THE ENERGY BLUEPRINT

THE TOP SCIENCE-BACKED SUPPLEMENTS

For Energy Enhancement

MITOCHONDRIAL HEALTH, PROTECTION & BIOGENESIS

Mitochondria are our body's cellular energy generators. They are the absolute most critical physiological system involved in our energy levels. If you are dealing with fatigue, that is almost certainly a sure sign that your mitochondria are not functioning well. Supporting your mitochondrial health is the single most important thing you can do to help overcome fatigue and increase your energy levels.

The following compounds are nutrients, nutraceuticals, and botanicals proven to support efficient mitochondrial metabolism and cellular energy production for increased vitality, energy, and health. They also support optimal mitochondrial biogenesis, a process critical for healthy aging and protection from oxidative stress.

ASTAXANTHIN

Astaxanthin is the red pigment in shrimp, salmon, krill and various other seafood. It is thought to be one of the most effective antioxidants known to man, able to increase blood flow, reduce the oxidation of LDL, help modulate blood glucose, and improve cognitive function. It may also improve endurance exercise ability in athletes, and increase muscle strength and mobility in the elderly. Several studies have shown that it can improve energy levels. [1,2,3,4,5,6]

Importantly for our purposes here, astaxanthin is a very unique compound because it has the ability to penetrate inside of cells and actually incorporate itself inside of mitochondrial membranes, where it protects them from damage and supports energy production. Because of that, it is one of the most powerful ingredients for supporting mitochondrial health and energy levels.

Dosage recommendations:

A standard dosage of astaxanthin is 6–8 mg per day, but an ideal dosage is not known. This dose is low enough to be obtained from wild-caught seafood

or krill oil supplements. Due to being fat-soluble, supplements should be taken with a fatty meal.

PQQ (Pyrroloquinoline Quinone)

Pyrroloquinoline quinone (PQQ) is a small quinone molecule which has the ability to be a REDOX agent, capable of reducing oxidants. Via its actions as a REDOX agent in cells, it can modify signalling and is thought to support mitochondrial function, which in turn can boost energy levels. It also promotes mitochondrial biogenesis.[7,8,9]

Dosage recommendations:

A standard dosage is 20–40 mg per day.

D-Ribose

D-ribose is a special type of sugar that is required to create energy and DNA. Some evidence suggests that D-ribose can help boost energy and physical function in situations where energy levels are reduced, such as people who have suffered from heart disease or stroke, or people engaging in regular intense exercise.[10,11,12,13,14,15]

Notably, D-ribose has been shown to improve energy, sleep, well-being, and pain threshold in people with fibromyalgia or chronic fatigue syndrome in just three weeks, using 15 grams per day in three divided doses. Another study reported similar findings after using 10 grams per day, with all benefits disappearing within a week of stopping supplementation.[16,17]

Dosage recommendations:

A standard dosage is 10–15 grams per day, taken in 2–3 divided doses.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a molecule found in mitochondria that has a critical role in energy production. It is considered a pseudovitamin because it

is vital for survival but does not need to be consumed in the diet of an otherwise healthy person — the body makes it on demand.

However, several diseases and low-energy conditions are associated with low CoQ10 levels, including people who have fibromyalgia, have survived heart attacks or heart failure, have multiple sclerosis, are infertile, or suffer migraines. Generally speaking, CoQ10 will enhance blood flow, protect blood vessels, lower oxidative stress, and boost vitality in anyone who suffers from fatigue, but especially those people with the aforementioned conditions.[18,19,20,21,22,23,24,25,26,27,28,29]

Additionally, statin drugs are known to deplete CoQ10 levels, so supplementation is mandatory in people taking a statin (even doctors know this and will co-prescribe CoQ10 with a statin).[30,31]

Dosage recommendations:

The standard dose for CoQ10 is 100–200 mg per day, taken once daily with a meal containing some fat. Supplements exist as either ubiquinone or ubiquinol, with ubiquinol being preferred due to having superior bioavailability.

RHODIOLA ROSEA

Rhodiola rosea is a herb with traditional usage as an anti-fatigue agent and adaptogen compound. It significantly reduces fatigue and stress in people suffering from 'burnout' which can (consequently) improve cognitive function. [32],[33]

Dosage recommendations:

A Standard Dosage Is 80–160 Mg Taken Once Per Day, With A Meal. A Single 500 Mg Dose Can Be Used One Hour Before An Acute Stressful Event. Look For The Shr-5 Extract Or An Equivalent, Which Confer Both 3% Rosavins And 1% Salidroside.

SPIRULINA

Spirulina is a species of cyanobacteria traditionally eaten by native African populations and the Aztecs of Central America. It is a decent source of protein and several vitamins, including vitamin B12, possesses strong anti-inflammatory and antioxidant effects mediated by its ability to inhibit NADPH oxidase,[225] and protects against mitochondrial dysfunction and degeneration.[226] This is also the basis for spirulina's ability to fight numerous diseases, including heart disease and diabetes.[34,35,36]

Spirulina is also one of the few compounds that can literally "detox" the body by helping minimize the buildup of heavy metals in the body, like arsenic.[37],[38]

Dosage recommendations:

A standard dosage is 2–8 grams per day.

CURCUMIN

Curcumin is the yellow pigment and primary bioactive substance in turmeric. It possesses powerful anti-inflammatory and antioxidant properties that can help reduce depression and anxiety.[39,40]

There is also evidence that curcumin can help slow cognitive decline with aging, promote cardiovascular health, reduce the risk of developing diabetes, and alleviate other inflammation-related conditions.[41]

One of the key mechanisms by which it exerts these effects is through protecting and stabilizing mitochondrial membranes, and helping the body build more mitochondria from scratch (mitochondrial biogenesis).

Dosage recommendations:

A standard dosage is 500 mg of a curcumin complex taken 1–2 times per day.

Curcumin by itself has horrible bioavailability, meaning that you absorb very little of what you ingest. There are many forms of curcumin on the market that have increased bioavailability, and most studies have used curcumin with piperine (a black pepper extract) or the patented forms called BCM-95® and Meriva®.

While these forms have 20–48-fold greater bioavailability than regular curcumin, the most bioavailable forms are NovaSol® (185-fold), CurcuWin® (136-fold), and LongVida® (100-fold).[224] These are the forms that we recommend.

QUERCETIN

Quercetin is a well known bioflavonoid found in fruits and vegetables, particularly onions and apples. It is a potent antioxidant and anti-inflammatory molecule that affects an array of mitochondrial processes, including mitochondrial biogenesis, mitochondrial energy production, and the protection of mitochondria from oxidative stress. [42],[43] It is also involved in helping the mitochondria to regenerate NAD+ -- a key molecule that supports mitochondrial health and energy production.

Dosage recommendations:

A standard dosage is 1,100–2,300 mg per day. The best form is dihydrate, followed by glycosides, aglycone, and rutinoside.

TAURINE

Taurine is a sulfur-containing amino acid essential for cardiovascular function and the development and function of skeletal muscle, the retina, and the brain.[44] It can help fight muscle loss with aging,[35] as well as benefit many other disease states, including neurodegenerative diseases, diseases of the eye, diabetes, heart failure, high blood pressure, and muscular dystrophies. [45] Taurine is also essential for the proper function of mitochondria. [46],[47]

Dosage recommendations:

A standard dosage is 1–3 grams taken 2–3 times per day.

ACETYL L-CARNITINE

Acetyl L-Carnitine (ALCAR) is a unique form of L-Carnitine that has brain- and body-boosting properties.

- Reduces depression with a potency comparable to drugs.[48]
- Protects and repairs neurons from damage (like that caused by diabetes). [49],[50]
- Increases mitochondrial function by increasing their ability to produce energy.[51,52,53]
- Alleviates the side effects of aging, like neurological decline and chronic fatigue. [54],[55],[56],[57],[58]
- Improves insulin sensitivity.[59]
- Improves cardiovascular health.[60],[61]

Notably, ALCAR has been known to cause fat loss, not because of any mechanism intrinsic to ALCAR, but simply because those taking it become more physically active due to the increased energy and vitality it provides.

Dosage recommendations:

The standard dosage for ALCAR is 1,000–2,500 mg per day, taken as 2–3 divided doses.

SHILAJIT/FULVIC ACID

Shilajit is a mixture of minerals used traditionally in Ayurveda, with the main bioactive being fulvic acid. It is a potent antioxidant that supports energy production and tissue recovery, improves blood flow, and reduces the negative impact of psychological and physical stress. Shilajit also promotes proper mitochondrial function and can alleviate the symptoms of chronic fatigue and neurodegeneration.[62],[63]

Dosage recommendations:

A standard dosage is 200–500 mg of Shilajit with 50% Fulvic acid content taken in two divided doses with meals.

POMEGRANATE AND ELLAGITANNINS

Ellagitannins are potent antioxidants found in pomegranates that can also be metabolized into other compounds (ellagic acid, urolithins) that themselves have antioxidant capabilities.[64,65] They can rejuvenate and rebuild the mitochondria, as well as improve muscle function and remove damaged

mitochondria that accumulate and cause cellular dysfunction in a process called mitophagy.[66],[67]

Dosage recommendations:

A standard dosage is 800 mg Pomegranate Extract (318 mg punicalagins) taken once per day.

ALPHA-LIPOIC ACID

Alpha-lipoic acid (ALA) is a mitochondrial compound involved in energy metabolism and the antioxidant system.[68] It provides a short but potent reduction of oxidation by increasing antioxidant enzymes, which protects against a variety of inflammatory and oxidative diseases like neurodegeneration.[69] ALA accumulates in various brain regions as soon as an hour after ingestion, and it has been shown to protect against neuronal cell death.[70,71,72]

Dosage recommendations:

A standard dosage of ALA is 300–600 mg per day, taken all at once or in multiple doses. It can be taken with meals or when fasted.

ALA exists as either an S or R isomer, with unspecified ALA being a 'racemic' solution of both. We want R-ALA because it is more bioavailable.[73] A study in mice found only R-ALA to extend life span in mice compared to S-ALA, even though the dose was 5.5 times lower.[74]

CITRUS BIOFLAVONOIDS (HESPERIDIN)

Hesperidin is the primary bioactive compound in orange peels, alongside naringenin. They are powerful antioxidant and anti-inflammatory molecules, capable of protecting against several degenerative diseases and particularly brain diseases.[75,76,77] These effects are mediated, in part, by their ability to prevent mitochondrial dysfunction and oxidative stress.[78]

Dosage recommendations:

A standard dosage is 500 mg per day.

GREEN TEA CATECHINS

Green tea (*Camellia Sinensis*) catechins are four phytochemical molecules, the most potent one being epigallocatechin-3-gallate (EGCG). It has been implicated in benefiting almost every organ system in the body in doses you can obtain easily from simply drinking green tea. [79, 80, 81] EGCG is neuroprotective, cardioprotective, anti-obesity, anti-carcinogenic, anti-diabetic, and an overall powerful protector of your mitochondria. [82, 83, 84,85,86,87,88,89,90,91,92,93,94]

In a 12-week double-blind trial published in the American Journal of Clinical Nutrition, researchers gave 38 overweight adults (ages 20 to 50) a daily polyphenol supplement or a placebo pill. The polyphenol supplement contained 282 milligrams EGCG (epigallocatechin-3-gallate, found in green tea) and 80 milligrams resveratrol (found in grape skins). People taking the polyphenol supplement had a highly significant increase in the function of mitochondria in their muscles compared to people given a placebo.

Dosage recommendations:

A standard dosage is 400–500 mg per day of EGCG, with one cup of green tea providing approximately 50 mg.

Most doses are standardized against EGCG. Although the amount of EGCG-equivalent varies from one cup of tea to another, depending on many factors (species of tea, length of steeping, time spent oxidizing), one cup of camellia sinensis green tea contains approximately 50mg of EGCG-equivalent.

CACAO

Like green tea extract, cacao is packed with several powerful phytochemicals, including flavan-3-ol and epicatechin. These catechins have wide-ranging health benefits, including everything from anti-aging effects in the skin, to boosting mood, to boosting mitochondrial energy production. It's also one of the richest sources of PQQ, which is a powerful stimulator of mitochondrial biogenesis.

Dosage recommendations:

A standard dosage is 400–500 mg per day of EGCG, with one cup of green tea providing approximately 50 mg.

We recommend getting an organic raw cacao powder or cacao nibs and adding them to smoothies or making healthy "hot chocolate."

