an important role in delaying the onset and progression of Parkinson's disease.

- **Precautions:**

- No side effects of theaflavins were reported in the above clinical study, but their long-term safety remains unknown in the lack of stronger clinical evidence.

- **Interactions:**

- No interactions of theaflavins were reported in the above clinical study, but their long-term safety remains unknown in the lack of stronger clinical evidence.

Theanine

L-theanine is a water-soluble amino acid found in green tea and mushrooms. Purified L-theanine is available as an oral dietary supplement and is used for its perceived antioxidant and relaxant effects. Several in vitro and animal studies suggest lipid-lowering, neuroprotective, anti-obesity, and antitumor properties. Other lab studies suggest L-theanine may affect levels of some neurotransmitters, prevent beta-amyloid-induced cognitive dysfunction, and promote longevity in *C. elegans*.

- **Mechanism of Action:**

- The underlying mechanism of L-theanine is to increase inhibitory neurotransmitter levels as well as act directly to block overproduction of excitatory neurotransmitters. L-theanine is a glutamic acid analog, a compound chemical similar to the neurotransmitter glutamate.

- **Dosage:**

- Studies reporting an anxiolytic effect used single doses of theanine 200–250 mg. Short-term studies conducted for psychiatric disorders examined doses ranging from 240 to 400 mg per day in divided doses. Single-dose studies evaluating effects on cognitive performance and mental alertness combined caffeine with L-theanine doses of 97–100 mg.

- **Evidence:**

- In a double-blind trial of adjunctive L-theanine for generalized anxiety disorder, there were no significant effects on anxiety although positive effects on sleep were observed. Other small trials in patients with various conditions also suggest improvements in sleep quality and possibly depression, anxiety, and cognitive impairments although larger well-designed trials are needed. Some trials evaluating L-theanine with caffeine suggest improvements in cognitive performance although effects observed with caffeine alone in one study were lost with concomitant L-theanine. When combined with antipsychotic treatment, L-theanine alleviated anxiety and related symptoms, and improved sleep in patients with schizophrenia.
 - Epidemiological data suggest green tea consumption may contribute to stroke prevention, but it is unclear whether L-theanine alone may confer this benefit. Preclinical studies suggest that L-theanine enhances chemotherapeutic effects of doxorubicin and idarubicin and alleviates adverse effects from use of these agents. However, patients undergoing chemotherapy should discuss the use of L-theanine with their physicians because these effects are not based on clinical trials, and epigallocatechin-3-gallate (EGCG) in green tea reduces activity of the chemotherapy drug bortezomib.

- **Precautions:**

- Information regarding adverse reactions to theanine alone (versus combined with caffeine, as in tea) is lacking. Clinical trials used small numbers of participants and reported poorly on adverse events. One study among elderly participants recorded a higher number of reported headaches among those receiving four doses of theanine 250 mg.

- **Interactions:**

- Lab experiments that suggest L-theanine may increase efficiency of chemotherapy drugs or reduce side effects have not been confirmed in humans.
 - Patients undergoing chemotherapy should discuss the use of L-theanine with their physicians because safety data in cancer patients are lacking, and another component found in green tea called epigallocatechin-3-gallate (EGCG) reduces activity of the chemotherapy drug bortezomib.

Thiamine

Thiamine is vitamin B1. Thiamine is found in foods such as cereals, whole grains, meat, nuts, beans, and peas. Thiamine is important in the breakdown of carbohydrates from foods into products needed by the body. Thiamine is used to treat or prevent vitamin B1 deficiency. Thiamine injection is used to treat beriberi, a serious condition caused by prolonged lack of vitamin B1. Thiamine taken by mouth (oral) is available without a prescription. Injectable thiamine must be given by a health-care professional.

- **Mechanism of Action:**

- Thiamine combines with adenosine triphosphate (ATP) in the liver, kidneys, and leukocytes to produce thiamine diphosphate. Thiamine diphosphate acts as a coenzyme in carbohydrate metabolism, in transketolation reactions, and in the utilization of hexose in the hexose-monophosphate shunt.

- **Dosage:**

- Usual adult dose for thiamine deficiency: If dextrose administered: to patients with marginal thiamine status, give 100 mg in each of the first few liters of IV fluid to avoid precipitating heart failure. Usual adult dose for vitamin/mineral supplementation: For beriberi, 10–20 mg IM three times daily for up to 2 weeks. Thereafter, use an oral therapeutic multivitamin preparation containing 5–10 mg thiamine daily for 1 month. 50–100 mg orally once a day usual adult dose for Wernicke's Encephalopathy: 100 mg IV as an initial dose followed by 50–100 mg/day IM or IV until the patient is on a regular, balanced diet. Usual pediatric dose for beriberi: 10–25 mg IM or IV daily (if critically ill), or 10–50 mg orally every day for 2 weeks, then 5–10 mg orally daily for 1 month. If collapse occurs: 25 mg IV. Administer with caution. Usual pediatric dose for thiamine deficiency: If dextrose administered to patients with marginal thiamine status, give 100 mg in each of the first few liters of IV fluid to avoid precipitating heart failure. Usual pediatric dose for vitamin/mineral supplementation: Infants: 0.3–0.5 mg orally once a day; children: 0.5–1 mg orally once a day.

- **Precautions:**

- Thiamine supplementation is reported to be well-tolerated and safe to use. A retrospective study on adverse effects of thiamine supplementation among more than 300,000 patients found no serious side effects. However, some commonly reported adverse effects include nausea, urticaria, lethargy, ataxia, and impaired gut motility.

- **Interactions:**

- Laboratory studies suggest that digoxin, a medication used to treat heart conditions, may reduce the ability of heart cells to absorb and use vitamin B1.

This may be particularly true when digoxin is combined with furosemide (Lasix, a loop diuretic). Diuretics, particularly furosemide (Lasix), which belongs to a class called loop diuretics, may reduce levels of vitamin B1 in the body. It is possible that other diuretics may have the same effect. Preliminary evidence suggests that some people taking phenytoin have lower levels of thiamine in their blood, which may contribute to the side effects of the drug. However, this is not true of all people who take phenytoin.

Threonine

Threonine is an amino acid. Amino acids are the building blocks the body uses to make proteins. Threonine is used to treat various nervous system disorders including spinal spasticity, multiple sclerosis, familial spastic paraparesis, and amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease).

- **Mechanism of Action:**

- Threonine is changed in the body to a chemical called glycine. Glycine works in the brain to reduce constant and unwanted spasticity.

- **Dosage:**

- For a certain movement disorders due to spinal cord damage (spinal spasticity): 6 g of threonine per day.

- **Evidence:**

- Early research suggests that taking 1.5–2 g of threonine by mouth three times daily might improve some symptoms in people with familial spastic paraparesis. Taking 2–4 g of threonine daily for up to 12 months does not seem to slow the progression of ALS or reduce symptoms. There is also some evidence that threonine might actually worsen lung function in people with ALS.

- **Precautions:**

- There is some concern that threonine might decrease lung function in patients with ALS. In one study, ALS patients taking 1 g of threonine four times per day for 6 months had significantly reduced lung function compared to patients who did not receive threonine.

- **Interactions:**

- There is some concern that threonine might decrease how well a Namenda, a medication used for Alzheimer's disease works.

Thuja

Thuja occidentalis, commonly known as Arbor Vitae, is a medicinal plant that is used as phytotherapy for acute and chronic infections of the upper respiratory tract. It has also been used as an adjuvant to antibiotics for severe bacterial infections.

- **Mechanism of Action:**

- *Thuja* is able to stimulate and costimulate cytokine and antibody production as well as activate macrophages and other immunocompetent cells.

- **Dosage:**

- The recommended daily dose of 36 mg is in the non-critical range.

- **Evidence:**

- A 12 mg daily dose given simultaneously with antibiotic therapy for chronic bronchitis showed a faster improvement in that group when compared to a placebo. Patients with a common cold taking 6 mg of *Thuja* three times daily demonstrated a therapeutic benefit for decreasing the duration of cold symptoms if taken as early as possible with symptom onset. A single dose of up to 75 mg or 1.25 mg per kilogram of bodyweight is considered safe in humans.

- **Precautions:**

- This herb has not shown to cause any adverse side effects; however, symptoms of intoxication include gastrointestinal issues like nausea, vomiting, and diarrhea. These extreme doses can lead to symptoms of liver and renal toxicity.

- **Interactions:**

- Taking *Thuja* along with medications that increase the chance of having a seizure can increase the risk of seizure. Anticonvulsants taken with *Thuja* can increase the risk of seizure due to decreased effectiveness. *Thuja* can decrease the effectiveness of medications taken to suppress the immune system.

Thunder God Vine

Thunder god vine, known as *Tripterygium wilfordii*, is a vine that grows in China. It is primarily promoted to be used for rheumatoid arthritis.

- **Mechanism of Action:**

- This vine contains chemicals that alter the way the immune system functions in order to relieve swelling.

- **Dosage:**

- When taken for rheumatoid arthritis, some studies have shown that 60–350 mg of the vine extract is safe if consumed orally.

- **Evidence:**

- Some studies have shown that taking thunder god vine along with standard treatment for rheumatoid arthritis has been shown to be more effective when compared to the standard treatment alone for reducing inflammation and swelling. This has led people to consume thunder god vine, while undergoing standard rheumatoid arthritis treatment. Although more research needs to be conducted, some studies are showing that thunder god vine can prove to be beneficial for treating Crohn's disease, kidney disorders, and psoriasis. Some studies have even shown that thunder god vine is more effective for treating rheumatoid arthritis than conventional disease modifying anti-rheumatic drugs (DMARDs).

- **Precautions:**

- Thunder god vine can cause upset stomach, vomiting, diarrhea, kidney issues, and missed menstrual periods. Thunder god vine can cause birth defects, so it should be avoided when pregnant. Due to its immunosuppressive effects, this vine should be avoided in patients who already have a weakened immune system due to another medical condition. It should be avoided in people who have osteoporosis as it can weaken bone strength. It can also alter sperm and lead to a decrease in male fertility.

- **Interactions:**

- Thunder god vine should not be taken with immunosuppressants and drugs that are metabolized by the liver.

Tiratricol

Tiratricol (triiodothyroacetic acid) is a naturally occurring thyroid hormone that is used to treat thyroid issues (i.e., cancer) and is also used as a supplement to increase metabolic rate and decrease cellulite. In the United States, the FDA has now classified this to be an unapproved drug due to it being a powerful metabolite of T3 and T4 thyroid hormones.

- **Mechanism of Action:**

- It works by targeting thyroid receptors on effector organs that respond to thyroid hormone.

- **Dosage:**

- 10–24 mg taken twice daily combined with levothyroxine has been shown to be safe when treating thyroid cancer. Dosing information for other uses isn't readily available.

- **Evidence:**

- Tiratricol is primarily effective for treating patients who have pituitary resistance to thyroid hormone (Reffetoff syndrome). In these patients, thyroid hormone levels are elevated, but the thyroid-stimulating hormone levels are not suppressed. Tiratricol in this case works to suppress thyroid-stimulating hormone. Tiratricol has shown some effectiveness for treating thyroid cancer when combined with levothyroxine. Tiratricol has also been used in trials studying the treatment of Allan-Herndon-Dudley syndrome, which is a rarer disorder of brain development that causes moderate to severe intellectual disability along with movement issues. It has been shown to be likely ineffective as a weight loss supplement and more research needs to be conducted to see its impact on reducing cellulite. It is considered to be unsafe for both of those uses.