PHOSPHOLIPIDS (NTFACTORS)

This is one of the most powerful compounds for mitochondrial regeneration. NTFactors is a compound used in lipid replacement therapy, a method of replacing damaged membrane glycerophospholipids that accumulate during aging and in various clinical conditions in order to restore cellular and mitochondrial function. It has been shown to reduce fatigue by a whopping 24–43% in people with chronic fatigue syndrome, as well as reduce cancer-associated fatigue and the fatigue effects of cancer therapy by similar amounts, in just a few weeks of use. [95,96,97,98,99,100]

Dosage recommendations:

A standard dosage is 1,000–4,000 mg per day.

BRAIN HEALTH AND MEMORY

These are compounds that support overall brain health to fight cognitive decline and memory impairments. They work through promoting neurogenesis and gliosis (the growth of new neurons and related cells in the nervous system), combatting neuroinflammation and oxidative stress, supporting blood-brain barrier integrity, and facilitating healthy neurotransmission.

BLUEBERRIES

Blueberries are a rich source of anthocyanins and pterostilbene (phytochemicals), and have been shown to increase the activity of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), neuropeptides that helps neurons grow, branch toward each other, and thus communicate better.[101,102,103] Accordingly, blueberries have been shown to increase cognitive function and slow cognitive decline with aging.[104,105,106,107]

Blueberries and their constituent phytochemicals are also protective against the development of cancer, obesity, cardiovascular diseases, diabetes, bone loss, poor immune function, fatty liver, vision loss, and chronic inflammation.[108]

Dosage recommendations:

A standard dosage is 60–120 grams per day of fresh blueberries, 500 mL per day of reconstituted blueberry juice concentrate (not the watered-down sugar-rich blueberry juice), 5.5–11 grams per day of blueberry powder, or 500–1,000 mg per day of blueberry anthocyanins.

BACOPA MONNIERI

Bacopa monnieri is a swamp plant used in traditional Indian medicine to improve memory and cognition. Bacopa monnieri reliably improves working memory (your RAM, so to speak, which determines how much information

you can keep at the forefront of your mind) in people of all ages, but only after one month of consistent supplementation. [109,110,111]

Bacopa works primarily by promoting neuronal communication — it enhances the rate at which the nervous system can communicate by increasing the growth of nerve endings. [112], [113] It also has antioxidant neuroprotective properties.[114]

Dosage recommendations:

A standard dosage is 150 mg per day of bacosides (the active ingredient in Bacopa monnieri), taken once per day with food (taking bacopa on an empty stomach may cause nausea, cramping, bloating, and diarrhea). A bacopa extra with 55% bacoside content would, therefore, require taking 300 mg of the supplement. Unspecified leaf powders are 10–20% bacosides, requiring 750–1,500 mg be taken.

ALPHA-LIPOIC ACID

Alpha-lipoic acid (ALA) is a mitochondrial compound involved in energy metabolism and the antioxidant system.[115] It provides a short but potent reduction of oxidation by increasing antioxidant enzymes, which protects against a variety of inflammatory and oxidative diseases like neurodegeneration.[116] ALA accumulates in various brain regions as soon as an hour after ingestion, and it has been shown to protect against neuronal cell death.[117,118,119]

Dosage recommendations:

A standard dosage of ALA is 300–600 mg per day, taken all at once or in multiple doses. It can be taken with meals or when fasted.

ALA exists as either an S or R isomer, with unspecified ALA being a 'racemic' solution of both. We want R-ALA because it is more bioavailable.[88] A study in mice found only R-ALA to extend life span in mice compared to S-ALA, even though the dose was 5.5 times lower.[120]

BERBERINE

Berberine is a plant-derived alkaloid with potent antidiabetic and anti-inflammatory effects that rival drugs like metformin and glibenclamide.[121,122] It works through increasing an enzyme called AMPK, which reduces glucose production and output in the liver, and increases glucose uptake in muscle tissue. [123,124]

Berberine crosses the blood-brain barrier, where it is able to protect against inflammation and neuronal damage.[125],[126] Berberine can also treat dementia by affecting neurotransmitter, antioxidant, and metabolic pathways, making it a therapeutic approach to prevent or delay Alzheimer's disease.[127],[128]

Dosage recommendations:

A standard dosage is 500 mg taken 2–4 times per day, with meals.

GREEN TEA CATECHINS

Green tea (*Camellia Sinensis*) catechins are four phytochemical molecules, the most potent one being epigallocatechin-3-gallate (EGCG). It has been implicated in benefiting almost every organ system in the body in doses you can obtain easily from simply drinking green tea. [129 , 130 , 131] EGCG is neuroprotective, cardioprotective, anti-obesity, anti-carcinogenic, anti-diabetic, and an overall powerful protector of your mitochondria. [132 , 133 , 134,135,136,137,138,139,140,141,142,143,144]

Dosage recommendations:

A standard dosage is 400–500 mg per day of EGCG, with one cup of green tea providing approximately 50 mg.

Most doses are standardized against EGCG. Although the amount of EGCG-equivalent varies from one cup of tea to another, depending on many factors (species of tea, length of steeping, time spent oxidizing), one cup of camellia sinensis green tea contains approximately 50mg of EGCG-equivalent.

LION'S MANE MUSHROOM

Lion's mane mushroom (*Yamabushitake*) is a dietary mushroom that can be a supplement. It appears to be a promising cognitive enhancer and immunomodulator (thought to stimulate or suppress inflammation depending on context).[145,146,147] Specifically, lion's mane triggers nerve growth and regeneration of damaged neurons.[148],[149]It also reduces anxiety and depression.[150]

Dosage recommendations:

A standard dosage is 3,000 mg per day, taken in three divided doses.

EPA AND DHA (MARINE OILS)

Marine oils, including fish oils and krill oils, are common terms used to refer to two kinds of omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They are heavily involved in regulating inflammation in the body and helping keep the pro-inflammatory actions of omega-6 fatty acids in check.[151]

Maintaining a low ratio of omega-6 to omega-3, around 1:4 or less, is associated with healthier cardiovascular system, reduced risk of diabetes, and lesser cognitive decline.[152,153,154,155] DHA is especially prominent in brain tissue, and supplementation with marine oils has been shown to benefit memory, reduce depression, and attenuate the rate of cognitive decline with aging.[156,157,158,159,160]

Dosage recommendations:

A standard dosage of marine oil is 250–3,000 mg of combined EPA + DHA per day. Since these can be obtained from eating seafood in the diet, less supplementation is required for those regularly eating seafood.

RESVERATROL

Resveratrol is a beneficial compound found in red wine that is associated with life extension and some of the health benefits in wine consumption.[161] It is produced in grape skins as a defense against toxins. It is a potent antioxidant that can protect against heart disease and insulin resistance,

while also increasing blood flow (and oxygen and nutrient delivery) to the brain.[162],[163]

Moreover, unlike other antioxidants that interfere with exercise-induced adaptations, like muscle protein synthesis and mitochondrial biogenesis, resveratrol appears to enhance the physiological benefits of exercise.[164],[165],[166]

Dosage recommendation:

A standard dosage depends on the goal: 5–10 mg per day for improving health in someone with poor health to begin with, and 250–500 mg for heart health blood flow benefits in healthy adults.

COFFEE, CHLOROGENIC ACID, AND GREEN COFFEE EXTRACT

Coffee is black gold; the world's second most popular non-water beverage (second only to all forms of tea combined). It is a source of man nutrients, including a variety of nutriceutical compounds like chlorogenic acid, ferulic acid, and caffeine (unless decaffeinated). Accordingly, coffee exerts effects just like any other supplement or drug, and can even rival many of them in potency. For all intents and purposes, coffee isn't a food, it is a drug.

Chlorogenic acid is one of the main bioactive compounds of coffee that holds promise in many aspects of health and cognition.[167],[168],[169] Green coffee extract is a supplement derived from green coffee beans, with similar chemical composition to regular coffee beans, but being more concentrated in chlorogenic acid.

Supplementing with coffee, chlorogenic acid, or green coffee beans can lower cardiovascular disease risk, enhance mood, and lower neuroinflammation.[170],[171],[172]

Dosage recommendations:

A standard dosage is 120–300 mg per day of chlorogenic acid. This dose is low enough to be obtainable by drinking 1–2 cups of coffee — 4 cups (1 liter) of coffee contains 500–800 mg of chlorogenic acid.

PHENYLETHYLAMINE

Phenethylamine (PEA) is an important molecule in the brain that influences the actions of many neurotransmitters, including dopamine and serotonin. Supplementation can rapidly increase brain levels of PEA, which has benefits for alleviating conditions like attention deficit hyperactivity disorder, depression, and schizophrenia.[173],[174],[175],[176]

Dosage recommendations:

A standard dosage is 300–1,000 mg per day, starting on the low-end and working up.

FOCUS AND MENTAL CLARITY

These compounds modulate neurotransmission to provide increased levels of focus and mental clarity. They help the brain be more vigilant and reactive, helping fight brain fog and indecision.

NOOPEPT

Noopept has a similar effect to piracetam, in that it provides a mild cognitive boost after supplementation, but requires a much lower dose. It also provides a subtle psychostimulatory and general neuroprotective effect after supplementation. [177] [178] This neuroprotective effect occurs during various states of cognitive trauma, including oxidative stress and physical trauma.[179,180]

Dosage recommendations:

Human studies stick with 20 mg, and some rodent data suggests a bimodal curve whereby too little and too much are both ineffective. Any reason you go with 30 mg over 20 mg?

COFFEE FRUIT (NEUROFACTOR)

Coffee fruit may be able to boost brain-derived neurotrophic factor in healthy adults after consuming 100 mg.[181]

Dosage recommendations:

A standard dosage is 100 mg taken once per day.

SCHIZANDRA

Schizandra is a fruit used in both Chinese and Russian traditional medicine to fight fatigue and promote general well being. It increases work capacity and provides a stress-protective effect against a broad spectrum of harmful factors, including heat shock, skin burn, cooling, frostbite, immobilisation,

inflammation, irradiation, and heavy metal intoxication.[182] It functions as a hormetic antioxidant cognitive enhancer.[183]

Dosage recommendations:

A standard dosage is 1–3 grams per day, taken with meals.

HUPERZINE A

Huperzine-A is a cognitive enhancer that works by inhibiting an enzyme that degrades the learning neurotransmitter, acetylcholine; due to this, it is helpful in fighting cognitive decline in the elderly, including Alzheimer's disease and vascular dementia.[184],[185], [186]

Dosage recommendations:

A standard dosage is 50–200 mcg taken once per day.

GINKGO BILOBA

Ginkgo biloba is the most commonly ingested herb for brain health. It reliably boosts cognition and lowers neuropsychiatric symptoms in older populations with mild cognitive impairment and dementia, as well as Alzheimer's disease.[187],[188],[189],[190],[191]

Dosage recommendations:

A standard dosage is 240–360 mg per day, taken in three divided doses with meals. You will want to use the patented EGb-761 extract, or another 50:1 concentrated extract.

VINPOCETINE

Vinpocetine is an alkaloid used for the treatment of cognitive decline, stroke recovery, and epilepsy. [192] It rapidly and easily enters the brain after supplementation, where it confers neuroprotection and reduces neuroinflammation.[193]

Dosage recommendations:

A standard dosage is 15–60 mg taken as three divided doses with meals.

CENTROPHENOXINE

Centrophenoxine is a cholinergic compound effective in reversing some of the signs of aging (particularly waste product buildup in the brain) when taken for an acute period (high doses for a month), and can act as a general neural enhancer and protector when taken continuously at a lower dose.[194],[195],[196]

Dosage recommendations:

A standard dosage is 250–1,500 mg per day, taken as three divided doses. It is sold under the brand name Lucidril, but can easily be bought over the counter or online.

SLEEP & RELAXATION

Sleep-promoting and relaxant compounds help lower stress and increase energy levels indirectly through promoting better sleep quality. Most provide a sedative effect and are recommended to be taken before bed for that reason. These supplements should not be taken during the day or when you intend to perform tasks requiring focused mental effort.

MAGNESIUM

Magnesium is an essential dietary mineral, and the second most prevalent electrolyte in the human body. Magnesium deficiencies are common in developed countries because prominent sources of magnesium, like leafy vegetables, are not often eaten.

A deficiency increases blood pressure, reduces glucose tolerance, and causes abnormal neural excitations that impair sleep.[197] Accordingly, magnesium supplementation can have sedative effect, particularly when correcting a deficiency.[198],[199]

Dosage recommendations:

A standard dosage is 200–400 mg of magnesium once a day before bed.

Commonly supplemented forms of magnesium include magnesium gluconate, diglycinate, and citrate. Magnesium oxide is not well absorbed and can cause intestinal discomfort and diarrhea; it is therefore not recommended for supplementation.

Avoid taking magnesium, calcium, zinc, and iron at the same time in combinations of 800+ mg, since high amounts of these minerals will compete for absorption and limit the overall effectiveness of supplementation.

MELATONIN

Melatonin is the hormone we make at night to help the body prepare for sleep and establish a circadian rhythm. Bright, blue, and green lights impair

its secretion at night. Supplementation can help decrease the time it takes to fall asleep and normalize sleep patterns.[200,201,202,203]

Irregular sleep patterns are associated with a wide variety of health problems and premature aging.[204] Other benefits of melatonin include general neuroprotective effects, as melatonin is a powerful antioxidant.[205,206,207,208,209] Melatonin supplementation also benefits eye health and improves mood (by helping you get better sleep).

Dosage recommendations:

A standard dosage is 0.5 mg (500 mcg) half an hour before bed. Increase by 0.5 mg each week until you find the lowest effective dose that works. The benefits of melatonin on sleep are not dose-dependent — taking more will not help you fall asleep faster.

Taking melatonin is not associated with negative feedback (when taking supplementation causes your body to produce less of a hormone). It is also not addictive, and is not toxic.

LAVENDER

Lavender is traditionally used in aromatherapy for its relaxing scent. Supplementation can improve sleep quality by easing anxiety and limiting intrusive thoughts disrupt sleep.[210,211,212] Some evidence suggests lavender can increase slow-wave sleep patterns.[213]

Dosage recommendations:

A standard dosage is 80 mg of Silexan 30–45 minutes before bed. Silexan is a lavender oil preparation standardized for 25–46% of total weight as linalool, the active component. After two weeks, if no benefit has been observed, the dose can be increased to 160 mg.

Lavender oil is also used in aromatherapy — burned as a candle, heated, placed in a vaporizer, or added to a hot bath. Studies have used at least 30 minutes of exposure in a well-ventilated room at night.

GLYCINE

Glycine is an amino acid and neurotransmitter that plays both stimulatory and depressant roles in the brain. Supplementation can reduce the time it takes to fall asleep and increase the feeling of restfulness the next day.[214,215] The perception of having had a good night's sleep makes for a comfortable and energetic morning.[216]

Dosage recommendations:

Take 3 g of glycine 30–60 minutes before sleep. Glycine is usually taken with food, but further research is needed to determine how important mealtime supplementation really is. If eating too close to bedtime disrupts your sleep, take glycine on an empty stomach instead.

Glycine can be purchased as pills but is cheaper as bulk powder. The powder should be mixed with water and tastes very sweet.

For glycemic and sleep benefits, doses of 3-5 grams with meals and before bed, respectivley, have been used successfully in clinical research.

VALERIAN

Valerian (*Valeriana officinalis*) root was one of the first sleep aids on the market, and is one of the best-researched. Like glycine, it seems to improve subjective reports on sleep and mood (well-being, alertness) the morning after supplementation.[217]

Dosage recommendations:

A standard dosage is 450 mg, standardized for 0.8–1% valerenic acids, taken 30–60 minutes before bed. Tea infusions are difficult to dose due to variations in steeping, but should also be taken within an hour of going to bed.

LEMON BALM

Lemon balm (*Melissa officinalis*) is a light sedative that can induce calmness and reduce the time it takes to fall asleep.[218],[219] It may work synergistically with lavender.

Dosage recommendations:

A standard dosage is 300–1,200 mg taken 30–60 minutes before bed.

Lemon Balm bioactives may also be consumed via tea or acquired via aromatherapy, although it is much harder to quantify 'the right dose' via these two methods.

PASSIONFLOWER

Passionflower (*Passiflora incarnata Linneaus*) is one of the oldest herbal anxiolytics that may work by increasing GABA signalling in the brain.[220] It does not appear to be effective acutely, but rather shows steady benefits after a month or more of daily supplementation.[221],[222]

Dosage recommendations:

A standard dosage is 500 mg of passionflower extract taken once per day. Passionflower infusions (tea), consumed at least twice a day, also appear to be effective.

GABA

GABA is the most potent depressive neurotransmitter in human brains. It regulates many of the depressive and sedative actions in brain tissue and is critical for relaxation.[223],[224] Supplementation can help you fall asleep faster and get deeper, more rejuvenative sleep.[225]

Dosage recommendations:

A standard dosage is 500–3,000 mg taken 30–60 minutes before bed.

KAVA

Kava (*Piper methysticum*) is a well-researched herb traditionally used to reduce anxiety. Some studies suggest it works as well as low-dose benzodiazepines, which is surprising since supplements seldom reach drug-level potency.[226],[227]

Dosage recommendations:

A standard dosage is 100 mg of an extract called WS-1490 taken three times per day.

If taking another type of Kava supplement, take however much is required to obtain 70 mg of kavalactones three times a day (kavalactones being the active molecules in kava).

L-THEANINE

L-Theanine is one of the main active ingredients found in green tea, alongside caffeine and green tea catechins. It helps promote relaxation without drowsiness, making it synergistic with stimulants.[228],[229],[230]

L-Theanine is known to reach the brain and act to promote relaxation and induce sleep.[231] Interestingly, when paired with a stimulant like caffeine, it is known to reduce the 'edge' of many stimulants.

Dosage recommendations:

A standard dosage is 100–200 mg taken 30–60 minutes before bed or alongside a stimulate. Taking L-Theanine alongside a stimulant like caffeine can help reduce the stimulant effects while preserving the benefits on cognition (attention and focus).

Adaptogens & Anti-Stress Supplements

Adaptogens are compounds that help the body handle stress through increasing its resilience towards physical, chemical, and psychological stressors. As the name suggests, they quite literally help the body adapt to the situation. The result is a reduction in anxiety, improvement in mood and mental clarity, increased energy and stamina.

Arginine with Lysine

Arginine and Lysine are both amino acids in the diet. Supplementing them together has been shown to benefit people with *state and trait anxiety*, a form of anxiety that can occur in otherwise healthy individuals in response to minor stressful events, such as having to give a presentation.[232],[233]

It is uncertain if their supplementation holds any benefit with regard to other forms of anxiety.

Dosage recommendations:

A standard dosage is 1.5 g of arginine and 1.5 g of lysine twice a day (i.e., 3 g of each per day), with or without a meal. Effects can be felt after a week of supplementation.

Kava

Kava (*Piper methysticum*) is a well-researched herb traditionally used to reduce anxiety. Some studies suggest it works as well as low-dose benzodiazepines, which is surprising since supplements seldom reach drug-level potency.[234],[235]

Dosage recommendations:

A standard dosage is 100 mg of an extract called WS-1490 taken thee times per day.

If taking another type of Kava supplement, take however much is required to obtain 70 mg of kavalactones three times a day (kavalactones being the active molecules in kava).

VITEX AGNUS-CASTUS

Vitex agnus-castus (VAC) is a very specific anti-anxiety supplement used to reduce the anxiety that can occur during the menstrual cycle, as well as to alleviate the symptoms associated with premenstrual syndrome (PMS).[236],[237] VAC may also reduce irritability and improve sleep during PMS, which can in turn improve mood and indirectly reduce anxiety.

VAC has no effect when supplemented by women not currently experiencing PMS and has not been tested for its anti-anxiety effects in men.

Dosage recommendations:

A standard dosage is 150–250 mg once a day with breakfast. Two patented extracts are more concentrated and require lower doses: Ze-110 extract requires 20 mg once a day; BNO-1095 extract requires 4 mg once a day.

AGMATINE

Agmatine is a neurotransmitter that reduces anxiety; it is the neurotransmitter released in response to alcohol and responsible for alcohol's calming effects. In fact, the hangover anxiety the day after drinking is a result of the body's agmatine reserves being depleted.[238] ,[239]

Agmatine may also make opioids more effective for pain relief (by reducing pain itself and reducing the development of painkiller tolerance) and reduce their addictive potential. It also protects the brain from toxins and strokes.[240],[241]

Dosage recommendations:

A standard dosage is 100–200 mg without food. Agmatine is not absorbed well when taken with dietary protein, because it uses the same transporters as arginine.

ASHWAGANDHA

Ashwagandha (*Withania somnifera*) is an adaptogen that can reduce the mental and physical effects of stress, including anxiety, possibly through an interaction with serotonin.[242] Social anxiety appears to benefit most, with supplementation leading to better general wellbeing and social functioning.[243]

The general stress-reducing properties of ashwagandha are comparable to those of other adaptogens, such as Rhodiola rosea and Panax ginseng. However, ashwagandha is the better choice for people with social anxiety.

Dosage recommendations:

A standard dosage is 2–6 g of the root powder (or 1–3 g of a 2:1 extract) one hour before a stressful event. To supplement ashwagandha continuously, take 300–500 mg of the root powder (or 150–250 mg of a 2:1 extract) once a day. If you have access to an extract that specifies its

withanolide content, aim for 15–60 mg of withanolides per day.

PASSIONFLOWER

Passionflower (*Passiflora incarnata Linneaus*) is one of the oldest herbal anxiolytics that may work by increasing GABA signalling in the brain.[244] It does not appear to be effective acutely, but rather shows steady benefits after a month or more of daily supplementation.[245],[246]

Dosage recommendations:

A standard dosage is 500 mg of passionflower extract taken once per day. Passionflower infusions (tea), consumed at least twice a day, also appear to be effective.

Rhodiola Rosea

Rhodiola rosea is a herb with traditional usage as an anti-fatigue agent and adaptogen compound. It significantly reduces fatigue and stress in people suffering from 'burnout' which can (consequently) improve cognitive function. [247],[248]

Dosage recommendations:

A standard dosage is 80–160 mg taken once per day, with a meal. A single 500 mg dose can be used one hour before an acute stressful event. Look for the SHR-5 extract or an equivalent, which confer both 3% rosavins and 1% salidroside.

Panax Ginseng

Panax Ginseng is commonly referred to as the 'True Ginseng' (being the most researched 'Ginseng' actually belonging to the plant family of 'Ginseng') and appears to be effective for mood, immunity, and cognition.[249],[250],[251252]

Dosage recommendations:

A standard dosage is 200–400 mg of an extract standardized for 2–3% ginsenosides, once per day.

CBD (Cannabidiol)

Cannabidiol (CBD) comprises up to 40% of cannabis, a family of plants that includes marijuana and hemp. CBD does not result in getting “high” (it is not psychoactive) and is legal in most countries (the U.S. included).

CBD has been shown to have a variety of anti-stress benefits, including helping with anxiety, insomnia, and depression. [253],[254] It may also help reduce inflammation, pain, and oxidative stress. [255] These benefits are derived primarily through cannabinoid signalling in the body, along with other neurotransmitter systems (serotonin, etc.)

Dosage recommendations:

A standard dosage is 15–80 mg per day, taken during times of increased stress of anxiety.

CURCUMIN

Curcumin is the yellow pigment and primary bioactive substance in turmeric. It possesses powerful anti-inflammatory and antioxidant properties that can help reduce depression and anxiety, although it may take a couple months before benefits are noticeable. [256],[257]

There is also evidence that curcumin can help slow cognitive decline with aging, promote cardiovascular health, reduce the risk of developing diabetes, and alleviate other inflammation-related conditions.[258]

Dosage recommendations:

A standard dosage is 500 mg of a curcumin complex taken 1–2 times per day.

Curcumin by itself has horrible bioavailability, meaning that you absorb very little of what you ingest. There are many forms of curcumin on the market that have increased bioavailability, and most studies have used curcumin with piperine (a black pepper extract) or the patented forms called BCM-95® and Meriva®.

While these forms have 20–48-fold greater bioavailability than regular curcumin, the most bioavailable forms are NovaSol® (185-fold), CurcuWin® (136-fold), and LongVida® (100-fold).[259] These are the forms that we recommend.