- **Precautions:**

- It can cause diarrhea, fatigue, and weakness. Tiratricol should be avoided in pregnancy unless it is being used to treat thyroid problems in the developing infant. It should be avoided in any person with heart issues, high blood pressure, diabetes, liver disease, myxedema, and clotting issues.

- **Interactions:**

- It should not be taken with other thyroid hormones unless specifically prescribed. It should not be taken with cholestyramine since that can impact how much tiratricol is absorbed. It should not be taken with antidiabetes drugs, anticoagulant, and antiplatelet drugs.

Tocotrienol

The Vitamin E family is comprised of four tocotrienols (alpha, beta, gamma, and delta). Tocotrienols has been used for high cholesterol, scars, familial dysautonomia, and non-alcoholic fatty liver disease. It is also being looked at as a potential anti-osteoporotic agent in order to treat osteoporosis as well as a supplement to protect against metabolic disease.

- **Mechanism of Action:**

- Tocotrienol is potent antioxidant. It works to scavenge free radicals and prevents oxidative damage on osteoblasts. This in term promotes the survival of osteoblasts.

- **Dosage:**

- More research needs to be performed to ascertain the appropriate dosing requirements based on the user's health, age, and medical conditions. This supplement has been safely used at a dose of up to 200 mg daily for 5 years.

- **Evidence:**

- Current studies are examining the potential of using tocotrienol to protect against metabolic diseases like diabetes and obesity. Due to its anti-inflammatory, antioxidant, and cell-signaling altering effects it is being used to complement current treatment modalities for diabetes and obesity. More studies need to be conducted in order to examine its usefulness in this scenario. It has been shown to be possibly ineffective for treating high cholesterol issues. There is insufficient evidence currently to examine its usefulness in treating scars, familial dysautonomia, and non-alcoholic fatty liver disease.

- **Precautions:**

- Current breast feeding and pregnancy studies have not been completed, so tocotrienol should be avoided in these scenarios. Diabetic patients should monitor their sugar levels closely if taking tocotrienol.

- **Interactions:**

- Tocotrienol may slow blood clotting, so it should be avoided with medications that also slow down blood clotting because that can lead to bruising and bleeding.

Tormentil

Tormentil is an herb that has been used in tea for people with upset stomachs and diarrhea. Some studies are examining its role in stopping bleeding.

- **Mechanism of Action:**

- Tormentil is composed of tannins that work to reduce inflammation and also has a drying effect on tissues.

- **Dosage:**

- More research needs to be conducted into appropriate dosing regimens for tormentil. It is considered possibly safe when taken by mouth or applied directly to the skin.

- **Evidence:**

- Early studies have shown that taking tormentil three times daily has reduced the duration of diarrhea in children with rotavirus. Other studies are showing

that tormentil can be beneficial in improving symptoms of ulcerative colitis. Gargling with a tormentil mouth wash has been shown to shorten flare-ups of lichen planus. Preliminary animal studies are being conducted to examine the effects of tormentil on thrombosis due to its anti-inflammatory and antioxidant properties.

- **Precautions:**

- Side effects can include mild abdominal pain along with instances of heart burn. There is not enough information to show if tormentil is safe to be taken while pregnant or breast feeding.

- **Interactions:**

- There is currently no significant information on the potential interactions of tormentil with other substances.

Tragacanth

Tragacanth is a shrub that grows in certain areas of the Middle East. It has commonly been used to relieve symptoms of constipation and diarrhea.

- **Mechanism of Action:**

- Tragacanth is able to stimulate the intestines of the user. **Dosage:** More research needs to be conducted in order to ascertain the appropriate dosage requirements for tragacanth; however, the dosage does depend on several variables like the age, gender, and body weight of the user.

- **Evidence:**

- More research needs to be done in order to see whether or not tragacanth is useful in combatting diarrhea or constipation.

- **Precautions:**

- Tragacanth can lead to a blockage of the intestinal tract if not consumed with enough fluid. It has been shown to cause breathing problems in people who are sensitive to quillaia bark.

- **Interactions:**

- Since tragacanth is a thick gel, it can effect how certain medications are absorbed when taken orally. For this reason, tragacanth should be consumed 30–60 min after consuming any medications.

Trypsin

Trypsin is an enzyme that is naturally found in the small intestine. It is given to people who lack this enzyme in order to aid in digestion. It is given in combination with bromelain and rutin in order to treat osteoarthritis. It has also been used to apply onto skin to remove dead tissue and promote healing.

- **Mechanism of Action:**

- Trypsin is a digestive enzyme that is used to hydrolyze proteins.

- **Dosage:**

- For treating osteoarthritis, two tablets containing 48 mg of trypsin have been taken safely twice daily. For wound healing, more research needs to be conducted to figure out how much is needed to be applied to the skin.

- **Evidence:**

- Studies have shown that taking trypsin along with bromelain, rutin, and diclofenac was beneficial in reducing pain in patients with TMJ osteoarthritis.
 - Other studies have shown that due to its anti-inflammatory, anti-edematous, fibrinolytic, anti-infective, and analgesic properties, trypsin is considered to be a promising treatment for facilitating healing from traumatic injuries. It was shown to promote a quicker recovery, while mitigating inflammatory signs and symptoms.

- **Precautions:**

- Most common side effect seen is pain and burning. **Interactions:** More research needs to be conducted into determining the interactions that trypsin has with other medications.

Turmeric

Turmeric is a spice that comes from a plant that is major source of a chemical called polyphenol curcumin. It has been used in several oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. People have also taken it to enhance muscle recovery after soreness. Curcumin has a poor bioavailability so in order to increase its bioavailability it can be combined with a substance like piperine which is found in black pepper.

- **Mechanism of Action:**

- The antioxidant and anti-inflammatory effects are the two major mechanisms that explain the effects that turmeric has. It leads to an increase in serum

antioxidants such as superoxide dismutase. It is able to scavenge free radicals, while also modulating the activity of several key enzymes. Turmeric, specifically curcumin, has been shown to suppress inflammation by blocking NF- κ B that should be activated from varying inflammatory stimuli. Downregulating NF- κ B can aid in treating many diseases involved with inflammation like Alzheimer's, Parkinson's, and multiple sclerosis.

- **Dosage:**

- For instances of high cholesterol, 1.4 g of turmeric has been safely divided into two daily doses for up to 3 months. 1500 mg of turmeric divided into three daily doses for 8 weeks has been safely taken for itching. 500 mg taken four times daily has been done safely for 4–6 weeks for treating osteoarthritis.

- **Evidence:**

- Studies have shown that taking turmeric has been able to reduce total cholesterol, LDL, and triglycerides in overweight people. Turmeric has been shown to reduce pain in people taking it for osteoarthritis. Its effectiveness in reducing pain for this population is comparable to ibuprofen. Turmeric has also been used to reduce itching in people who suffer from long-term kidney disease.

- **Precautions:**

- Some people can experience upset stomach, nausea, or dizziness. Turmeric is likely unsafe when taken by mouth during pregnancy. Turmeric can worsen gallbladder problems. It may slow down blood clotting. It can decrease blood sugar in diabetic patients. It can worsen symptoms of gastroesophageal reflux disease. Turmeric should be avoided in people with hormone-sensitive conditions such as breast cancer.

- **Interactions:**

- Avoid combining turmeric with medications that are metabolized by the liver since turmeric can decrease how quickly the medication is broken down. Taking turmeric with diabetes medication can cause a significant drop in blood sugar. Taking turmeric with anticoagulants or antiplatelets can increase bruising and bleeding. Turmeric can increase the side effects of sulfasalazine when taken concurrently. Turmeric can increase the amount of tarolimus available in the body. Turmeric can decrease how much talinolol is absorbed.

Tylophora

Tylophora is a plant that is found in tropical climates of Asia. People have been primarily taking it in order to reduce allergic reactions and increase airflow in asthma.

- **Mechanism of Action:**

- Tylophora has some anti-inflammatory mechanism that works to increase airflow in a patient who has asthma. The specific mechanism is not known at this time.

- **Dosage:**

- More dosing studies need to be conducted; however, current dosing regimens depend on the user's age, weight, and gender.

- **Evidence:**

- Studies showing the effectiveness that tylophora has on asthma has been inconsistent. Some studies have shown that taking Tylophora daily for 6 days has improved asthma symptoms for up to 8 weeks after treatment has begun.

- **Precautions:**

- More research needs to be conducted on consuming Tylophora while pregnant or breast feeding. Some noted side effects are upset stomach, mouth sores, and loss of taste for salt.

- **Interactions:**

- More studies need to be conducted to confirm the interactions of Tylophora with other medications.

Tyrosine

Tyrosine is an amino acid that the body can make from a precursor of phenylalanine. It can be found in dairy products, meat, and fish. It is used to treat phenylketonuria as well as neurologic and cognitive issues like attention deficit disorder.

- **Mechanism of Action:**

- Tyrosine is used as a precursor in the synthesis of neurotransmitters like dopamine and norepinephrine.

- **Dosage:**

- For phenylketonuria the current regimen is 6 g of tyrosine per 100 g of protein. 150 mg/kg/day has been used safely for alertness.

- **Evidence:**

- People with phenylketonuria are unable to produce their own tyrosine, leading to their own levels. These patients require a tyrosine supplementation.
- Some studies are showing that tyrosine is effective in improving mental performance and memory when put under stressful conditions like military training and sleep deprivation due to the effects of dopamine and norepinephrine.

- **Precautions:**

- Some noted side effects are nausea, headache, fatigue, heartburn, and joint pain. Tyrosine can worsen hyperthyroidism or Grave's disease because it is used to make thyroxine. Therefore, it should be avoided in these conditions.

- **Interactions:**

- Tyrosine can decrease how much levodopa is absorbed, so it can decrease the effectiveness of it. Tyrosine should be avoided with thyroid hormones since it can lead to an increase of effects of thyroid hormones.

Umckaloabo

- **Mechanism of Action:**

- Polyphenols (e.g., catechin) and 7-hydroxy-coumarins (e.g., umckalin), the main constituents, have antimicrobial and immunomodulatory effects. Other constituents include polymeric proanthocyanidins, monomeric flavan-3-ols, phenolic acids, and gallic acid as well as small amounts of quercetin and sitosterol-glucoside. *P. sidoides* extract increased natural killer cell formation, tumor necrosis factor alpha, iNO, and interferon-beta release, and also demonstrated anti-adhesive effects. In addition, the extract improved peripheral blood phagocytes by enhancing oxidative burst and intracellular killing in vitro.
- Anti-HIV effects may occur through inhibiting the attachment of viral particles to target cells.

- **Dosage:**

- For bronchitis: 30 drops (about 1.5 mL) three times daily or 10–30 mg tablets three times daily of a specific extract of Umckaloabo for 7 days. In children age 7–12 years, 20 drops of this extract three times daily. In children age 6 years or less, 10 drops of this extract three times daily. Some studies have not found the tablet formulation to work in children. For sore throat and swollen tonsils in children age 6–10 years: 20 drops of a specific extract of Umckaloabo three times daily (about 3 mL/day) for 7 days.