SPIRULINA

Spirulina is a species of cyanobacteria traditionally eaten by native African populations and the Aztecs of Central America. It is a decent source of protein and several vitamins, including vitamin B12, possesses strong anti-inflammatory and antioxidant effects mediated by its ability to inhibit NADPH oxidase, and protects against mitochondrial dysfunction and degeneration.[260]

This is also the basis for spirulina's ability to fight numerous diseases, including heart disease and diabetes. [261],[262]

Spirulina is also one of the few compounds that can literally "detox" the body by helping minimize the buildup of heavy metals in the body, like arsenic.[263]

Dosage recommendations:

A standard dosage is 2–8 grams per day.

Marine Phytoplankton

CHLORELLA

Chlorella is a freshwater algae (similar to Spirulina) with the ability to help detox the body from heavy metals, reduce inflammation, and boost overall immune function.[264]

Dosage recommendations:

A standard dosage is 6–10 grams per day.

NON-STIMULANT PERFORMANCE ENHANCERS

ALPHA-GPC

Alpha-glycerophosphocholine (Alpha-GPC or α-GPC) is currently the best known cholinergic for increasing plasma and brain choline levels, as it has better transportation into the brain than does pure choline. Additionally, the provision of glycerophosphate (the molecule bound to choline in alpha-GPC) supports the structure of cellular membranes.[265],[266],[267]

Alpha-GPC is a nootropic for enhancing cognition and slowing cognitive decline, even in people with mild to moderate Alzheimer's disease (albeit at higher required doses).[268],[269],[270],[271],[272] Taking alpha-GPC before a workout enhances power output.[273],[274],[275]

Dosage recommendations:

A standard dosage is 600–1,800 mg per day, taken in 2–3 divided doses. To enhance power output, take 600 mg an hour before the workout. Alpha-GPC is 40% choline by weight, meaning that 1,000 mg of alpha-GPC confers 400 mg of choline.

ASTAXANTHIN

Astaxanthin is the red pigment in shrimp, salmon, krill and various other seafood. It is thought to be one of the most effective antioxidants known to man, able to increase blood flow, reduce the oxidation of LDL, help modulate blood glucose, and improve cognitive function. It may also improve endurance exercise ability in athletes, and increase muscle strength and mobility in the elderly.[276,277,278,279,280,281]

Dosage recommendations:

A standard dosage is 6–8 mg per day, but an ideal dosage is not known. This dose is low enough to be obtained from wild-caught seafood or krill oil supplements. Due to being fat-soluble, supplements should be taken with a fatty meal.

BETAINE

Betaine (also called trimethylglycine) is an active metabolite of choline that serves a vital role in methylation alongside folate, and also benefits exercise performance and body composition.[282],[283],[284],[285],[286]

Betaine's role in methylation underlies many of its cardioprotective benefits, as it donates a methyl group to reduce homocysteine or maintain the activity of other methyl donors in the body like SAMe.[287],[288],[289] The exercise performance enhancing effects are secondary to betaine promoting cellular hydration and resilience to stressors.[290],[291]

Dosage recommendations:

A standard dosage is 1,000 to 3,000 mg taken 2–3 times per day.

L-CITRULLINE

Citrulline is a nonprotein amino acid that increases nitric oxide concentrations in the body.[292],[293] The increase in nitric oxide is believed to underlie its benefits on cardiovascular health, blood flow, and blood pressure.[294],[295],[296]Supplementation also benefits weight-lifting performance and reduces muscle soreness on the days following.[297],[298],[299],[300]

Dosage recommendations:

A standard dosage of L-citrulline is 1000 mg taken three times per day. If using citrulline malate, take 1.76 g of citrulline malate for every 1 gram of citrulline you would normally take. To supplement L-citrulline to enhance sports performance, take 6,000 to 8,000 mg of citrulline malate about an hour before exercise.

CREATINE

Creatine is among the most well-researched and effective supplements. It is a molecule produced in the body that stores energy for immediate use, and supplementation increases the amount of immediate energy that can be stored for use.

This effect causes strength increases after creatine supplementation, and can also benefit the brain, bones, muscles, and liver. Most of the benefits of creatine are a result of this mechanism. Although it is most widely researched for its ability to increase both power output and lean mass in athletes, creatine also confers neuroprotective and cardioprotective benefits, and increases cognitive function.[301],[302],[303],[304],[305],[306],[307]

For a comprehensive report on creatine, we refer you to its encyclopedia entry on Examine.com.

Dosage recommendations:

A standard dosage is 3–5 grams per day, taken indefinitely. Its benefits come from saturating bodily creatine stores, so there is no need to cycle. Stores can be saturated more quickly with a loading protocol of 20–25 grams per day for one week, but this isn't necessary.

There are many different forms of creatine available on the market, but creatine monohydrate is the most well researched, most effective, and least expensive. Micronized creatine monohydrate dissolves more easily in water, which can be advantageous to minimize the risk of an upset stomach.

NITRATES

Nitrates are naturally produced in a variety of foods and break down into nitric oxide (NO) after we consume it. Elevated NO levels provide a variety of benefits for cardiovascular health and physical vitality by increasing blood flow and reducing blood pressure.[308],[309] During exercise, these effects translate into greater endurance performance and better muscle recovery.[310],[311]

Dosage recommendations:

A standard dosage is 500–1,500 mg per day, taken 1–2 hours before exercise or taken throughout the day if not exercising.

Because nitrates cannot be purchased as a standalone supplement due to regulations against high quantities of sodium nitrate (a food additive frequently used to preserve processed meats), they should be obtained from foods rich in nitrates — most studies use beetroot juice or powder. Leafy

greens and cruciferous vegetables are also good sources. These foods should be eaten raw or minimally cooked, as heat greatly reduces the nitrate content.

Nitrate content per 100 grams of food	Nitrate-rich vegetables
Excellent (>300 mg)	Arugula, turnip greens
Great (200–300 mg)	Dill, collard greens, spinach, Swiss chard, turnips, rhubarb, beetroot
Good (100–200 mg)	Celery, mustard greens, radish, lettuce, watercress, bok choy, kale, parsley

L-ORNITHINE

Ornithine is a nonprotein amino acid involved in disposing of ammonia in the body. Accordingly, supplementation is thought to be of benefit for conditions characterized by an excess level of ammonia, such as liver diseases and prolonged endurance exercise.

Ammonia is a neurotoxin, and reductions through ornithine supplementation can reduce mental fatigue and increase physical energy (by increasing the amount of ammonia that can be produced without detriment).[312],[313],[314] Supplementation can also benefit sleep.[315]

Dosage recommendations:

A standard dosage is 2–6 grams per day, taken as 1–2 doses. Most studies use ornithine hydrochloride (ornithine HCl), ornithine L-Aspartate, or ornithine α-ketoglutarate. The two latter forms are theoretically more effective, but lack sufficient comparative testing.

CORDYCEPS

Cordyceps is a medicinal mushroom traditionally used in the east for thousands of years. It grows on the bodies of caterpillars, but is now more typically farmed (no caterpillars necessary). It has long been known as an energizer and fatigue fighter, and modern research backs these traditional claims up.

Dosage recommendations:

A standard dosage is 1,000-3,000mg a day.

D-RIBOSE

D-ribose is a special type of sugar that is required to create energy and DNA. Some evidence suggests that D-ribose can help boost energy and physical function in situations where energy levels are reduced, such as people who have suffered from heart disease or stroke, or people engaging in regular intense exercise.[316,317,318,319,320,321]

Notably, D-ribose has been shown to improve energy, sleep, well-being, and pain threshold in people with fibromyalgia or chronic fatigue syndrome in just three weeks, using 15 grams per day in three divided doses. Another study reported similar findings after using 10 grams per day, with all benefits disappearing within a week of stopping supplementation.[322,323]

Dosage recommendations:

A standard dosage is 10–15 grams per day, taken in 2–3 divided doses.

BAKING SODA

Sodium Bicarbonate (baking soda) is a molecule that acts as a buffering agent against acidity in the human body, and appears to enhance physical performance in athletes through this mechanism.[324,325] It may also have health benefits in conditions of chronic acidosis.

Exercise performance benefits are reliably seen during exercise when failure is associated with "the burn".[326,327] If failure is due to the cardiorespiratory

system (low-intensity endurance exercise) or the nervous system (single sprints), benefits are not reliable.[328]

Dosage recommendations:

A standard dosage is 200–300 mg/kg (3–4 teaspoons) taken 60–90 minutes before exercise. Taking large doses at once can cause GI distress, and breaking a dose up into smaller doses taken every 30 minutes can alleviate this side effect.

Additionally, as 27% of sodium bicarbonate is sodium, every teaspoon confers about 1300 mg of sodium that needs to be accounted for.

TAURINE

Taurine is a sulfur-containing amino acid essential for cardiovascular function and the development and function of skeletal muscle, the retina, and the brain.[329] It can help fight muscle loss with aging, as well as benefit many other disease states, including neurodegenerative diseases, diseases of the eye, diabetes, heart failure, high blood pressure, and muscular dystrophies. [330] Taurine is also essential for the proper function of mitochondria. [331],[332]

For young athletes, supplementing with 1–6 g of taurine per day improves endurance exercise performance.[333] This benefit was seen regardless of how much taurine athletes took or for how long, suggesting that 1 g has the same effect as 6 g and that chronic supplementation isn't necessary (just take it pre-workout).

Dosage recommendations:

A standard dosage is 1–3 grams taken 2–3 times per day.

ACETYL L-CARNITINE

Acetyl L-Carnitine (ALCAR) is a unique form of L-Carnitine that has brain- and body-boosting properties.

- Reduces depression with a potency comparable to drugs.[334]
- Protects and repairs neurons from damage (like that caused by diabetes). [335],[336]
- Increases mitochondrial function by increasing their ability to produce energy.[337,338,339]
- Alleviates the side effects of aging, like neurological decline and chronic fatigue. [340],[341],[342],[343],[344]
- Improves insulin sensitivity.[345]
- Improves cardiovascular health.[346],[347]

Notably, ALCAR has been known to cause fat loss, not because of any mechanism intrinsic to ALCAR, but simply because those taking it become more physically active due to the increased energy and vitality it provides.

Dosage recommendations:

The standard dosage for ALCAR is 1,000–2,500 mg per day, taken as 2–3 divided doses.

COENZYME Q10

Coenzyme Q10 (CoQ10) is a molecule found in mitochondria that has a critical role in energy production. It is considered a pseudovitamin because it is vital for survival but does not need to be consumed in the diet of an otherwise healthy person — the body makes it on demand.

However, several diseases and low-energy conditions are associated with low CoQ10 levels, including people who have fibromyalgia, have survived heart attacks or heart failure, have multiple sclerosis, are infertile, or suffer migraines. Generally speaking, CoQ10 will enhance blood flow, protect blood vessels, lower oxidative stress, and boost vitality in anyone who suffers from fatigue, but especially those people with the aforementioned conditions.[348,349,350,351,352,353,354,355,356,357,358,359]

Additionally, statin drugs are known to deplete CoQ10 levels, so supplementation is mandatory in people taking a statin (even doctors know this and will co-prescribe CoQ10 with a statin).[360,361]

Dosage recommendations:

The standard dose for CoQ10 is 100–200 mg per day, taken once daily with a meal containing some fat. Supplements exist as either ubiquinone or ubiquinol, with ubiquinol being preferred due to having superior bioavailability.

STIMULANTS

Stimulants have direct effects on energy levels — they are compounds that cause an immediate and temporary increase in mental and physical performance by increasing the activity of the central and peripheral nervous systems.

Generally speaking, the effects of stimulants include enhanced alertness, awareness, focus, wakefulness, and physical vitality, all of which tend to result in more motivation, greater productivity, a better mood, and a reduced perception for needing food or sleep.

While the short-lived effects of stimulants can be a powerful tool when used correctly, they can be a double-edged sword if overly relied upon by decreasing energy levels with chronic use — the body adapts to their effects and requires higher and higher doses to obtain the same effects. Eventually, no dose will suffice to provide energy and you will feel burned out and lethargic as you wean off the stimulants to regain your sensitivity to them.

Accordingly, we recommend using stimulants only occasionally, no more than every other day or roughly four days per week. You can also simply avoid them altogether.

CAFFEINE

Caffeine is a powerful stimulant naturally found in coffee, tea, yerba mate, and (to a lesser degree) cacao and dark chocolates. It is also added to many soft drinks and a key component of energy drinks and pre-workout supplements.