- **Evidence:**

- Data from clinical trials suggest effectiveness against acute bronchitis and against rhinosinusitis. Meta-analyses suggest a significant decrease in bronchitis symptoms with *P. sidoides* use and benefit in pediatric respiratory tract infections. An herbal preparation from *P. sidoides* root was found effective for moderate to severe chronic obstructive pulmonary disease (COPD).
- **Precautions:**
 - Allergic reactions. Gastrointestinal upset. Ear and labyrinth disorders. Exacerbation of respiratory symptoms, fever, exanthema, psychomotor unrest, and diarrhea in children have been reported.
- **Interactions:**
 - Due to its coumarin content, *P. sidoides* may increase the risk of bleeding. However, coadministration with warfarin did not change the blood coagulation values in animals. Clinical relevance has yet to be determined.

Uva Ursi

Uva ursi is a plant that has been used mostly for disorders of the urinary tract. It has been used in cases of kidney, bladder, and urethra infections as well as kidney and bladder stones.

- **Mechanism of Action:**
 - The active component of Uva ursi is hydroquinone glycosides, which is believed to have anti-inflammatory and antiseptic activities that get excreted in the urine.
- **Dosage:**
 - More research needs be conducted for appropriate dosing regimens; however, dosing does depend on age, weight, and gender.
- **Evidence:**
 - Studies have not been able to show the effectiveness of Uva ursi in decreasing the recurrence rate of UTIs. More studies need to be conducted in order to examine the effectiveness of Uva ursi in combatting other urinary tract issues.
- **Precautions:**
 - In small doses, Uva ursi can cause nausea, vomiting, and upset stomach. In large doses, it can lead to liver damage, eye issues, and discoloration of urine with a greenish color. Uva ursi contains a chemical that can lead to thinning of the retina and should be avoided in people who have thin retinas.
- **Interactions:**

- Since Uva ursi can have a diuretic effect, it should be avoided taken at the same time as lithium.

Valerian

Valerian is sold as a dietary supplement for calmness and to improve sleep quality. It has a distinct odor that some may find unpleasant. In lab studies, valerian extract appears to have calming effects related to the nervous system. Studies in humans suggest valerian products have a modest effect on sleep quality.

- **Mechanism of Action:**

- In vitro, valerian protects against lipid peroxidation, deoxyribose degradation, and reactive oxygen species production. Iridoids, germacrane-type sesquiterpenoids, and lignans in valerian are associated with neuroprotective effects. Valerian constituents can also bind to various neurotransmitter receptors implicated in circadian rhythms and anxiety such as serotonin receptors.

- **Dosage:**

- For insomnia: 400–900 mg valerian extract up to 2 h before bedtime for as long as 28 days, or Valerian extract 120 mg, with lemon balm extract 80 mg three times daily for up to 30 days, or a combination product containing valerian extract 187 mg plus hops extract 41.9 mg per tablet, two tablets at bedtime for 28 days.

Evidence

In vitro and animal models indicate that anxiolytic activity is due to valerenic acid (VA) which could be inhibited by derivatives such as hydroxy-VA that do not modulate GABA_A receptors. VA in animals inhibits the enzyme system responsible for central catabolism of GABA, increasing GABA concentration and decreasing CNS activity, and direct binding of this constituent to GABA-receptors has been demonstrated. VA interaction with the GABAergic system has been noted to act in a manner similar to that of benzodiazepines. Sesquiterpenes and valepotriates were identified as having varying levels of antidepressant activity.

Chronic treatment of rodents with valepotriate-rich extract increased norepinephrine and dopamine levels. Valerian exhibits antispasmodic and hypotensive effects via potassium channel activation, which may be useful in gastrointestinal and cardiovascular disorders. Valerian also exhibited a protective effect against vasopressin-induced coronary spasm and pressor response, suggesting coronary and systemic vasodilation.

In healthy volunteers, valerian was found to modulate intracortical facilitatory circuits. Valerenic iridoids may have choleric activity and this may increase the risk of gallstone formation, and therefore explain the increased risk for the development of acute pancreatitis.

- **Precautions:**

- Valerian might also cause sleepiness and drowsiness. Taking large amounts of valerian along with alcohol, sedative medications such as benzodiazepines, might cause too much sleepiness.

- **Interactions:**

- Cytochrome P450 2D6 (CYP2D6) substrates. Some medications are changed and broken down by the liver. Valerian might decrease how quickly the liver breaks down some medications. Taking valerian along with some medications that are broken down by the liver can increase the effects and side effects of some medications.

Vanadium

Vanadium is the twenty-first most abundant element in the Earth's crust and the second- to most abundant transition metal in seawater. The element is ubiquitous also in freshwater and nutrients. The average body load of a human individual amounts to 1 mg. Since vanadate can be considered a close blueprint of phosphate with respect to its built-up, vanadate likely takes over a regulatory function in metabolic processes depending on phosphate. At common concentrations, vanadium is non-toxic.

Vanadium is an over-the-counter mineral used for treating diabetes, low blood sugar, high cholesterol, heart disease, tuberculosis, syphilis, anemia, and water retention (edema); for improving athletic performance in weight training; and for preventing cancer.

Potential health benefits of vanadium: May improve sensitivity to insulin in type 1 and 2 diabetes; may also lower cholesterol levels and blood pressure.

- **Mechanism of Action:**

- The similarity between vanadate and phosphate accounts for the interplay between vanadate and phosphate-dependent enzymes: phosphatases can be inhibited, kinases activated.

- **Dosage:**

- 50–100 mcg/day.

- **Evidence:**

- It has been reported that in human beings, pharmacologic amounts of, i.e., 10–100 times higher than the normal intake, affect cholesterol and triglyceride metabolism, influence the erythrocyte shape, and stimulate hepatic glucose oxidation and glycogen synthesis. Multidirectional studies on Vanadium have shown that further analyses are still required for this element to be used as a metallodrug in the fight against certain life-threatening diseases.

- **Precautions:**

- Little is known about the safety of taking vanadium regularly. However, there's some evidence that vanadium may be harmful to people with certain health conditions including disorders of the blood, respiratory system, and immune system. In addition, some research suggests that excessive consumption of vanadium may cause damage to the liver and/or kidneys.

- **Interactions:**

- Vanadium may lower blood glucose and may also slow blood clotting.

Vinpocetine

Vinpocetine is a chemical that is made in a laboratory. It is sold as a prescription drug in Germany. It has been used to enhance memory in Alzheimer's and to prevent disability following an ischemic stroke.

- **Mechanism of Action:**

- Vinpocetine can increase the blood flow to the brain and therefore have a neuroprotective effect. Vinpocetine has anti-inflammatory effects. It is able to antagonize injury-induced vascular remodeling and diet-induced atherosclerosis. It can also reduce the effect of cardiac remodeling.

- **Dosage:**

- Vinpocetine has an excellent safety profile. 5–10 mg taken three times daily has been used to treat memory and associated cognitive issues of Alzheimer's.

- **Evidence:**

- Vinpocetine has multiple actions. It is a vasodilator that also acts as an antioxidant, anti-inflammatory, anti-thrombotic, and anti-remodeling agent.
- Current studies are looking to show that it can provide benefit to people with multifactorial cerebrovascular and cardiovascular diseases. In the short term, vinpocetine has been shown to help improve cognitive skills in people with Alzheimer's or dementia. Vinpocetine inhibits the enzyme PDE1, therefore blocking vasoconstriction, vascular remodeling, cardiac remodeling, and neurotransmission. Vinpocetine blocks sodium channels, therefore preventing cell toxicity and death. Vinpocetine also blocks IKK, therefore blocking inflammation. **Precautions:** Some potential side effects are anxiety, sleep

disturbance, headache, and flushing. Vinpocetine can increase the risk of miscarriage and should be avoided in pregnant people. Vinpocetine can increase the risk of bleeding and should be avoided for people with a bleeding disorder.

- **Interactions:**

- Vinpocetine can increase the risk of bleeding and bruising if taken with anti-coagulant to antiplatelet.

Vitex agnus-castus

Vitex agnus-castus is a shrub that is taken for menstrual cycle irregularities, premenstrual syndrome, premenstrual dysphoric disorder, and menopause.

- **Mechanism of Action:**

- *Vitex agnus-castus* effects many hormones that regulate female reproductive cycles. One proposed mechanism is that it causes a decrease in prolactin, which reverses suppression of LH and increases progesterone.

- **Dosage:**

- 20–40 mg has been safely used for up to 8 weeks to treat premenstrual dysphoric disorder. 4 mg has been taken three times daily for three menstrual cycles to treat premenstrual syndrome.

- **Evidence:**

- Studies have shown that *Vitex agnus-castus* is as effective as Prozac for combatting premenstrual dysphoric disorder. It is also more beneficial in treating the other symptoms associated like breast tenderness, swelling, cramps, and food cravings. *Vitex agnus-castus* can also lead to a relief of premenstrual syndrome symptoms like breast pain or tenderness as well as mood swings and headache.

- **Precautions:**

- Some people can have a change in menstrual flow when starting *Vitex agnus-castus*. More research needs to be conducted to determine the after profile of this supplement in breastfeeding and pregnant people. *Vitex agnus-castus* should be avoided in people with hormone-sensitive conditions like endometriosis, uterine fibroids, or breast cancer. *Vitex agnus-castus* can affect Parkinson's therapy due to similarities of the chemical components that are used to treat Parkinson's.

- **Interactions:**

- Since *Vitex agnus-castus* alters the levels of hormones, it should be used cautiously for people who are also taking contraceptive and estrogen-based

medications. *Vitex agnus-castus* can lead to a significant decrease in how effective antipsychotic and dopamine agonist medications are in combatting their respective conditions.

Further Reading

- Abebe W, Mozaffari MS. Role of taurine in the vasculature: an overview of experimental and human studies. *Am J Cardiovasc Dis.* 2011;1(3):293–311. https://www.mskcc.org/cancer-care/integrative-medicine/herbs/taurine#msk_consumer
- Agabio R. Thiamine administration in alcohol-dependent patients. *Alcohol Alcohol.* 2005;40(2):155–6.
- Anon. FDA warns against consuming dietary supplements containing tiratricol. FDA; 2000.
- Bagoly E, Fehér G, Szapáry L. A vinpocetin szerepe az agyérbetegségek kezelésében az eddigi humán vizsgálatok alapján [The role of vinpocetine in the treatment of cerebrovascular diseases based in human studies]. *Orv Hetil.* 2007;148(29):1353–8. <https://doi.org/10.1556/OH.2007.28115>.
- Banderet LE, Lieberman HR. Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans. *Brain Res Bull.* 1989;22(4):759–62. [https://doi.org/10.1016/0361-9230\(89\)90096-8](https://doi.org/10.1016/0361-9230(89)90096-8).
- Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea tree oil versus benzol peroxide in the treatment of acne. *Med J Aust.* 1990;153:455–8.
- Carson CF, Hammer KA, Riley TV. Melaleuca alternifolia (tea tree) oil: a review of antimicrobial and other medicinal properties. *Clin Microbiol Rev.* 2006;19(1):50–62.
- Chen YP, Cheng YF, Li XH, Yang WL, Wen C, Zhuang S, Zhou YM. Effects of threonine supplementation on the growth performance, immunity, oxidative status, intestinal integrity, and barrier function of broilers at the early age. *Poult Sci.* 2017;96:405–13. <https://doi.org/10.3382/ps/pew240>.
- Chin KY, Mo H, Soelaiman IN. A review of the possible mechanisms of action of tocotrienol—A potential antiosteoporotic agent. *Curr Drug Targets.* 2013;14(13):1533–41. <https://doi.org/10.2174/13894501113149990178>.
- Circosta C, De Pasquale R, Samperi S, et al. Biological and analytical characterization of two extracts from *Valeriana officinalis*. *J Ethnopharmacol.* 2007;112(2):361–7.
- Cohen-Lehman J, Charitou MM, Klein I. Tiratricol-induced periodic paralysis: a review of nutraceuticals affecting thyroid function. *Endocr Pract.* 2011;17(4):610–5. <https://doi.org/10.4158/EP10137.RA>.
- Dwivedi S, Chansouria JP, Somani PN, Udupa KN. Effect of *Terminalia arjuna* on ischaemic heart disease. *Altern Med.* 1989;3:115–22.
- Eastwood MA, Brydon WG, Anderson DM, et al. The effects of dietary gum Tragacanth in man. *Toxicol Lett.* 1984;21:73–81.
- Fernandez-San-Martin MI, Masa-Font R, Palacios-Soler L, et al. Effectiveness of valerian on insomnia: a meta-analysis of randomized placebo-controlled trials. *Sleep Med.* 2010;11(6):505–11.
- Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J.* 2013;15(1):195–218. <https://doi.org/10.1208/s12248-012-9432-8>.
- Hewlings SJ, Kalman DS. Curcumin: A review of its effects on human health. *Foods.* 2017;6(10):92. Published 2017 Oct 22. <https://doi.org/10.3390/foods6100092>.
- <https://www.medicinenet.com/terminalia/supplements-vitamins.htm>
- <https://www.ncbi.nlm.nih.gov/health/thunder-god-vine>.
- Huber R, Ditfurth AV, Amann F, Guthlin C, Rostock M, Trittler R, Kummerer K, Merfort I, Tormentil for active ulcerative colitis: an open- label, dose-escalating study. *J Clin Gastroenterol.* 2007;41(9):834–8.

- Jayachandran S, Khobre P. Efficacy of bromelain along with trypsin, rutoside trihydrate enzymes and diclofenac sodium combination therapy for the treatment of TMJ osteoarthritis—A randomised clinical trial. *J Clin Diagn Res.* 2017;11(6):ZC09–11. <https://doi.org/10.7860/JCDR/2017/25771.9964>.
- Jongkees BJ, Hommel B, Kühn S, Colzato LS. Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands—A review. *J Psychiatr Res.* 2015;70:50–7. <https://doi.org/10.1016/j.jpsychires.2015.08.014>.
- Kim CE, Griffiths WJ, Taylor PW. Components derived from pelargonium stimulate macrophage killing of mycobacterium species. *J Appl Microbiol.* 2009;106(4):1184–93.
- Kong L, Qi X, Huang S, Chen S, Wu Y, Zhao L. Theaflavins inhibit pathogenic properties of *P. ginvialis* and MMPs production in *P. gingivalis*-stimulated human gingival fibroblasts. *Arch Oral Biol.* 2015;60:12–22. <https://doi.org/10.1016/j.archoralbio.2014.08.019>.
- Kuhman DJ, Joyner KJ, Bloomer RJ. Cognitive performance and mood following ingestion of a theacrine-containing dietary supplement, caffeine, or placebo by young men and women. *Nutrients.* 2015;7(11):9618–32. Published 2015 Nov 19. <https://doi.org/10.3390/nu7115484>.
- Li X, Duan S, Chu C, et al. Melaleuca alternifolia concentrate inhibits in vitro entry of influenza virus into host cells. *Molecules.* 2013;18(8):9550–66.
- Marcinczyk N, Jarmoc D, Leszczynska A, et al. Antithrombotic potential of tormentil extract in animal models. *Front Pharmacol.* 2017;8:534. Published 2017 Aug 15. <https://doi.org/10.3389/fphar.2017.00534>.
- May J, et al. Time-kill studies of tea tree oils on clinical isolates. *J Antimicrob Chemother.* 2000;45:639–43.
- Miller AL. The etiologies, pathophysiology, and alternative/complementary treatment of asthma. *Altern Med Rev.* 2001;6(1):20–47.
- Moore M, Trill J, Simpson C, et al. Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomized trial. *Clin Microbiol Infect.* 2019;25(8):973–80. <https://doi.org/10.1016/j.cmi.2019.01.011>.
- Naser B, Bodinet C, Tegtmeier M, Lindequist U. *Thuja occidentalis* (arbor vitae): A review of its pharmaceutical, pharmacological and clinical properties. *Evid Based Complement Alternat Med.* 2005;2(1):69–78. <https://doi.org/10.1093/ecam/neh065>.
- Rivers MC, Mark J. *Tamarindus indica*. IUCN red list of threatened species. 2017: e.T62020997A62020999. <https://doi.org/10.2305/IUCN.UK.2017-3.RLTS.T62020997A62020999.en>. Retrieved November 19, 2021. <https://www.rxlist.com/tamarind/supplements.htm>
- Saeed M, Naveed M, Arif M, Kakar MU, Manzoor R, El-Hack MEA, Alagawany M, Tiwari R, Khandia R, Munjal A, et al. Green tea (*Camellia sinensis*) and L-theanine: Medicinal values and beneficial applications in humans—a comprehensive review. *Biomed Pharmacother.* 2017;95:1260–75. <https://doi.org/10.1016/j.bioph.2017.09.024>.
- Santos EM. Final report on the safety assessment of Tragacanth gum. *J Am Coll Toxicol.* 1987;6:1–22.
- Scabors JE, de Lima MC, Lopes A, et al. Impact of taurine supplementation on blood pressure in gestational protein-restricted offspring: Effect on the medial solitary tract nucleus cell numbers, angiotensin receptors, and renal sodium handling. *J Renin-Angiotensin-Aldosterone Syst.* 2015;16(1):47–58.
- Schulz V. Liquid herbal drug preparation from the root of pelargonium sidoides is effective against acute bronchitis: results of a double-blind study with 124 patients. *Phytomedicine.* 2007;14(Suppl 6):74–5.
- Shah D, Mital K. The role of trypsin: Chymotrypsin in tissue repair. *Adv Ther.* 2018;35(1):31–42. <https://doi.org/10.1007/s12325-017-0648-y>.
- Sharma S, Sheehy T, Kolonel LN. Ethnic differences in grains consumption and their contribution to intake of B-vitamins: results of the multiethnic cohort study. *Nutr J.* 2013;12:65.

- Shaw S, Wyatt K, Campbell J, Ernst E, Thompson-Coon J. *Vitex agnus castus* for premenstrual syndrome. Cochrane Database Syst Rev. 2018;2018(3):CD004632. Published 2018 Mar 2. <https://doi.org/10.1002/14651858.CD004632.pub2>.
- Silva LA, Silveira PC, Ronsani MM, et al. Taurine supplementation decreases oxidative stress in skeletal muscle after eccentric exercise. Cell Biochem Funct. 2011;29(1):43–9.
- Sriram K, Manzanares W, Joseph K. Thiamine in nutrition therapy. Nutr Clin Pract. 2012;27(1):41–50.
- Sudati JH, Fachinetto R, Pereira RP, et al. In vitro antioxidant activity of *Valeriana officinalis* against different neurotoxic agents. Neurochem Res. 2009;34(8):1372–9.
- Sur S, Panda CK. Molecular aspects of cancer chemopreventive and therapeutic efficacies of tea and tea polyphenols. Nutrition. 2017;43:8–15. <https://doi.org/10.1016/j.nut.2017.06.006>.
- Taylor L, Mumford P, Roberts M, Hayward S, Mullins J, Urbina S, Wilborn C. Safety of TeaCrine®, a non-habituating, naturally-occurring purine alkaloid over eight weeks of continuous use. J Int Soc Sports Nutr. 2016;13:2.
- Uva Ursi. LiverTox: Clinical and research information on drug-induced liver injury [Internet]. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
- van Die MD, Burger HG, Teede HJ, Bone KM. *Vitex agnus-castus* extracts for female reproductive disorders: a systematic review of clinical trials. Planta Med. 2013;79(7):562–75. <https://doi.org/10.1055/s-0032-1327831>.
- Varghese A, Pandita N, Gaud RS. In vitro and in vivo evaluation of CYP1a interaction potential of *terminalia arjuna* bark. Indian J Pharm Sci. 2014;76:138–47.
- Vuong QV. Epidemiological evidence linking tea consumption to human health: A review. Crit Rev Food Sci Nutr. 2014;54:523–36. <https://doi.org/10.1080/10408398.2011.594184>.
- Wang HL, Jiang Q, Feng XH, et al. Tripterygium wilfordii Hook F versus conventional synthetic disease-modifying anti-rheumatic drugs as monotherapy for rheumatoid arthritis: a systematic review and network meta-analysis. BMC Complement Altern Med. 2016;16:215. Published 2016 Jul 13. <https://doi.org/10.1186/s12906-016-1194-x>.
- Wang Y, Yang X, Zheng X, Li J, Ye C, Song X. Theacrine, a purine alkaloid with anti-inflammatory and analgesic activities. Fitoterapia. 2010;81(6):627–31. <https://doi.org/10.1016/j.fitote.2010.03.008>. Epub 2010 Mar 20
- Wooley JA. Characteristics of thiamin and its relevance to the management of heart failure. Nutr Clin Pract. 2008;23(5):487–93.
- Wu Y, Jin F, Wang Y, Li F, Wang L, Wang Q, Ren Z, Wang Y. In vitro and in vivo anti-inflammatory effects of theaflavin-3,3'-digallate on lipopolysaccharide-induced inflammation. Eur J Pharmacol. 2017;794:52–60. <https://doi.org/10.1016/j.ejphar.2016.11.027>.
- Zaporowska H, Ścibior A. Hematological effects of vanadium on living organisms. In: Nriagu JO, editor. Vanadium in the environment. Part 2: Health effects, vol. 31. New York, NY/Chichester/Weinheim/Brisbane/Singapore/Toronto: John Wiley and Sons; 1998. p. 135–57.
- Zhang YS, Li JD, Yan C. An update on vinpocetine: new discoveries and clinical implications. Eur J Pharmacol. 2018;819:30–4. <https://doi.org/10.1016/j.ejphar.2017.11.041>.

Chapter 7

Wallflower–Zinc



Caroline Varlotta and Gaurav Majmudar

Wallflower

Wallflower (scientific name *Cheiranthus cheiri*) is a plant native to southern Europe commonly known as beeflower, gillyflower, keiri, and wallstock-gillofer. Medicinal parts of the plant include the flower, seed, and any other above ground components. Wallflower may be used as a diuretic to promote onset of the menstrual cycle, stimulation of the heart (like digitalis or digoxin), and a treatment for constipation or gallbladder and liver disease. This supplement has cardiac glycoside components (like the ones found in diuretics) to control an irregular heartbeat, reduce backup of blood in the body, increase blood flow to the kidneys, help excrete sodium, and decrease peripheral edema.