Roughly 85% of the US population consumes at least one caffeinated beverage per day, with an average caffeine intake of 190 mg per day (mg/d) or 2.5 mg per kg of body weight (mg/kg).[362,363] It is the world's most loved stimulant, and one of the most well-researched.

Caffeine can be used to improve physical strength and endurance exercise performance when taken before a workout session.[364,365,366,367] It can also boost fat burning with about three regular cups of coffee taken at once (~300 mg caffeine).[368]

However, caffeine's main mechanism of action is to compete with adenosine in the brain.[369] Adenosine is the molecule that causes fatigue and sleepiness; by competing with it, caffeine is able to prevent these effects and cause us to feel more awake, alert, and energized.[370]

Inhibition of adenosine can influence the dopamine, serotonin, acetylcholine, and adrenaline systems — all of them directly or indirectly cause enhanced mood, cognition, and physical performance. Caffeine also directly influences orexin.[371]

Regular caffeine consumption causes habituation to its effects, requiring even more caffeine to bring about benefits.[372] This tolerance sets in after just a few days of use. Yet, regular use for a couple weeks can cause an "insurmountable" tolerance whereby no amount of caffeine will provide a benefit, and a prolonged 2–4 week break is required to reset the body.[373]

Dosage Recommendations:

A standard dosage is 200–300 mg of caffeine above your regular intake level. This can be 500–600 mg if you regularly have several cups of coffee. If you never consume caffeine, then effects are noticeable with as little as 100–200 mg.

Caffeine is best consumed in the morning where it will not interfere with circadian rhythms. Caffeine use in the afternoon and evening is discouraged due to its variable half-life of 3–10 hours.[374],[375] Consuming caffeine after 3–4 p.m. can reduce sleep quality and make it difficult to fall asleep, and you should know by now how important sleep is for your health and wellbeing.

Caffeine should be used infrequently to prevent habituation, such as every other day.

Powdered and pilled caffeine forms are more potent than coffee, but there are other compounds in coffee that are linked to health benefits. This is something you have to make a personal decision on. Black and green tea, as well as the South-American beverage Yerba Mate also contain caffeine and various cofactors that have been linked to health.

If you regularly consume large amounts of caffeine, then you will need to spend at least two weeks abstaining from any intake to help resensitize the

body to its effects. You may experience several days of withdrawal: sleepiness, lethargy, and headaches are common.

NICOTINE

Nicotine is one of the many naturally occurring alkaloids in tobacco. It works primarily through mimicking the neurotransmitter acetylcholine and directly activating acetylcholine receptors, which can increase catecholamines such as adrenaline and dopamine.[376]

Nicotine is also pro-oxidative at a level which may be hormetic — it works with the acetylcholine mechanism just mentioned to exert anti-inflammatory effects. Nicotine also happens to directly increase orexin, as well as orexin receptor sensitivity over time, meaning that the wakefulness effects actually improve with habitual usage. [377]

This increase in catecholamines underlies many benefits of nicotine on cognition (mostly attention and focus) while the acetylcholine mimicking may promote a nootropic effect. Increased adrenaline output also underlies nicotine's ability to increase metabolic rate and increase fat burning.[378],[379]

Addiction is not inherent to nicotine, as is evidenced by nicotine therapy being used to curb cigarette addictions. Gums and patches have less potential risk for addiction than do cigarettes (with inhalers in the middle) due to speed nicotine reaches the brain.

To be clear, WE DO NOT recommend smoking ANY nicotine-containing substances. Smoking ANYTHING carries risk of harm to the body and lungs in particular.

Although we still have to warn against the addictive potential of nicotine in this section, it is important to note that caffeine has a far higher addictive potential and risk profile in its commonly ingested forms and dosages, so we feel nicotine has been unfairly stigmatized.

Moreover, there are a host of documented scientific benefits from using nicotine in non-smoking forms — the harm associated with nicotine likely comes as a result of smoking and inhaling combustion products directly into the lungs, NOT the effects of nicotine itself.

Dosage Recommendations:

A standard dosage is 1–4 mg of nicotine gum, starting at 1–2 mg and working up to a maximum of 4 mg. Patches don't have any significant cognitive benefits, so the only form of nicotine we recommend is chewing gum. Nicotine seems to work better early in the day.

Chew a few times until you taste the strong, pepper-like nicotine, then place it either below your tongue or between your cheek and your gums. Leave it there for 5–15 minutes, then chew a little more, then put it back under your tongue or between your cheek and gums — repeat the process for the next 1–1.5 hours.

SYNEPHRINE

Synephrine, also called "bitter orange", is a mild stimulant that can increase metabolic rate and energy levels.[380],[381] It isn't a top pick, but can help accentuate the effects of other stimulants without notable side effects.

Dosage Recommendations:

A standard dosage is 10–30 mg taken 2–3 times per day away from meals.

THEACRINE

Theacrine is an alkaloid structurally similar to caffeine, and preliminary evidence suggests that it activates similar signalling pathways (adenosine and catecholamine systems).[382] Yet, theacrine appears to have less of an ability to induce tolerance.[383]

While daily caffeine use leads to habituation, no such effects are seen with theacrine — you can use it every day and still get the benefits on energy, mood, and focus! [384],[385]

Dosage Recommendations:

A standard dosage is 100–300 mg taken 2–3 times per day away from meals, with 200 mg generally recommended as the most beneficial dose.

TOP 20 SUPPLEMENTS FOR HEALTH AND ENERGY

1. Phospholipids (NTFactors)
2. Spirulina
3. Astaxanthin
4. Acetyl L-Carnitine (ALCAR)
5. Bacopa monnieri
6. EPA and DHA (marine oils)
7. D-Ribose
8. Ginkgo biloba
9. Melatonin
10. R-ALA
11. Rhodiola Rosea
12. Curcumin
13. Alpha-GPC
14. Creatine
15. Cacao
16. Coenzyme Q10
17. Cordyceps
18. Schizandra
19. Pomegranate
20. Green tea catechins

REFERENCES

[1] Pashkow, F. J., Watumull, D. G. & Campbell, C. L. Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. Am. J. Cardiol. 101, 58D–68D (2008).

[2] Goulinet, S. & Chapman, M. J. Plasma LDL and HDL subspecies are heterogenous in particle content of tocopherols and oxygenated and hydrocarbon carotenoids. Relevance to oxidative resistance and atherogenesis. Arterioscler. Thromb. Vasc. Biol. 17, 786–796

[3] Mashhadi, N. S. et al. Astaxanthin improves glucose metabolism and reduces blood pressure in patients with type 2 diabetes mellitus. Asia Pac. J. Clin. Nutr. 27, 341–346 (2018).

[4] Ito, N., Saito, H., Seki, S., Ueda, F. & Asada, T. Effects of Composite Supplement Containing Astaxanthin and Sesamin on Cognitive Functions in People with Mild Cognitive Impairment: A Randomized, Double-Blind, Placebo-Controlled Trial. J. Alzheimers. Dis

[5] Earnest, C. P., Lupo, M., White, K. M. & Church, T. S. Effect of astaxanthin on cycling time trial performance. Int. J. Sports Med. 32, 882–888 (2011).

[6] Liu, S. Z. et al. Building strength, endurance, and mobility using an astaxanthin formulation with functional training in elderly. J. Cachexia Sarcopenia Muscle 9, 826–833 (2018).

[7] Harris, C. B. et al. Dietary pyrroloquinoline quinone (PQQ) alters indicators of inflammation and mitochondrial-related metabolism in human subjects. J. Nutr. Biochem. 24, 2076–2084 (2013).

[8] Chowanadisai, W. et al. Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1alpha expression. J. Biol. Chem. 285, 142–152 (2010).

[9] Hwang, P. & Willoughby, D. S. Mechanisms Behind Pyrroloquinoline Quinone Supplementation on Skeletal Muscle Mitochondrial Biogenesis: Possible Synergistic Effects with Exercise. J. Am. Coll. Nutr. 1–11 (2018).

[10] Mahoney, D. E. et al. Understanding D-Ribose and Mitochondrial Function. Adv Biosci Clin Med 6, 1–5 (2018).

[11] Omran, H., Illien, S., MacCarter, D., St Cyr, J. & Lüderitz, B. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. Eur. J. Heart Fail. 5, 615–619 (2003).

[12] MacCarter, D. et al. D-ribose aids advanced ischemic heart failure patients. Int. J. Cardiol. 137, 79–80 (2009).

[13] Pliml, W. et al. Effects of ribose on exercise-induced ischaemia in stable coronary artery disease. Lancet 340, 507–510 (1992).

[14] Hellsten, Y., Skadhauge, L. & Bangsbo, J. Effect of ribose supplementation on resynthesis of adenine nucleotides after intense intermittent training in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 286, R182–8 (2004).

[15] Seifert, J. G., Brumet, A. & St Cyr, J. A. The influence of D-ribose ingestion and fitness level on performance and recovery. J. Int. Soc. Sports Nutr. 14, 47 (2017).

[16] Teitelbaum, J. E., Johnson, C. & St Cyr, J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. J. Altern. Complement. Med. 12, 857–862 (2006).

[17] Gebhart, B. & Jorgenson, J. A. Benefit of ribose in a patient with fibromyalgia. Pharmacotherapy 24, 1646–1648 (2004).

[18] Cordero, M. D. et al. Coenzyme Q10 distribution in blood is altered in patients with fibromyalgia. Clin. Biochem. 42, 732–735 (2009).

[19] Di Pierro, F., Rossi, A., Consensi, A., Giacomelli, C. & Bazzichi, L. Role for a water-soluble form of CoQ10 in female subjects affected by fibromyalgia. A preliminary study. Clin. Exp. Rheumatol. 35 Suppl 105, 20–27 (2017).

[20] Cordero, M. D. et al. Can coenzyme q10 improve clinical and molecular parameters in fibromyalgia? Antioxid. Redox Signal. 19, 1356–1361 (2013).

[21] Jafari, M., Mousavi, S. M., Asgharzadeh, A. & Yazdani, N. Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews. Indian Heart J. 70 Suppl 1, S111–S117 (2018).

[22] DiNicolantonio, J. J., Bhutani, J., McCarty, M. F. & O'Keefe, J. H. Coenzyme Q10 for the treatment of heart failure: a review of the literature. Open Heart 2, e000326 (2015).

[23] 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. 19, 138–143 (2016).
[24] Sanoobar, M. et al. Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. Nutr. Neurosci. 18, 169–176 (2015).
[25] Lafuente, R. et al. Coenzyme Q10 and male infertility: a meta-analysis. J. Assist. Reprod. Genet. 30, 1147–1156 (2013).
[26] Xu, Y. et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reprod. Biol. Endocrinol. 16, 29 (2018).
[27] Ben-Meir, A. et al. Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging. Aging Cell 14, 887–895 (2015).
[28] Shoeibi, A. et al. Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled trial. Acta Neurol. Belg. 117, 103–109 (2017).
[29] Sándor, P. S. et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology 64, 713–715 (2005).
[30] Deichmann, R., Lavie, C. & Andrews, S. Coenzyme q10 and statin-induced mitochondrial dysfunction. Ochsner J. 10, 16–21 (2010).
[31] Skarlovnik, A., Janić, M., Lunder, M., Turk, M. & Šabovič, M. Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: a randomized clinical study. Med. Sci. Monit. 20, 2183–2188 (2014).
[32] Kasper, S. & Dienel, A. Multicenter, open-label, exploratory clinical trial with extract in patients suffering from burnout symptoms. Neuropsychiatr. Dis. Treat. 13, 889–898 (2017).
[33] Anghelescu, I.-G., Edwards, D., Seifritz, E. & Kasper, S. Stress management and the role of Rhodiola rosea: a review. Int. J. Psychiatry Clin. Pract. 1–11 (2018).
[34] McCarty, M. F. Clinical potential of Spirulina as a source of phycocyanobilin. J. Med. Food 10, 566–570 (2007).
[35] Nawrocka, D., Kornicka, K., Śmieszek, A. & Marycz, K. Spirulina platensis Improves Mitochondrial Function Impaired by Elevated Oxidative Stress in Adipose-Derived Mesenchymal Stromal Cells (ASCs) and Intestinal Epithelial Cells (IECs), and Enhances Insuli
[36] Zheng, J. et al. Phycocyanin and phycocyanobilin from Spirulina platensis protect against diabetic nephropathy by inhibiting oxidative stress. Am. J. Physiol. Regul. Integr. Comp. Physiol. 304, R110–20 (2013).
[37] Saha, S. K., Misbahuddin, M., Khatun, R. & Mamun, I. R. Effect of hexane extract of spirulina in the removal of arsenic from isolated liver tissues of rat. Mymensingh Med. J. 14, 191–195 (2005).
[38] Saha, S. K., Misbahuddin, M. & Ahmed, A. U. Comparison between the effects of alcohol and hexane extract of spirulina in arsenic removal from isolated tissues. Mymensingh Med. J. 19, 27–31 (2010).
[39] Ng, Q. X., Koh, S. S. H., Chan, H. W. & Ho, C. Y. X. Clinical Use of Curcumin in Depression: A Meta-Analysis. J. Am. Med. Dir. Assoc. 18, 503–508 (2017).
[40] Noorafshan, A., Vafabin, M., Karbalay-Doust, S. & Asadi-Golshan, R. Efficacy of Curcumin in the Modulation of Anxiety Provoked by Sulfite, a Food Preservative, in Rats. Prev Nutr Food Sci 22, 144–148 (2017).
[41] Hewlings, S. J. & Kalman, D. S. Curcumin: A Review of Its' Effects on Human Health. Foods 6, (2017).
[42] de Oliveira, M. R. et al. Quercetin and the mitochondria: A mechanistic view. Biotechnol. Adv. 34, 532–549 (2016).
[43] Davis, J. M., Murphy, E. A., Carmichael, M. D. & Davis, B. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am. J. Physiol. Regul. Integr. Comp. Physiol. 296, R1071–7 (2009).
[44] Ripps, H. & Shen, W. Review: taurine: a 'very essential' amino acid. Mol. Vis. 18, 2673–2686 (2012).
[45] Scicchitano, B. M. & Sica, G. The Beneficial Effects of Taurine to Counteract Sarcopenia. Curr. Protein Pept. Sci. 19, 673–680 (2018).
[46] Schaffer, S. & Kim, H. W. Effects and Mechanisms of Taurine as a Therapeutic Agent. Biomol. Ther. 26, 225–241 (2018).

[47] Jong, C. J., Ito, T., Prentice, H., Wu, J.-Y. & Schaffer, S. W. Role of Mitochondria and Endoplasmic Reticulum in Taurine-Deficiency-Mediated Apoptosis. Nutrients 9, (2017).
[48] Veronese, N. et al. Acetyl-L-Carnitine Supplementation and the Treatment of Depressive Symptoms: A Systematic Review and Meta-Analysis. Psychosom. Med. 80, 154–159 (2018).
[49] Rump, T. J. et al. Acetyl-L-carnitine protects neuronal function from alcohol-induced oxidative damage in the brain. Free Radic. Biol. Med. 49, 1494–1504 (2010).
[50] Scafidi, S., Racz, J., Hazelton, J., McKenna, M. C. & Fiskum, G. Neuroprotection by acetyl-L-carnitine after traumatic injury to the immature rat brain. Dev. Neurosci. 32, 480–487 (2010).
[51] Nicassio, L. et al. Dietary supplementation with acetyl-l-carnitine counteracts age-related alterations of mitochondrial biogenesis, dynamics and antioxidant defenses in brain of old rats. Exp. Gerontol. 98, 99–109 (2017).
[52] Patel, S. P., Sullivan, P. G., Lyttle, T. S. & Rabchevsky, A. G. Acetyl-L-carnitine ameliorates mitochondrial dysfunction following contusion spinal cord injury. J. Neurochem. 114, 291–301 (2010).
[53] Rosca, M. G., Lemieux, H. & Hoppel, C. L. Mitochondria in the elderly: Is acetylcarnitine a rejuvenator? Adv. Drug Deliv. Rev. 61, 1332–1342 (2009).
[54] Rai, G. et al. Double-blind, placebo controlled study of acetyl-l-carnitine in patients with Alzheimer's dementia. Curr. Med. Res. Opin. 11, 638–647 (1990).
[55] Passeri, M. et al. Acetyl-L-carnitine in the treatment of mildly demented elderly patients. Int. J. Clin. Pharmacol. Res. 10, 75–79 (1990).
[56] Thal, L. J. et al. A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. Neurology 47, 705–711 (1996).
[57] Tomassini, V. et al. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. J. Neurol. Sci. 218, 103–108 (2004).
[58] Plioplys, A. V. & Plioplys, S. Amantadine and L-carnitine treatment of Chronic Fatigue Syndrome. Neuropsychobiology 35, 16–23 (1997).
[59] Xu, Y. et al. L-carnitine treatment of insulin resistance: A systematic review and meta-analysis. Adv. Clin. Exp. Med. 26, 333–338 (2017).
[60] Song, X. et al. Efficacy and Safety of L-Carnitine Treatment for Chronic Heart Failure: A Meta-Analysis of Randomized Controlled Trials. Biomed Res. Int. 2017, 6274854 (2017).
[61] Shang, R., Sun, Z. & Li, H. Effective dosing of L-carnitine in the secondary prevention of cardiovascular disease: a systematic review and meta-analysis. BMC Cardiovasc. Disord. 14, 88 (2014).
[62] Carrasco-Gallardo, C., Guzmán, L. & Maccioni, R. B. Shilajit: a natural phytocomplex with potential procognitive activity. Int. J. Alzheimers. Dis. 2012, 674142 (2012).
[63] Surapaneni, D. K. et al. Shilajit attenuates behavioral symptoms of chronic fatigue syndrome by modulating the hypothalamic-pituitary-adrenal axis and mitochondrial bioenergetics in rats. J. Ethnopharmacol. 143, 91–99 (2012).
[64] Heber, D. Pomegranate Ellagitannins. in Herbal Medicine: Biomolecular and Clinical Aspects (eds. Benzie, I. F. F. & Wachtel-Galor, S.) (CRC Press/Taylor & Francis, 2012).
[65] Ismail, T. et al. Ellagitannins in Cancer Chemoprevention and Therapy. Toxins 8, (2016).
[66] Rodriguez, J. et al. Urolithin B, a newly identified regulator of skeletal muscle mass. J. Cachexia Sarcopenia Muscle 8, 583–597 (2017).
[67] Zhao, W. et al. Metabolite of ellagitannins, urolithin A induces autophagy and inhibits metastasis in human sw620 colorectal cancer cells. Mol. Carcinog. 57, 193–200 (2018).
[68] Shay, K. P., Moreau, R. F., Smith, E. J., Smith, A. R. & Hagen, T. M. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. Biochim. Biophys. Acta 1790, 1149–1160 (2009).
[69] Poon, H. F. et al. Proteomic analysis of specific brain proteins in aged SAMP8 mice treated with alpha-lipoic acid: implications for aging and age-related neurodegenerative disorders. Neurochem. Int. 46, 159–168 (2005).
[70] Panigrahi, M. et al. alpha-Lipoic acid protects against reperfusion injury following cerebral ischemia in rats. Brain Res. 717, 184–188 (1996).
[71] Arivazhagan, P., Shila, S., Kumaran, S. & Panneerselvam, C. Effect of DL-alpha-lipoic acid on the status of lipid peroxidation and antioxidant enzymes in various brain regions of aged rats. Exp. Gerontol. 37, 803–811 (2002).

[72] Zhang, L. et al. Alpha-lipoic acid protects rat cortical neurons against cell death induced by amyloid and hydrogen peroxide through the Akt signalling pathway. Neurosci. Lett. 312, 125–128 (2001).
[73] Breithaupt-Grögler, K. et al. Dose-proportionality of oral thioctic acid--coincidence of assessments via pooled plasma and individual data. Eur. J. Pharm. Sci. 8, 57–65 (1999).
[74] Freisleben, H. J., Neeb, A., Lehr, F. & Ackermann, H. Influence of selegiline and lipoic acid on the life expectancy of immunosuppressed mice. Arzneimittelforschung 47, 776–780 (1997).
[75] Tejada, S. et al. Potential Anti-inflammatory Effects of Hesperidin from the Genus Citrus. Curr. Med. Chem. 25, 4929–4945 (2018).
[76] Manchope, M. F., Casagrande, R. & Verri, W. A., Jr. Naringenin: an analgesic and anti-inflammatory citrus flavanone. Oncotarget 8, 3766–3767 (2017).
[77] Benavente-García, O. & Castillo, J. Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. J. Agric. Food Chem. 56, 6185–6205 (2008).
[78] Kumar, A., Prakash, A. & Dogra, S. Naringin alleviates cognitive impairment, mitochondrial dysfunction and oxidative stress induced by D-galactose in mice. Food Chem. Toxicol. 48, 626–632 (2010).
[79] Singhal, K., Raj, N., Gupta, K. & Singh, S. Probable benefits of green tea with genetic implications. J. Oral Maxillofac. Pathol. 21, 107–114 (2017).
[80] Suzuki, Y., Miyoshi, N. & Isemura, M. Health-promoting effects of green tea. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 88, 88–101 (2012).
[81] Chacko, S. M., Thambi, P. T., Kuttan, R. & Nishigaki, I. Beneficial effects of green tea: a literature review. Chin. Med. 5, 13 (2010).
[82] Ortiz-López, L. et al. Green tea compound epigallo-catechin-3-gallate (EGCG) increases neuronal survival in adult hippocampal neurogenesis in vivo and in vitro. Neuroscience 322, 208–220 (2016).
[83] Pervin, M. et al. Beneficial Effects of Green Tea Catechins on Neurodegenerative Diseases. Molecules 23, (2018).
[84] Babu, P. V. A. & Liu, D. Green tea catechins and cardiovascular health: an update. Curr. Med. Chem. 15, 1840–1850 (2008).
[85] Bhardwaj, P. & Khanna, D. Green tea catechins: defensive role in cardiovascular disorders. Chin. J. Nat. Med. 11, 345–353 (2013).
[86] Rains, T. M., Agarwal, S. & Maki, K. C. Antiobesity effects of green tea catechins: a mechanistic review. J. Nutr. Biochem. 22, 1–7 (2011).
[87] Hursel, R. & Westerterp-Plantenga, M. S. Catechin- and caffeine-rich teas for control of body weight in humans. Am. J. Clin. Nutr. 98, 1682S–1693S (2013).
[88] Hursel, R., Viechtbauer, W. & Westerterp-Plantenga, M. S. The effects of green tea on weight loss and weight maintenance: a meta-analysis. Int. J. Obes. 33, 956–961 (2009).
[89]Cooper, R., Morré, D. J. & Morré, D. M. Medicinal benefits of green tea: part II. review of anticancer properties. J. Altern. Complement. Med. 11, 639–652 (2005).
[90] Lambert, J. D. Does tea prevent cancer? Evidence from laboratory and human intervention studies. Am. J. Clin. Nutr. 98, 1667S–1675S (2013).
[91] Park, J.-H., Bae, J.-H., Im, S.-S. & Song, D.-K. Green tea and type 2 diabetes. Integr Med Res 3, 4–10 (2014).
[92] Forester, S. C. & Lambert, J. D. The role of antioxidant versus pro-oxidant effects of green tea polyphenols in cancer prevention. Mol. Nutr. Food Res. 55, 844–854 (2011).
[93] Ohishi, T., Goto, S., Monira, P., Isemura, M. & Nakamura, Y. Anti-inflammatory Action of Green Tea. Antiinflamm. Antiallergy Agents Med. Chem. 15, 74–90 (2016).
[94] Bernatoniene, J. & Kopustinskiene, D. M. The Role of Catechins in Cellular Responses to Oxidative Stress. Molecules 23, (2018).
[95] Nicolson, G. L. & Ash, M. E. Lipid Replacement Therapy: a natural medicine approach to replacing damaged lipids in cellular membranes and organelles and restoring function. Biochim. Biophys. Acta 1838, 1657–1679 (2014).
[96] Nicolson, G. L. & Ellithorpe, R. Lipid Replacement and Antioxidant Nutritional Therapy for Restoring Mitochondrial Function and Reducing Fatigue in Chronic Fatigue Syndrome and Other Fatiguing Illnesses. J. Chronic Fatigue Syndr. 13, 57–68 (2006).
[97] L. Nicolson, G., Settineri, R. & Ellithorpe, R. Lipid Replacement Therapy with a Glycophospholipid Formulation with NADH and CoQ10 Significantly Reduces Fatigue in Intractable Chronic Fatiguing Illnesses and Chronic Lyme Disease Patients. IJCM 03, 163–170