The typical dose of wallflower is three to four cups of a mixture containing 2–3 g of herbs and 100 mL of hot water, steeped for about 10 min and strained. Side effects of wallflower supplementation include death if intravenous or injected, arrhythmia, heart failure, and death.

Many drugs interact with wallflower including PhosLo (calcium acetate), Tums/Rolaids extra strength (calcium carbonate), calcium chloride, Osteocit (calcium citrate), calcium glubionate, calcium gluceptate, and calcium gluconate. Additionally, many drugs when combined with wallflower can increase cardiac glycoside toxicity, including acetazolamide, azosemide, beclomethasone, betamethasone, budesonide, Symbicort (budesonide and formoterol combination), bumetanide, cascara, chlorothiazide, chlorthalidone, cortisone, deflazacort, dexamethasone, digitalix, docusate, senna, ethacrynic acid, etozolin, flunisolide, fluorometholone,

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fluticasone, furosemide, hydrochlorothiazide, hydrocortisone, hydroflumethiazide, indapamide, mannitol, mefruside, methazolamide, methyclothiazide, methylprednisolone, metolazone, olmesartan and hydrochlorothiazide combination (Benicar HCT), polythiazide, prednisolone, prednisone, quinidine, quinine, torsemide, triamcinolone, trichlormethiazide, urea, and xipamide. Other supplements that may interact with wallflower are also those that increase cardiac glycoside toxicity or increase potassium depletion. This includes black hellebore, calotropis, motherwort, adonis, digitalis, lily-of-the-valley, and squill, horsetail plant or licorice, stimulant laxative herbs such as black root, cascara sagrada, castor oil, and senna, and mahuang [1].

Wasabi

Wasabi (scientific name *Wasabia japonica*) is a plant native to the mountain river valleys in Japan. It is commonly known as *Eutrema japonicum*, Japanese horseradish, Korean wasabi, and Japanese spice. This supplement has no scientific uses, but traditionally is used for its analgesic, antibacterial, antioxidant, and antiplatelet properties. Wasabi may also be used in cancer to induce cell apoptosis, to preserve food, treat gastric ulcers, and prevent melanoma and osteoporosis. There is no standard dosing recommended based on evidence and minimal reported adverse effects. Topical wasabi should be used cautiously in patients using analgesics on the skin, such as capsaicin. The most significant drug interaction is the increased risk of bleeding with anticoagulation medications. Additionally, wasabi has adverse interactions with non-steroidal anti-inflammatories and drugs metabolized by the liver. Lastly, there may be some anabolic effects of wasabi on bone metabolism, and so individuals taking SERMS***, hormonal agents, and bisphosphonates should use this supplement with caution. Herbal interactions include garlic, ginseng, ginkgo, and any other herb known to increase the risk of bleeding [2].

Water Dock

Great water dock (scientific name *Lapathi radix*) is used worldwide to treat dysentery, bacterial skin disorders, and enteritis. Its extract may produce silver nanoparticles that may be used to protect food from spoiling when exposed to ultraviolet light and may be used as an antioxidant. One article reported the dosage of water dock to be 10 g in 100 mL of distilled water, heated to 80 °C for 30 min and mixed with a magnetic stirrer. Next, the mixture was filtered three times and cooled at room temperature. Adverse effects and drug or herbal interactions were not reported [3].

Water Hemlock

Water hemlock (scientific names *Cicuta* and *Oenanthe*) is one of the most poisonous plants in North America and the United Kingdom. The principal toxins include cicutoxin and oenanthotoxin, which act as noncompetitive gamma-aminobutyric acid antagonists in the central nervous system, resulting in seizure from neuronal depolarization. Any amount of this supplement may result in severe toxicity. Other clinical signs of water hemlock use include nausea, vomiting, diarrhea, tachycardia, mydriasis, rhabdomyolysis, renal failure, coma, respiratory failure, and cardiac arrhythmias. Water hemlock is not often intentionally used as a supplement, but is commonly mistaken for other edible supplements, such as watercress, wild carrot, wild ginseng, and pignut. Without adequate identification of ingestion and treatment, individuals who ingest water hemlock are at risk of death [4].

Watercress

Watercress (scientific name *Nasturtium officinale*) is a plant native to the Mediterranean and areas of Asia commonly known as berro, garden cress, scurvy grass, scrubby grass, and spoonwort. Similar to wasabi, this supplement has no scientific uses. However, watercress was historically used against scurvy. Other traditional uses include abortion, acne, alopecia, antifungal, anti-inflammatory, anti-parasitic, chemoprotection, vitamin deficiencies, warts, and cough. The most used dosage is 4–6 g of dry herb, 20–30 g of fresh herb, or 60–150 g of liquid dose in juice or tea. The dosing is not evidence based. Possible side effects include dermatitis and gastrointestinal irritation, especially in patients with ulcers. Chronic use may lead to renal injury. Raw watercress should also be avoided, as it is commonly infested with liver fluke parasites. Because one of the indications of watercress is to induce abortion, this medication is toxic to fetus and should be avoided in pregnancy and breastfeeding.

This supplement has a high Vitamin K content and will interfere with anticoagulants to increase the risk of bleeding. It also decreases oxidative metabolites of acetaminophen circulating in the serum. Use of watercress with Chlorzoxazone may alter the effects of both due to reduced metabolism. Herbs with the adverse effects of increased bleeding and those metabolized by the cytochrome P450 enzyme system should be avoided with watercress [5].

Wheatgrass

Wheatgrass (scientific name *Triticum aestivum*) is a common plant supplement popular in the United States, also known as bugday, breadwheat, cheng ping, common wheat, and wheat. Prior studies have demonstrated uses of wheatgrass in beta thalassemia to reduce the number of required blood transfusions and in ulcerative colitis. Wheatgrass has also been used in acne, blood flow disorders, inflammatory disorders, weight loss, wound care, and as an antipyretic. Dosing for adults depends on the indication. For supplementation in beta thalassemia and ulcerative colitis, 100 mL of wheatgrass juice should be consumed daily. Doses of 8–32 ounces may also be used as a colonic or enema. Adverse effects include life-threatening allergic reactions, likely due to its wheatberry component. Wheatgrass is consumed raw and is grown in soils, and so it should be avoided in women who are pregnant or breast-feeding. There is insufficient evidence of interactions of wheatgrass with other drugs or herbs [6].

Whey Protein

Whey protein is a commonly used supplement with benefits well described in the literature. Whey is the aqueous part of the milk and with processing, proteins such as alpha lactalbumin, beta lactoglobulin, bovine serum albumin, and immunoglobulins may be extracted. Among athletes, whey protein is the most widely used supplement due to its vital role in increasing lean muscle mass, metabolism of carbohydrates, and increased protein synthesis, resulting in higher physical performance [7]. Dosage depends on an individual's activity level and current body composition [8, 9]. Some studies propose a dose between 20 and 25 g per day of whey protein is sufficient [10]. Whey protein is also antibacterial, antiviral, antifungal, and has positive effects on immunomodulation [11]. Adverse effects include increased presence of acne, dysfunctional gut microbiome, and impaired hepatorenal function [12–16]. A literature review concluded chronic use of high doses of whey protein above 40 g per day had negative effects in sedentary individuals and the dose of consumption is closely related to the presence or severity of adverse effects [10, 11].

White Horehound

White horehound (scientific name *Marrubium vulgare* L.) is a gray-leaved herb found in the Mediterranean and Northern Africa with features similar to the mint plant. Distinct extracts of the white horehound can be used for different indications, including expectorant for bronchitis in the form of cough drops and lozenges,

decreasing blood sugar in diabetics, analgesic, and antibacterial, especially against methicillin-resistant *Staphylococcus aureus* [17, 18]. Powders of *White Horehound* are preferred over the liquid extracts because of higher stability and concentration of bioactive components [19]. Dosage is not defined.

White Lily

White lily (scientific name *Lilium candidum*) is a bulbous flower native to Northern Iran. Historically, it was used for the treatment of burns, erythema, external inflammation, and wound healing. The supplement is also known for its analgesic and anti-inflammatory properties. One double-blinded placebo did conclude the use of topical white lily when mixed with sesame oil resulted in statistically significant decrease in Oswestry disability index and a numeric rating scale for pain compared to placebo in chronic low back pain [20]. Dosages and adverse effects were not reported.

White Mustard

White mustard (scientific name *Sinapis alba*) is a plant known for its important role in plant defense against fungi and bacteria because of its high concentration of glucosinolates. When a plant is injured, these glucosinolates are hydrolyzed to create isothiocyanates (ITC), which are recognized for their benefits to humans, as a polysaccharide and source of protein [21]. The white mustard is a component of Mustard Brand and Mustard Seed Flour, which are both natural preservatives of bread [22]. There is no specific dosing reported for white mustard specifically. Potential adverse effects are due to the toxic compounds that may occur within extreme ingested amounts of seeds, including impairment of long chain fatty acid transport, leading to accumulation of triacylglycerols in the heart and other tissues [23]. Interactions with drugs and other herbs were not reported.

White Pepper

Pepper berries (scientific name *Piper nigrum* L.) undergo removal of pericarp, resulting in dry seeds known as white pepper. This supplement has a milder taste than black pepper and is a coveted seasoning for food preparation. The pepper berries are a tropical plant found in subtropical and tropical regions, including India, Indonesia, Malaysia, Thailand, Africa, and Brazil. The white pepper can be used to make oleoresin, piperine, and essential oils [24].

Wild Carrot

Wild carrot is a supplement used to treat gout, indigestion, and heart disease. Some individuals also use it as an aphrodisiac. There is no dosing reported. Potential adverse effects of wild carrot include hypotension, drowsiness, nausea, and allergic reaction with skin contact [25].

Wild Cherry

Wild cherry (scientific name *Prunus serotina*) is a tree found in North America and Canada. The bark of the wild cherry tree contains prussic acid, which calms the coughing reflex. Early settlers of North America and the Native Americans used this supplement as a cough syrup. Many cough medicines and lozenges still contain this supplement. The typical dosage has not been established. Adverse effects include headache, constipation, and gastrointestinal ulcers. Wild cherry should be used in caution with the following drugs, as it may increase the serum levels of benzodiazepines, amlodipine, atorvastatin, bepridil, cyclosporine, clorazepate, diltiazem, estradiol, estrogens, many oral contraceptives, azole antifungal agents, lercanidipine, midazolam, and nifedipine. It also may worsen benign prostatic hypertension and narrow angle glaucoma. Wild cherry may increase sedative properties of St. John's wort, valerian, 5-HTP, and kava kava [26].

Wild Indigo

Wild Indigo (Scientific name *Baptisia* species) is a violet colored plant native to North America commonly known as blue false indigo, blue wild indigo, horsefly weed, indigo carmine, indigo weed, rattle bush, rattle weed, and wild indigo root. This supplement has low toxicity levels, exacerbated when used in combination with *Baptisia tinctoria* root, *Echinacea pallida purpurca* root, and *Thuja occidentalis*. Uses of wild indigo have included antiviral, antiemetic, immunomodulating, and as a laxative. There is no standard dosing. It should not be taken with antiviral drugs or immunosuppressants. According to the evidence, benefits of this supplement do not outweigh the risk [27].

Wild Yam

Wild yam (scientific name *Dioscorea villosa*) is a plant with an active portion in the root, diosgenin, a steroid like substance that was previously used in oral contraceptives, as it is similar to progesterone. As a supplement, wild yam may be used to resolve menopausal symptoms, such as cramps and rheumatic conditions. There is no reported dosage. Adverse effects of wild yam include changes in menstruation. Drugs that may interact with this supplement include all oral contraceptives and estrogens [28].

Willow Bark

Willow bark (scientific name *Salix*) is a plant found in the Mediterranean region usually used in weight loss and to treat fever and inflammatory conditions. The antipyretic and anti-inflammatory characteristics are likely due to the salicin content, which is a salicylate glycoside. Multiple studies support willow bark is effective in treating low back pain, osteoarthritis, and rheumatoid arthritis [29–31]. The mechanism of willow bark in weight loss is theorized to be due to pain relief resulting in increased mobility, exercise performance, and energy consumption [32–34].

This supplement should be avoided during breastfeeding or children because it contains salicylic acid, which can induce Reye's syndrome. Because willow bark contains salicin, those allergic to aspirin and salicylic acid should not use this supplement. Other warnings have been issues regarding the use of willow bark with gastritis, stomach ulcers, diabetes, asthma, or hemophilia. Willow bark may also interact with anticoagulants, beta blockers, and diuretics but changing their effectiveness, and increasing the risk of stomach bleeding if combined with NSAIDs [35]. Dosage was not reported [36].

Wintergreen

Wintergreen is used for headaches, flatulence, and fever. Usually, wintergreen is found in food or candy. It has also been cited to treat low back pain when formulated as an oil [37]. Possible side effects of wintergreen include lack of appetite, lethargy, and gastrointestinal irritation. Wintergreen interacts with a variety of drugs, including etodolac, ibuprofen, ketorolac, methotrexate, metformin, morphine, naproxen, nitrofurantoin, penicillin, tramadol, valacyclovir, and zidovudine. If taken with aspirin, antithrombin III, or other blood thinners, then the individual will have significant increased risk of bleeding. This supplement also may worsen gastrointestinal inflammatory diseases and trigger salicylate allergies [38]. Dosages are not reported.

Wormseed

Wormseed (scientific name *Chenopodium ambrosioides*) is a plant native to Central America, commonly known as Chenopodium, feather geranium, goosefoot, Jerusalem oak, and Jesuit tea. The main use of wormseed is as an anthelmintic to treat worm infestation. There is no standard dosing. Potential adverse effects include muscle twitching, stupor, and renal injury. Drug interactions include all anticonvulsants and acetazolamide. No known herbal supplements interact adversely with wormseed [39].

Wormwood

Wormwood (scientific name *Artemisia absinthium*) is a tonic historically used to treat worm infestation. Since its discovery, wormwood is also used for liver pathology, bloating, appetite stimulation, and anemia. In Germany, wormwood is approved to treat mild gastrointestinal complaints and is commonly dosed at 1–2 mL of liquid extract two to three times daily. Adverse effects include worsening gastric or duodenal ulcers, headache, nausea, vomiting, and dizziness. Wormwood should not be taken with anticonvulsant medications and may impact absorption of iron supplements and ascorbic acid. One case study has shown wormwood taken concurrently with warfarin can cause an elevated INR and bleeding [39, 40].

Yarrow

Yarrow (scientific name *Achillea millefolium*) is a plant found in Asia, Europe, and North America traditionally used for wound care. It may commonly be referred to as bloodwort, milfoil, nosebleed, one man's pepper, sanguinary, soldier's wound-wort, stanchgrass, and thousand-leaf. This supplement is used in respiratory complaints, gastrointestinal issues, urinary tract infections, bleeding disorders, wound care to promote wound healing, and superficial skin infections. There are animal studies demonstrating effects on contraception and antitumor factors as well. There is no standard reported dosing, but common doses include: fluid extract 1–2 mL three times per day (in a 1:1 dilution of 25% of alcohol), 2–4 g three times a day drank as tea, as a tincture of 2–4 mL three times daily (1:5 dilution in 45% alcohol), or as a topical sitz bath using 100 g of herbs in five gallons of hot water. Adverse effects of yarrow include contact allergic reactions, gastrointestinal ulcers, and amplification of diuretic and sedative medications. It should be avoided in pregnancy as it has shown to decrease fetal weight in high doses. There are no drug or supplement interactions reported, but because yarrow may increase the risk of bleeding and should be avoided with anticoagulants or antiplatelets [41, 42].

Yew

Yew (scientific name *Taxus baccata*) is a 40- to 50-foot tall tree which is used as an anticancer substance, taxol, which has become a drug used to treat breast cancer. The medicinal parts are the leaves, branches, and twig tips. There is no dosage reported [43].

Yucca

Yucca is a plant native to North America, Central America, and the Caribbean. It is commonly confused with cassava (*Manihot esculenta*), which may also be called yucca in some regions. Other names for yucca include Adam's needle, alexin, and resveratrol. Evidence demonstrates blending yucca and soapbark (*Quillaja saponaria*) may reduce cholesterol levels. Other uses of yucca include antifungal, anti-viral, anti-inflammatory, and as an adjunctive to cancer treatments. There is no standard dosing. There are no reported drug interactions [44].

Zinc

Zinc is the second most abundant trace metal in the human body after iron. It is an essential part of protein structure and function, as it comprises ~750 zinc-finger transcription factors for gene transcription and 2000 enzymes. Therefore, cellular processes of the human body essential in growth and development rely on zinc. There is little free zinc circulating throughout the human body. Most zinc remains bound to proteins, such as albumin in the serum and metallothionein intracellularly. Zinc also plays a role as an antiviral agent and can be used to increase immunity in those with zinc deficiency and can be used to inhibit viral replication.

Reduced dietary zinc intake increased. Alcohol intake and ingestion of dietary phytate (a natural chelator of zinc in corn, rice, and cereals) may lead to zinc deficiency [45]. Elderly individuals are more susceptible to zinc deficiency, contributing to their increased likelihood of acquiring viral infection [46]. Zinc deficiency may also lead to type 1 diabetes, autoimmune disease, growth retardation, taste disturbances, and skin disorders.

Polaprezinc is a common supplement consisting of zinc and L-carnosine dosed at 34 mg/150 g zinc. Zinc toxicity may be acute or chronic in presentation. Toxicity will present as epigastric pain, nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches. There may also be copper deficiency, altered iron function, impaired immune response, and decreased serum cholesterol with zinc toxicity [47].

Ziziphus

Ziziphus (commonly known as sour date) is a fruit used in Chinese medicine as a sedative to relieve irritability and aid in sleep. In combination with other herbs, such as in the LZComplex3, it may improve mood and performance for individuals with anxiety. Dosage of LZComplex3 is one or two tablets prior to sleep. In one trial, the safety efficacy was similar to placebo and there were mild gastrointestinal adverse events reported [48].

References

1. Grossberg GT, Fox B. Wallflower. In: The essential herb-drug-vitamin interaction guide; 2008. p. 480–4.
2. Grossberg GT, Fox B. Wasabi. In: The essential herb-drug-vitamin interaction guide; 2008. p. 756.
3. Jamróz E, Cabaj A, Juszczak L, et al. Active double-layered films enriched with AgNPs in great water dock root and pu-erh extracts. Materials (Basel). 2021;14:6925. <https://doi.org/10.3390/ma14226925>.
4. Schep LJ, Slaughter RJ, Becket G, Beasley DMG. Poisoning due to water hemlock. Clin Toxicol. 2009;47:270. <https://doi.org/10.1080/15563650902904332>.
5. Grossberg GT, Fox B. Watercress. In: The essential herb-drug-vitamin interaction guide; 2008. p. 758–9.
6. Grossberg GT, Fox B. Wheatgrass. In: The essential herb-drug-vitamin interaction guide; 2008. p. 759–61.
7. Pasiakos SM. Metabolic advantages of higher protein diets and benefits of dairy foods on weight management, glycemic regulation, and bone. J Food Sci. 2015;80:A2. <https://doi.org/10.1111/1750-3841.12804>.
8. Areta JL, Burke LM, Ross ML, et al. Timing and distribution of protein ingestion during prolonged recovery from resistance exercise alters myofibrillar protein synthesis. J Physiol. 2013;591:2319. <https://doi.org/10.1113/jphysiol.2012.244897>.
9. Breen L, Philp A, Shaw CS, Jeukendrup AE, Baar K, Tipton KD. Beneficial effects of resistance exercise on glycemic control are not further improved by protein ingestion. PLoS One. 2011;6:e20613. <https://doi.org/10.1371/journal.pone.0020613>.
10. Witard OC, Jackman SR, Breen L, Smith K, Selby A, Tipton KD. Myofibrillar muscle protein synthesis rates subsequent to a meal in response to increasing doses of whey protein at rest and after resistance exercise. Am J Clin Nutr. 2014;99:86. <https://doi.org/10.3945/ajcn.112.055517>.
11. Vasconcelos QDJS, Bachur TPR, Aragão GF. Whey protein supplementation and its potentially adverse effects on health: a systematic review. Appl Physiol Nutr Metab. 2021;46:27. <https://doi.org/10.1139/apnm-2020-0370>.
12. Pontes TC, Fernandes Filho GMC, Trindade ASP, Sobral Filho JF. Incidence of acne vulgaris in young adult users of protein-calorie supplements in the city of João Pessoa—PB. An Bras Dermatol. 2013;88:907. <https://doi.org/10.1590/abd1806-4841.20132024>.
13. Moreno-Pérez D, Bressa C, Bailén M, et al. Effect of a protein supplement on the gut microbiota of endurance athletes: a randomized, controlled, double-blind pilot study. Nutrients. 2018;10:337. <https://doi.org/10.3390/nu10030337>.