[98] Agadjanyan, M. et al. Nutritional Supplement (NT FactorTM) Restores Mitochondrial Function and Reduces Moderately Severe Fatigue in Aged Subjects. J. Chronic Fatigue Syndr. 11, 23–36 (2003).
[99] Nicolson, G. L. & Conklin, K. A. Reversing mitochondrial dysfunction, fatigue and the adverse effects of chemotherapy of metastatic disease by molecular replacement therapy. Clin. Exp. Metastasis 25, 161–169 (2008).
[100] Nicolson, G. L. Lipid replacement/antioxidant therapy as an adjunct supplement to reduce the adverse effects of cancer therapy and restore mitochondrial function. Pathol. Oncol. Res. 11, 139–144 (2005).
[101] Tan, L. et al. Investigation on the Role of BDNF in the Benefits of Blueberry Extracts for the Improvement of Learning and Memory in Alzheimer's Disease Mouse Model. J. Alzheimers. Dis. 56, 629–640 (2017).
[102] Rendeiro, C. et al. Blueberry supplementation induces spatial memory improvements and region-specific regulation of hippocampal BDNF mRNA expression in young rats. Psychopharmacology 223, 319–330 (2012).
[103] Bensalem, J. et al. Polyphenol-rich extract from grape and blueberry attenuates cognitive decline and improves neuronal function in aged mice. J. Nutr. Sci. 7, e19 (2018).
[104] Krikorian, R. et al. Blueberry supplementation improves memory in older adults. J. Agric. Food Chem. 58, 3996–4000 (2010).
[105] Boespflug, E. L. et al. Enhanced neural activation with blueberry supplementation in mild cognitive impairment. Nutr. Neurosci. 21, 297–305 (2018).
[106] Whyte, A. R., Cheng, N., Fromentin, E. & Williams, C. M. A Randomized, Double-Blinded, Placebo-Controlled Study to Compare the Safety and Efficacy of Low Dose Enhanced Wild Blueberry Powder and Wild Blueberry Extract (ThinkBlueTM) in Maintenance of Episod
[107] Bowtell, J. L., Aboo-Bakkar, Z., Conway, M. E., Adlam, A.-L. R. & Fulford, J. Enhanced task-related brain activation and resting perfusion in healthy older adults after chronic blueberry supplementation. Appl. Physiol. Nutr. Metab. 42, 773–779 (2017).
[108] Ma, L., Sun, Z., Zeng, Y., Luo, M. & Yang, J. Molecular Mechanism and Health Role of Functional Ingredients in Blueberry for Chronic Disease in Human Beings. Int. J. Mol. Sci. 19, (2018).
[109] Kongkeaw, C., Dilokthornsakul, P., Thanarangsarit, P., Limpeanchob, N. & Norman Scholfield, C. Meta-analysis of randomized controlled trials on cognitive effects of Bacopa monnieri extract. J. Ethnopharmacol. 151, 528–535 (2014).
[110] Kean, J. D., Downey, L. A. & Stough, C. A systematic review of the Ayurvedic medicinal herb Bacopa monnieri in child and adolescent populations. Complement. Ther. Med. 29, 56–62 (2016).
[111] Pase, M. P. et al. The cognitive-enhancing effects of Bacopa monnieri: a systematic review of randomized, controlled human clinical trials. J. Altern. Complement. Med. 18, 647–652 (2012).
[112] Chaudhari, K. S., Tiwari, N. R., Tiwari, R. R. & Sharma, R. S. Neurocognitive Effect of Nootropic Drug () in Alzheimer's Disease. Ann Neurosci 24, 111–122 (2017).
[113] Kwon, H. J. et al. extract improves novel object recognition, cell proliferation, neuroblast differentiation, brain-derived neurotrophic factor, and phosphorylation of cAMP response element-binding protein in the dentate gyrus. Lab. Anim. Res. 34, 239–247
[114] Aguiar, S. & Borowski, T. Neuropharmacological review of the nootropic herb Bacopa monnieri. Rejuvenation Res. 16, 313–326 (2013).
[115] Shay, K. P., Moreau, R. F., Smith, E. J., Smith, A. R. & Hagen, T. M. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. Biochim. Biophys. Acta 1790, 1149–1160 (2009).
[116] Poon, H. F. et al. Proteomic analysis of specific brain proteins in aged SAMP8 mice treated with alpha-lipoic acid: implications for aging and age-related neurodegenerative disorders. Neurochem. Int. 46, 159–168 (2005).
[117] Panigrahi, M. et al. alpha-Lipoic acid protects against reperfusion injury following cerebral ischemia in rats. Brain Res. 717, 184–188 (1996).
[118] Arivazhagan, P., Shila, S., Kumaran, S. & Panneerselvam, C. Effect of DL-alpha-lipoic acid on the status of lipid peroxidation and antioxidant enzymes in various brain regions of aged rats. Exp. Gerontol. 37, 803–811 (2002).
[119] Zhang, L. et al. Alpha-lipoic acid protects rat cortical neurons against cell death induced by amyloid and hydrogen peroxide through the Akt signalling pathway. Neurosci. Lett. 312, 125–128 (2001).

[120] Freisleben, H. J., Neeb, A., Lehr, F. & Ackermann, H. Influence of selegiline and lipoic acid on the life expectancy of immunosuppressed mice. Arzneimittelforschung 47, 776–780 (1997).
[121] Lan, J. et al. Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. J. Ethnopharmacol. 161, 69–81 (2015).
[122] Jia, Y., Lao, Y., Zhu, H., Li, N. & Leung, S.-W. Is metformin still the most efficacious first-line oral hypoglycaemic drug in treating type 2 diabetes? A network meta-analysis of randomized controlled trials. Obes. Rev. 20, 1–12 (2019).
[123] Han, Y., Wang, Q., Song, P., Zhu, Y. & Zou, M.-H. Redox regulation of the AMP-activated protein kinase. PLoS One 5, e15420 (2010).
[124] Kim, W. S. et al. Berberine improves lipid dysregulation in obesity by controlling central and peripheral AMPK activity. Am. J. Physiol. Endocrinol. Metab. 296, E812–9 (2009).
[125] Wang, X. et al. The uptake and transport behavior of berberine in Coptidis Rhizoma extract through rat primary cultured cortical neurons. Neurosci. Lett. 379, 132–137 (2005).
[126] Wang, H. et al. Berberine attenuated pro-inflammatory factors and protect against neuronal damage via triggering oligodendrocyte autophagy in spinal cord injury. Oncotarget 8, 98312–98321 (2017).
[127] Huang, M., Chen, S., Liang, Y. & Guo, Y. The Role of Berberine in the Multi-Target Treatment of Senile Dementia. Curr. Top. Med. Chem. 16, 867–873 (2016).
[128] Cai, Z., Wang, C. & Yang, W. Role of berberine in Alzheimer's disease. Neuropsychiatr. Dis. Treat. 12, 2509–2520 (2016).
[129] Singhal, K., Raj, N., Gupta, K. & Singh, S. Probable benefits of green tea with genetic implications. J. Oral Maxillofac. Pathol. 21, 107–114 (2017).
[130] Suzuki, Y., Miyoshi, N. & Isemura, M. Health-promoting effects of green tea. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 88, 88–101 (2012).
[131] Chacko, S. M., Thambi, P. T., Kuttan, R. & Nishigaki, I. Beneficial effects of green tea: a literature review. Chin. Med. 5, 13 (2010).
[132] Ortiz-López, L. et al. Green tea compound epigallo-catechin-3-gallate (EGCG) increases neuronal survival in adult hippocampal neurogenesis in vivo and in vitro. Neuroscience 322, 208–220 (2016).
[133] Pervin, M. et al. Beneficial Effects of Green Tea Catechins on Neurodegenerative Diseases. Molecules 23, (2018).
[134] Babu, P. V. A. & Liu, D. Green tea catechins and cardiovascular health: an update. Curr. Med. Chem. 15, 1840–1850 (2008).
[135] Bhardwaj, P. & Khanna, D. Green tea catechins: defensive role in cardiovascular disorders. Chin. J. Nat. Med. 11, 345–353 (2013).
[136] Rains, T. M., Agarwal, S. & Maki, K. C. Antiobesity effects of green tea catechins: a mechanistic review. J. Nutr. Biochem. 22, 1–7 (2011).
[137] Hursel, R. & Westerterp-Plantenga, M. S. Catechin- and caffeine-rich teas for control of body weight in humans. Am. J. Clin. Nutr. 98, 1682S–1693S (2013).
[138] Hursel, R., Viechtbauer, W. & Westerterp-Plantenga, M. S. The effects of green tea on weight loss and weight maintenance: a meta-analysis. Int. J. Obes. 33, 956–961 (2009).
[139] Cooper, R., Morré, D. J. & Morré, D. M. Medicinal benefits of green tea: part II. review of anticancer properties. J. Altern. Complement. Med. 11, 639–652 (2005).
[140] Lambert, J. D. Does tea prevent cancer? Evidence from laboratory and human intervention studies. Am. J. Clin. Nutr. 98, 1667S–1675S (2013).
[141] Park, J.-H., Bae, J.-H., Im, S.-S. & Song, D.-K. Green tea and type 2 diabetes. Integr Med Res 3, 4–10 (2014).
[142] Forester, S. C. & Lambert, J. D. The role of antioxidant versus pro-oxidant effects of green tea polyphenols in cancer prevention. Mol. Nutr. Food Res. 55, 844–854 (2011).
[143] Ohishi, T., Goto, S., Monira, P., Isemura, M. & Nakamura, Y. Anti-inflammatory Action of Green Tea. Antiinflamm. Antiallergy Agents Med. Chem. 15, 74–90 (2016).
[144] Bernatoniene, J. & Kopustinskiene, D. M. The Role of Catechins in Cellular Responses to Oxidative Stress. Molecules 23, (2018).
[145] Rossi, P. et al. Dietary Supplementation of Lion's Mane Medicinal Mushroom, Hericium erinaceus (Agaricomycetes), and Spatial Memory in Wild-Type Mice. Int. J. Med. Mushrooms 20, 485–494 (2018).

[146] Mori, K., Ouchi, K. & Hirasawa, N. The Anti-Inflammatory Effects of Lion's Mane Culinary-Medicinal Mushroom, Hericium erinaceus (Higher Basidiomycetes) in a Coculture System of 3T3-L1 Adipocytes and RAW264 Macrophages. Int. J. Med. Mushrooms 17, 609–618 (