14. Aparicio VA, Nebot E, Porres JM, et al. Effects of high-whey-protein intake and resistance training on renal, bone and metabolic parameters in rats. *Br J Nutr.* 2011;105:836. <https://doi.org/10.1017/S0007114510004393>.
15. Aparicio VA, Nebot E, Tassi M, et al. Whey versus soy protein diets and renal status in rats. *J Med Food.* 2014;17:1011. <https://doi.org/10.1089/jmf.2013.0117>.
16. Gürgen SG, Yücel AT, Karakuş A, Çeçen D, Özén G, Koçtürk S. Usage of whey protein may cause liver damage via inflammatory and apoptotic responses. *Hum Exp Toxicol.* 2015;34:769. <https://doi.org/10.1177/0960327114556787>.
17. Masoodi MH, Ahmed B, Zargar IM, Khan SA, Khan S, Singh P. Antibacterial activity of whole plant extract of *Marrubium vulgare*. *Afr J Biotechnol.* 2008; <https://doi.org/10.4314/ajb.v7i2.58328>.
18. Boudjelal A, Henchiri C, Siracusa L, Sari M, Ruberto G. Compositional analysis and in vivo anti-diabetic activity of wild Algerian *Marrubium vulgare* L. infusion. *Fitoterapia.* 2012;83:286. <https://doi.org/10.1016/j.fitote.2011.11.005>.
19. Gavarić A, Vladić J, Ambrus R, et al. Spray drying of a subcritical extract using *Marrubium vulgare* as a method of choice for obtaining high quality powder. *Pharmaceutics.* 2019; <https://doi.org/10.3390/pharmaceutics11100523>.
20. Rasoulinezhad S, Yekta N, Fallah E. Promising pain-relieving activity of an ancient Persian remedy (mixture of white lily in sesame oil) in patients with chronic low back pain. *J Fam Med Prim Care.* 2019;8:634. https://doi.org/10.4103/jfmpc.jfmpc_423_18.
21. Grubb CD, Abel S. Glucosinolate metabolism and its control. *Trends Plant Sci.* 2006;11:89. <https://doi.org/10.1016/j.tplants.2005.12.006>.
22. Torrijos R, Nazareth TM, Quiles JM, Mañes J, Meca G. Application of white mustard bran and flour on bread as natural preservative agents. *Food Secur.* 2021; <https://doi.org/10.3390/foods10020431>.
23. Lietzow J. Biologically active compounds in mustard seeds: a toxicological perspective. *Food Secur.* 2021; <https://doi.org/10.3390/foods10092089>.
24. Aziz NS, Sofian-Seng NS, Mohd Razali NS, Lim SJ, Mustapha WAW. A review on conventional and biotechnological approaches in white pepper production. *J Sci Food Agric.* 2019;99:2665. <https://doi.org/10.1002/jsfa.9481>.
25. Grossberg GT, Fox B. Wild carrot. In: The essential herb-drug-vitamin interaction guide; 2008. p. 484.
26. Grossberg GT, Fox B. Wild cherry. In: The essential herb-drug-vitamin interaction guide; 2008. p. 488–91.
27. Ulbricht C. Wild indigo. In: Natural standard herb & supplement guide; 2016. p. 765.
28. Grossberg GT, Fox B. Wild yam. In: The essential herb-drug-vitamin interaction guide; 2008. p. 491.
29. Vlachojannis JE, Cameron M, Chrubasik S. A systematic review on the effectiveness of willow bark for musculoskeletal pain. *Phytother Res.* 2009;23:897. <https://doi.org/10.1002/ptr.2747>.
30. Chrubasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conradt C. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med.* 2000;109:9. [https://doi.org/10.1016/S0002-9343\(00\)00442-3](https://doi.org/10.1016/S0002-9343(00)00442-3).
31. Schmid B, Lüdtke R, Selbmann HK, et al. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial. *Phytother Res.* 2001;15:344. <https://doi.org/10.1002/ptr.981>.
32. Armstrong WJ, Johnson P, Duhme S. The effect of commercial thermogenic weight loss supplement on body composition and energy expenditure in obese adults. *J Exerc Physiol Online.* 2001;4(2).
33. Hudson GM, Green JM, Bishop PA, Richardson MT. Effects of caffeine and aspirin on light resistance training performance, perceived exertion, and pain perception. *J Strength Cond Res.* 2008;22:1950. <https://doi.org/10.1519/JSC.0b013e31818219cb>.
34. Mauger AR, Jones AM, Williams CA. Influence of acetaminophen on performance during time trial cycling. *J Appl Physiol.* 2010;108:98. <https://doi.org/10.1152/japplphysiol.00761.2009>.

35. Anon. Willow bark. University of Maryland Med. Center.
36. Shara M, Stohs SJ. Efficacy and safety of white willow bark (*Salix alba*) extracts. *Phytother Res*. 2015;29:1112. <https://doi.org/10.1002/ptr.5377>.
37. Hebert PR, Barice EJ, Hennekens CH. Treatment of low back pain: the potential clinical and public health benefits of topical herbal remedies. *J Altern Complement Med*. 2014;20:219. <https://doi.org/10.1089/acm.2013.0313>.
38. Grossberg GT, Fox B. Wintergreen. In: The essential herb-drug-vitamin interaction guide; 2008. p. 492–3.
39. Lust J. Wormseed. In: The herb book: the most complete catalog of herbs ever published; 2014. p. 397–8.
40. Açıkgöz SK, Açıkgöz E. Gastrointestinal bleeding secondary to interaction of *Artemisia absinthium* with warfarin. *Drug Metabol Drug Interact*. 2013;28:187. <https://doi.org/10.1515/dmdi-2013-0021>.
41. Skidmore-Roth L. Yarrow. In: Mosby's handbook of herbs & natural supplements. Elsevier; 2009.
42. Van Son CR, Stasyuk O. Older immigrants from the former Soviet Union and their use of complementary and alternative medicine. *Geriatr Nurs (Minneap)*. 2014;35:S45. <https://doi.org/10.1016/j.gerinurse.2014.02.019>.
43. Grossberg GT, Fox B. Yew. In: The essential herb-drug-vitamin interaction guide; 2008. p. 504.
44. Grossberg GT, Fox B. Yucca. In: The essential herb-drug-vitamin interaction guide; 2008. p. 781.
45. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The role of zinc in antiviral immunity. *Adv Nutr*. 2019;10:696. <https://doi.org/10.1093/advances/nmz013>.
46. Prasad AS, Beck FWJ, Bao B, et al. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. *Am J Clin Nutr*. 2007;85:837. <https://doi.org/10.1093/ajcn/85.3.837>.
47. Furihata K, Tsuchikawa M, Miwa T, Naito Y, Oba K, Sakagami M. Efficacy and safety of polaprezinc (zinc compound) on zinc deficiency: a systematic review and dose-response meta-analysis of randomized clinical trials using individual patient data. *Nutrients*. 2020; <https://doi.org/10.3390/nu12041128>.
48. Scholey A, Benson S, Gibbs A, Perry N, Sarris J, Murray G. Exploring the effect of lactium™ and zizyphus complex on sleep quality: a double-blind, randomized placebo-controlled trial. *Nutrients*. 2017; <https://doi.org/10.3390/nu9020154>.

Index

A

Acarbose, 1, 2
Acetaminophen
 overdose, 125
 poisoning, 125
Acetylcholine deficiency, 93
3-Acetyl-7 oxo dehydroepiandrosterone, 2, 3
Achillea millefolium, 206
Adenosine triphosphate (ATP), 3, 4, 179
ADHD, 97, 129, 131
Adiponectin, 95
Age-related macular degeneration (AMD), 141
Age-related muscle loss, 29
Alcohol, 90, 128
Alcoholic or hepatitis induced liver disease, 123
Allergies, 129
Allium Sativum, 56
Alopecia, 167
Alpha-linolenic acid (ALA), 51
Alpha lipoic acid (ALA), 4, 5
Alpha-tocopherol, 5–7
Alzheimer’s disease, 25, 135, 180
2-Aminoethanesulfonic acid, 172
Aminoglycosides, 100, 114
Analgesic activity, 87
Angina, 125
Angle glaucoma, 12
Antacids, 114, 117, 135
Anti-acne, 86
Anti-AIDS drugs, 58
Anti-anxiety, 54
Antibacterial, 87
Anticancer agents, 76
Anticholinesterase activity, 49

Antidiabetic, 87

Antihyperlipidemic effects, 87
Anti-hypertensive, 54
Anti-inflammatory, 85, 90, 124, 186
Antimicrobial effects, 86, 124
Antioxidants, 87, 124, 186
Antispasmodic effects, 92
Anxiety disorder, 115, 159
Anxiolytic disorder, 90
Arabidopsis, 76
Arachidonic acid (AA), 128
Arbor Vitae, 181
Area under the curve/mean arterial pressure (AUC/MAP) ratios, 74
Arginine-alpha-ketoglutarate (AAKG), 7, 8
Artemisia absinthium, 206
Arthritis, 116
Ascorbic acid (AA), 8–10
Aspirin, 128, 172
Asthma, 131
Atropine, 61

B

Baptisia species, 204
Beeflower, 199
BeneFlax, 52
Benign prostate hyperplasia (BPH), 167
Berro, 201
β-amyloid, 71
Beta-hydroxy-beta-methylbutyrate (HMB), 75
Bile acid sequestrants, 128
Biotin, 9
Bipolar disorder, 130
Bitter orange, 10–12

- Black tea leaves, 176
 Bleeding, 95
 Blood pressure, 23, 25, 139
 Blood sugar, 23
 Blue green algae, 12–14
 Bone loss, 27
 Bone Mineral Density, 177
 Breadwheat, 202
 Breast cancer, 129
 Breast pain, 129
 Bronchitis, 189
 Bugday, 202
 Butyrylcholinesterase (BChE), 50
- C**
 Caffeine, 14, 15
 Calcium, 15–16, 114
 Calcium supplements, 100
 Calponin, 74
Camellia assamica var. *kucha*, 175
Camellia sinensis, 66
 Cancer, 26, 98, 115, 121, 123, 131
 Cancer prevention, 76
 Capsaicin, 200
 Cardiovascular disease (CVD), 127, 130, 135
 Catechin (CA), 16–18
 Ceftazidime, 129
 Chamomile, 159
 Chemotherapy, 120
 Cheng ping, 202
Chenopodium ambrosioides, 206
 Chitosan, 18, 19
 Chlorogenic acid, 19, 20
 Cholazoxazole, 201
 Cholestasis, 162
 Cholesterol, 25, 135, 136
 Cholestyramine, 183
 Chromium, 20, 21
 Chromodulin, 20
 Chronic obstructive pulmonary disease (COPD), 126
 Chronic venous disease, 50
 Chyme viscosity, 47
Clostridium difficile (*C. Diff*) diarrhea, 160
 Coenzyme Q10 (CoQ10), 21–23, 30
 Cognition, 162, 166
 Cognitive decline/dementia, 131
 Cognitive function, 29
 Cognivia, 162
Coleus amboinicus, 46
 Colostrum, 24, 25
 Common wheat, 202
 Congestion, 115
- Congestive heart failure, 70, 83, 172
 Conjugated linoleic acids (CLA), 25, 26
 Contact lenses, 93
 Copper, 26–28
 deficiency, 27
 toxicity, 27
 CoQ10, 157
 deficiency, 22
Corylus avellana, 71
Crataegus laevigata, 69
Crataegus monogyna, 69
 Creatine, 28–30
 Curcumin, 44
 Cyanobacteria, 12, 13
 Cysteamine, 135
 Cytochrome P450 (CYP450) enzyme, 90, 169, 175, 201
 Cytochrome P450 2D6 (CYP2D6)
 substrates, 192
- D**
 Dandelion, 43, 44
 Decreased absorption, 28
 Depression, 115, 130, 162
 Dextrose, 179
 Diabetes, 46, 132, 141, 171, 187
 Diabetes mellitus (DM), 23, 115, 116, 124, 127
 Diabetics, 128
 Diallyl disulfide, 57
 Diarrhea, 24
 Digoxin, 71
 Dihydroxy-eicosatrienoic acid (DiHETre), 51
 3,3'-Diindolylmethane (DIM), 76
Dioscorea villosa, 205
 Diuretics, 73, 83, 180
 Docosahexaenoic acid (DHA), 46, 47
 Doxorubicin, 178
 Dried herb, 155
- E**
 Eczema, 129
 Eicosapentaenoic acid (EPA), 46
 Endogenous polyphenol oxidase, 176
 Epigallocatechin-3-gallate (EGCG), 66, 178
 Epilepsy, 116, 121
Epimedium, 74
 Epoxy-eicosatrienoic acid (EpETre), 51
 European herbal medicine, 70
 Exercise performance, 28
 Exhaustive prolonged exercise, 63, 64
 Eye health, 98

F

Fat burning, 132
Fatty acids, 47
Fatty liver, 26, 135
Favinoids, 153
Feather geranium, 206
Fennel, 44, 45
Fenugreek, 30, 45–46
Fiber, 47–48
Fibromyalgia, 23
Fine motor skills, 141
Fish oil, 48
Flavonoids, 44, 49–51, 175
Flax seed, 51–52
Foeniculum vulgare, 44
Folic acid, 52–53
Free radicals, 158
Furosemide, 180

G

Gamma-aminobutyric acid (GABA), 54–55
Gamma-linolenic acid (GLA), 72, 128
Garcinia cambogia, 55–56
Garden cress, 201
Garlic, 56–58
Genital herpes, 164
GI, 124
Gillyflower, 199
Ginger, 58–61
Gingerol, 59
Glibenclamide, 87
Glucosamine, 62–63
Glutamine, 63–64
Glutathione, 65
Glycine, 180
Glycyrrhiza glabra, 94
Goji, 61–62
Goosefoot, 206
Green tea, 66

H

Haloperidol, 117
Hawthorn, 70, 71
Hazelnut extract/oil, 71–72
Headaches, 115
Heart disease, 22, 25, 142
Helicobacter pylori, 154, 160
Heme synthesis, 81
Hemoglobin, 81
Hemp seed oil (HSO), 72–73
Hepatitis, 172
Hepatitis induced liver disease, 123

Hepatoprotection, 97

Hepatoprotective activity, 86
Herbal interactions, 200
Herpes simplex virus, 99
Hip, 161
Hirsutism, 166
HIV/AIDS, 125
HIV-induced diarrhea, 163
Honokiol, 115
Horny goat weed, 73–74
Hydroxycitric acid (HCA), 55
Hydroxymethylbutyrate (HMB), 75
3-Hydroxy-3-methylglutaryl CoA (HMG CoA), 57
Hypercalcemia, 139
Hypericum perforatum, 164
Hyperlipidemia (HLD), 162
Hypersensitivity reactions, 95
Hypertension, 50, 71, 83, 95, 140
Hypoglycemia, 171
Hypokalemia, 73
Hypoxanthine, 77

I

Ibuprofen, 172
Icarin (ICA), 73, 74
Idarubicin, 178
IFN-gamma, 24
IL-2, 24
Immune, 24
Increased absorption, 28
Indole-3-carbinol (I3C), 76–77
Inflammation, 23
Inflammatory bowel disease (IBD), 131
Inosine, 77
Inositol nicotinate, 78–79
Insoluble fiber, 47
Insomnia, 120, 191
Intracavernous pressure/mean arterial pressure (ICP/MAP), 74
Iodine, 80–81
Ipriflavone, 79
Iron, 81–83
Irritable bowel syndrome (IBS), 121, 137, 166
Isothiocyanates (ITC), 203

J

Java tea, 83
Jerusalem oak, 206
Jesuit tea, 206
Jimson weed, 84–85

Jojoba, 85–86
 Juniper, 86–88
Juniperus communis, 86

K

Kava Kava, 90–91
 Keiri, 199
Khella Baldi, 91–93
 Kidney disorders, 92
 Knee, 161
Kratom, 88–90

L

Lactulose, 64
 Laxative effect, 47
Lecithin, 93–94
Licorice, 94–95
Lilium candidum, 203
Lingonberry, 95–96
 Liquid wax, 85
 Liver transplantation, 56
 Liverwort, 96–97
Lobelia inflata, 97–98
 L-theanine, 177, 178
 Lutein, 98–99
 Lysine, 99–100

M

Maca, 111, 112
Maclruaxanthone, 50
 Macular degeneration, 131
 Magnesium, 112–114
Magnolia, 115, 116
 Manganese, 116, 117
Mangosteen xanthones, 117, 118
 Medium chain triglycerides (MCT), 118, 119
 Melatonin, 119–121
 Memory, 162
 Memory loss, 25
 Menopausal symptoms, 163
 Metabolism/fat burning, 132
*Methicillin-resistant *Staphylococcus aureus**, 203
 Methionine, 121, 122
 Micronized purified flavonoid fraction (MPFF), 50
 Migraines, 23, 120
 Milk thistle, 122, 123
 Mitochondrial encephalomyopathy (MELAS), 22
Monascus purpureus, 157

Mucilage, 154
 Multiple sclerosis, 23
 Muscle damage and fatigue, 29
 Muscle enhancement, 24
 Muscle soreness, 172
 Muscle strength, 28
 Mushroom poisoning, 123
Myrtle, 124

N

N-acetyl-L-cysteine (NAC), 125, 126
 Napkin rash, 85
Nasturtium officinale, 201
 Nausea, 138, 172
 during pregnancy, 141
 Necrotizing enterocolitis, 161
 Neural tube defect prevention, 53
 Neurologic disorders, 93
 Neuronal nitrous oxide synthase (nNOS), 74
 Neutralization of free radicals, 65
NF-kB, 187
Niacin, 78, 126–128
 Niacin equivalents (NE), 78
 Nitrates, 71
 Non-alcoholic fatty liver disease (NAFLD), 26
 NSAIDs, 95, 205

O

Obesity, 26
 Omega-3 fatty acids, 72, 130, 131
 Omega-6 fatty acids, 128, 129
Oolong tea, 132
 Opioids, 90
Oral mucositis, 63, 64
 Osteoarthritis, 161, 166
 Osteoporosis, 116, 129, 139, 140
 Oswestry disability index, 203
 Oxidative stress, 95, 96

P

Pain relief, 141
Pancreatin, 134, 135
Pancrelipase, 133, 134
Pantethine, 135
Pantothenic acid, 136, 137
 Parkinson's disease, 94
PDE1, 193
Peganum harmala, 168
 Pepper berries, 203
 Peppermint oil, 137, 138
Peroxidase, 176

- P450 1A2, 15
Phosphatidylcholine, 93
Phosphodiesterase-5 inhibitors, 70
Phosphorus, 138, 139
Photodermatitis, 97
Piper nigrum L., 203
PMS, 116, 129
Polaprezinc, 207
Polyamines, 121
Polyphenol, 66
Polyphenol curcumin, 186
Polyphenol oxidase, 176
Polyphenols, 189
Poston's VIP trial, 6
Postprandial glycemic control, 47
Potassium, 140, 141
Potassium-sparing diuretics, 81
Powdered herb, 155
Pregnancy, 10
Pregnancy-related nausea, 171
Premenstrual dysphoric disorder, 194
Proton pump inhibitors, 83
Prunus serotina, 204
Pyridoxine, 111, 112, 141, 142
- Q**
Quercetin, 153, 154
Quine, 154
- R**
Raynaud's phenomenon, 78
Red clover, 155
Red raspberry, 155, 156
Red sandalwood, 156, 157
Red yeast rice, 157
Relaxation, 54
Respiratory depression, 90
Respiratory infections, 24
Retinitis pigmentosa, 98
Reye's syndrome, 205
Rhabdomyolysis, 12
Rheumatoid arthritis (RA), 128, 130
Rhinosinusitis, 165
Rhubarb, 157, 158
Riboflavin, 158, 159
Roman chamomile, 159, 160
- S**
Saccharomyces Boulardii, 160
S-adenosylhomocysteine hydrolase (SAHH/AHCY), 121
S-adenosyl-L-methionine (SAMe), 161
S-adenosylmethionine (SAM), 121
Sage, 162, 163
Salicylates, 95
Salix, 205
Salvage cycle, 121
Sangre de Grado, 163
Saw Palmetto, 167, 168
Schizophrenia, 131
Scrubby grass, 201
Scurvy grass, 201
Seasonal affective disorder, 120
SELECT trial, 6
Serenoa repens, 167
Shellfish allergies, 19
Short bowel syndrome, 63
Short gut syndrome, 64
Sickle cell disease, 63, 64
Silymarin, 122, 123
Silymarin-phosphatidylcholine, 123
Simultaneous ingestion of iron, 83
Sinapis alba, 203
Skin, 27, 127
 irritation, 173
Sleep, 54
 patterns, 120
Smoking, 10
Soluble Epoxide Hydroxylase (seH), 51
Somatoform disorders, 164
Sorrel, 165, 166
Sour date, 208
SP-303, 163
Spearmint, 166, 167
Spirulina, 13
Spoonwort, 201
SSRIs, 56
St. John's Wort, 164, 165
STOP-NIDDM randomized trial, 1
Stroke, 140
Sunburn ointments, 121
Superfruit, 95
Superoxide dismutase, 187
Syrian Rue, 168, 169
- T**
Tamarind, 171, 172
Tanins, 96
Taraxacum officinale, 44
Taraxasterol, 44
Taraxerol, 44
Taurine, 172, 173
Taxus baccata, 207
Tea tree oil, 173, 174

Terminalia arjuna, 174, 175

Terpenes, 72

Terpinen-4-ol, 173

1,3,7,9-Tetramethyluric acid, 175

Theacrine, 175, 176

Theaflavin (TF), 176, 177

Thiamine, 179, 180

Thioctic acid, 4

Threonine, 180

Thuja occidentalis, 181

Thunder god vine, 181, 182

Tiratricol, 182, 183

TLR4 receptor, 96

Tobacco cessation, 97

Tocotrienols, 183, 184

Tormentil, 184, 185

Traditional Chinese medicine, 70, 73

Tragacanth, 185

Transsulfuration pathway, 121

Traveler's diarrhea, 163

Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD) trial, 6

Triglycerides, 135, 136

Trigonella foenum-graecum, 45

Triodothyroacetic acid, 182

Tripterygium wilfordii, 181

Triterpenoids, 175

Triticum aestivum, 202

Trypsin, 186

Turmeric, 186, 187

Tylophora, 188

Tyrosine, 188, 189

U

Umckaloabo, 189, 190

Uric acid, 77

Uva Ursi, 190, 191

V

Valerenic acid (VA), 191

Valerian, 191, 192

Valproic acid (VA), 5

Vanadium, 192, 193

Vascular health, 22

Vasoconstriction, 12

Vasodilating effects, 92

Vinpocetine, 193, 194

Viral hepatitis, 123

Viral infections, 76

Viscous gel forming fiber, 47

Vitamin B1, 179

Vitamin B2, 158, 159

Vitamin B3, 126

Vitamin B5, 136, 137

Vitamin B6, 111, 141, 142

Vitamin C, 44

Vitamin E, 5–7, 183, 184

Vitamin K, 201

Vitex Agnus-castus, 194

W

Wallflower, 199, 200

Wallstock-gillofer, 199

Warfarin, 23, 58, 62

Wasabi, 200

Wasabia Japonica, 200

Watercress, 201

Water dock, 200

Water hemlock, 201

Wernicke's encephalopathy, 179

Wheat, 202

Wheatgrass, 202

Whey protein, 202

White horehound, 202

White lily, 203

White mustard, 203

White pepper, 203

Wild carrot, 204

Wild cherry, 204

Wild indigo, 204

Wild yam, 205

Willow bark, 205

Wintergreen, 205

Wormseed, 206

Wormwood, 206

Wound healing, 136

Y

Yarrow, 206

Yew, 207

Yucca, 207

Z

Zinc, 207

Zingiber officinale, 58

Zizyphus, 208