[147] Mori, K., Inatomi, S., Ouchi, K., Azumi, Y. & Tuchida, T. Improving effects of the mushroom Yamabushitake (Hericium erinaceus) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. Phytother. Res. 23, 367–372 (2009).
[148] Sabaratnam, V., Kah-Hui, W., Naidu, M. & Rosie David, P. Neuronal health - can culinary and medicinal mushrooms help? Afr. J. Tradit. Complement. Altern. Med. 3, 62–68 (2013).
[149] Lai, P.-L. et al. Neurotrophic properties of the Lion's mane medicinal mushroom, Hericium erinaceus (Higher Basidiomycetes) from Malaysia. Int. J. Med. Mushrooms 15, 539–554 (2013).
[150] Nagano, M. et al. Reduction of depression and anxiety by 4 weeks Hericium erinaceus intake. Biomed. Res. 31, 231–237 (2010).
[151] Calder, P. C. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochem. Soc. Trans. 45, 1105–1115 (2017).
[152] Weitz, D., Weintraub, H., Fisher, E. & Schwartzbard, A. Z. Fish oil for the treatment of cardiovascular disease. Cardiol. Rev. 18, 258–263 (2010).
[153] Harris, W. S. & Zotor, F. B. n-3 Fatty acids and risk for fatal coronary disease. Proc. Nutr. Soc. 1–6 (2019).
[154] Gao, H., Geng, T., Huang, T. & Zhao, Q. Fish oil supplementation and insulin sensitivity: a systematic review and meta-analysis. Lipids Health Dis. 16, 131 (2017).
[155] Chen, C., Yu, X. & Shao, S. Effects of Omega-3 Fatty Acid Supplementation on Glucose Control and Lipid Levels in Type 2 Diabetes: A Meta-Analysis. PLoS One 10, e0139565 (2015).
[156] Singh, M. Essential fatty acids, DHA and human brain. Indian J. Pediatr. 72, 239–242 (2005).
[157] Yurko-Mauro, K., Alexander, D. D. & Van Elswyk, M. E. Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. PLoS One 10, e0120391 (2015).
[158] Sarris, J., Mischoulon, D. & Schweitzer, I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J. Clin. Psychiatry 73, 81–86 (2012).
[159] Sublette, M. E., Ellis, S. P., Geant, A. L. & Mann, J. J. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J. Clin. Psychiatry 72, 1577–1584 (2011).
[160] Derbyshire, E. Brain Health across the Lifespan: A Systematic Review on the Role of Omega-3 Fatty Acid Supplements. Nutrients 10, (2018).
[161] Pezzuto, J. M. Resveratrol: Twenty Years of Growth, Development and Controversy. Biomol. Ther. 27, 1–14 (2019).
[162] Xia, N., Daiber, A., Förstermann, U. & Li, H. Antioxidant effects of resveratrol in the cardiovascular system. Br. J. Pharmacol. 174, 1633–1646 (2017).
[163] Carrizzo, A. et al. Antioxidant effects of resveratrol in cardiovascular, cerebral and metabolic diseases. Food Chem. Toxicol. 61, 215–226 (2013).
[164] Merry, T. L. & Ristow, M. Do antioxidant supplements interfere with skeletal muscle adaptation to exercise training? J. Physiol. 594, 5135–5147 (2016).
[165] Kan, N.-W. et al. The Synergistic Effects of Resveratrol combined with Resistant Training on Exercise Performance and Physiological Adaption. Nutrients 10, (2018).
[166] Alway, S. E. et al. Resveratrol Enhances Exercise-Induced Cellular and Functional Adaptations of Skeletal Muscle in Older Men and Women. J. Gerontol. A Biol. Sci. Med. Sci. 72, 1595–1606 (2017).
[167] https://www.ncbi.nlm.nih.gov/pubmed/30241302
[168] Kato, M., Ochiai, R., Kozuma, K., Sato, H. & Katsuragi, Y. Effect of Chlorogenic Acid Intake on Cognitive Function in the Elderly: A Pilot Study. Evid. Based. Complement. Alternat. Med. 2018, 8608497 (2018).
[169] Heitman, E. & Ingram, D. K. Cognitive and neuroprotective effects of chlorogenic acid. Nutr. Neurosci. 20, 32–39 (2017).
[170] Rodríguez-Artalejo, F. & López-García, E. Coffee Consumption and Cardiovascular Disease: A Condensed Review of Epidemiological Evidence and Mechanisms. J. Agric. Food Chem. 66, 5257–5263 (2018).
[171] Cropley, V. et al. Does coffee enriched with chlorogenic acids improve mood and cognition after acute administration in healthy elderly? A pilot study. Psychopharmacology 219, 737–749 (2012).

[172] Liang, N. & Kitts, D. D. Role of Chlorogenic Acids in Controlling Oxidative and Inflammatory Stress Conditions. Nutrients 8, (2015).
[173] Baker, G. B., Coutts, R. T. & Rao, T. S. Neuropharmacological and neurochemical properties of N-(2-cyanoethyl)-2-phenylethylamine, a prodrug of 2-phenylethylamine. Br. J. Pharmacol. 92, 243–255 (1987).
[174] Kusaga A. [Decreased beta-phenylethylamine in urine of children with attention deficit hyperactivity disorder and autistic disorder]. No To Hattatsu 34, 243–248 (2002).
[175] Kusaga, A. et al. Increased urine phenylethylamine after methylphenidate treatment in children with ADHD. Ann. Neurol. 52, 372–374 (2002).
[176] Irsfeld, M., Spadafore, M. & Prüß, B. M. β-phenylethylamine, a small molecule with a large impact. Webmedcentral 4, (2013).
[177] Neznamov, G. G. & Teleshova, E. S. Comparative studies of Noopept and piracetam in the treatment of patients with mild cognitive disorders in organic brain diseases of vascular and traumatic origin. Neurosci. Behav. Physiol. 39, 311–321 (2009).
[178] Ostrovskaya, R. U. et al. Noopept stimulates the expression of NGF and BDNF in rat hippocampus. Bull. Exp. Biol. Med. 146, 334–337 (2008).
[179] Ostrovskaya, R. U. et al. Neuroprotective effect of novel cognitive enhancer noopept on AD-related cellular model involves the attenuation of apoptosis and tau hyperphosphorylation. J. Biomed. Sci. 21, 74 (2014).
[180] Ostrovskaya, R. U. et al. The nootropic and neuroprotective proline-containing dipeptide noopept restores spatial memory and increases immunoreactivity to amyloid in an Alzheimer's disease model. J. Psychopharmacol. 21, 611–619 (2007).
[181] Reyes-Izquierdo, T. et al. Modulatory effect of coffee fruit extract on plasma levels of brain-derived neurotrophic factor in healthy subjects. Br. J. Nutr. 110, 420–425 (2013).
[182] Panossian, A. & Wikman, G. Pharmacology of Schisandra chinensis Bail.: an overview of Russian research and uses in medicine. J. Ethnopharmacol. 118, 183–212 (2008).
[183] Aslanyan, G. et al. Double-blind, placebo-controlled, randomised study of single dose effects of ADAPT-232 on cognitive functions. Phytomedicine 17, 494–499 (2010).
[184] Li, J., Wu, H. M., Zhou, R. L., Liu, G. J. & Dong, B. R. Huperzine A for Alzheimer's disease. Cochrane Database Syst. Rev. CD005592 (2008).
[185] Yang, G., Wang, Y., Tian, J. & Liu, J.-P. Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. PLoS One 8, e74916 (2013).
[186] Xu, Z.-Q. et al. Treatment with Huperzine A improves cognition in vascular dementia patients. Cell Biochem. Biophys. 62, 55–58 (2012).
[187] Yuan, Q., Wang, C.-W., Shi, J. & Lin, Z.-X. Effects of Ginkgo biloba on dementia: An overview of systematic reviews. J. Ethnopharmacol. 195, 1–9 (2017).
[188] Hashiguchi, M., Ohta, Y., Shimizu, M., Maruyama, J. & Mochizuki, M. Meta-analysis of the efficacy and safety of Ginkgo biloba extract for the treatment of dementia. J Pharm Health Care Sci 1, 14 (2015).
[189] Tan, M.-S. et al. Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. J. Alzheimers. Dis. 43, 589–603 (2015).
[190] Yang, G., Wang, Y., Sun, J., Zhang, K. & Liu, J. Ginkgo Biloba for Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Curr. Top. Med. Chem. 16, 520–528 (2016).
[191] Zhang, H.-F. et al. An Overview of Systematic Reviews of Extracts for Mild Cognitive Impairment and Dementia. Front. Aging Neurosci. 8, 276 (2016).
[192] Zhang, Y.-S., Li, J.-D. & Yan, C. An update on vinpocetine: New discoveries and clinical implications. Eur. J. Pharmacol. 819, 30–34 (2018).
[193] Patyar, S., Prakash, A., Modi, M. & Medhi, B. Role of vinpocetine in cerebrovascular diseases. Pharmacol. Rep. 63, 618–628 (2011).
[194] Fülöp, T., Jr et al. Effects of centrophenoxine on body composition and some biochemical parameters of demented elderly people as revealed in a double-blind clinical trial. Arch. Gerontol. Geriatr. 10, 239–251 (1990).
[195] Bhalla, P. & Nehru, B. Modulatory effects of centrophenoxine on different regions of ageing rat brain. Exp. Gerontol. 40, 801–806 (2005).
[196] Nandy, K. Centrophenoxine: effects on aging mammalian brain. J. Am. Geriatr. Soc. 26, 74–81 (1978).

[197] Schwalfenberg, G. K. & Genuis, S. J. The Importance of Magnesium in Clinical Healthcare. Scientifica 2017, 4179326 (2017).
[198] Abbasi, B. et al. The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial. J. Res. Med. Sci. 17, 1161–1169 (2012).
[199] Chollet, D. et al. Magnesium involvement in sleep: genetic and nutritional models. Behav. Genet. 31, 413–425 (2001).
[200] Pandi-Perumal, S. R. et al. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. Prog. Neurobiol. 85, 335–353 (2008).
[201] Auger, R. R. et al. Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), a
[202] Buscemi, N. et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ 332, 385–393 (2006).
[203] van Geijlswijk, I. M., Korzilius, H. P. L. M. & Smits, M. G. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. Sleep 33, 1605–1614 (2010).
[204] Pandi-Perumal, S. R. et al. Melatonin antioxidative defense: therapeutical implications for aging and neurodegenerative processes. Neurotox. Res. 23, 267–300 (2013).
[205] Hardeland, R. Melatonin metabolism in the central nervous system. Curr. Neuropharmacol. 8, 168–181 (2010).
[206] Zhu, L. Q., Wang, S. H., Ling, Z. Q., Wang, D. L. & Wang, J.-Z. Effect of inhibiting melatonin biosynthesis on spatial memory retention and tau phosphorylation in rat. J. Pineal Res. 37, 71–77 (2004).
[207] Zhang, H.-M. & Zhang, Y. Melatonin: a well-documented antioxidant with conditional pro-oxidant actions. J. Pineal Res. 57, 131–146 (2014).
[208] Tan, D.-X. et al. Mechanistic and comparative studies of melatonin and classic antioxidants in terms of their interactions with the ABTS cation radical. J. Pineal Res. 34, 249–259 (2003).
[209] Tan, D.-X., Manchester, L. C., Terron, M. P., Flores, L. J. & Reiter, R. J. One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? J. Pineal Res. 42, 28–42 (2007).
[210] Lillehei, A. S., Halcón, L. L., Savik, K. & Reis, R. Effect of Inhaled Lavender and Sleep Hygiene on Self-Reported Sleep Issues: A Randomized Controlled Trial. J. Altern. Complement. Med. 21, 430–438 (2015).
[211] Keshavarz Afshar, M. et al. Lavender fragrance essential oil and the quality of sleep in postpartum women. Iran. Red Crescent Med. J. 17, e25880 (2015).
[212] Koulivand, P. H., Khaleghi Ghadiri, M. & Gorji, A. Lavender and the nervous system. Evid. Based. Complement. Alternat. Med. 2013, 681304 (2013).
[213] Goel, N., Kim, H. & Lao, R. P. An olfactory stimulus modifies nighttime sleep in young men and women. Chronobiol. Int. 22, 889–904 (2005).
[214] Bannai, M., Kawai, N., Ono, K., Nakahara, K. & Murakami, N. The effects of glycine on subjective daytime performance in partially sleep-restricted healthy volunteers. Front. Neurol. 3, 61 (2012).
[215] Inagawa, K., Hiraoka, T., Kohda, T., Yamadera, W. & Takahashi, M. Subjective effects of glycine ingestion before bedtime on sleep quality. Sleep Biol. Rhythms 4, 75–77 (2006).
[216] Yamadera, W. et al. Glycine ingestion improves subjective sleep quality in human volunteers, correlating with polysomnographic changes: Effects of glycine on polysomnography. Sleep Biol. Rhythms 5, 126–131 (2007).
[217] Bent, S., Padula, A., Moore, D., Patterson, M. & Mehling, W. Valerian for sleep: a systematic review and meta-analysis. Am. J. Med. 119, 1005–1012 (2006).
[218] Cases, J., Ibarra, A., Feuillère, N., Roller, M. & Sukkar, S. G. Pilot trial of Melissa officinalis L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. Med. J. Nutrition Metab. 4, 211–21
[219] Scholey, A. et al. Anti-stress effects of lemon balm-containing foods. Nutrients 6, 4805–4821 (2014).
[220] Elsas, S.-M. et al. Passiflora incarnata L. (Passionflower) extracts elicit GABA currents in hippocampal neurons in vitro, and show anxiogenic and anticonvulsant effects in vivo, varying with extraction method. Phytomedicine 17, 940–949 (2010).
[221] Akhondzadeh, S. et al. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J. Clin. Pharm. Ther. 26, 363–367 (2001).

[222] Krenn, L. [Passion Flower (Passiflora incarnata L.)--a reliable herbal sedative]. Wien. Med. Wochenschr. 152, 404–406 (2002).
[223] Gottesmann, C. GABA mechanisms and sleep. Neuroscience 111, 231–239 (2002).
[224] Abdou, A. M. et al. Relaxation and immunity enhancement effects of gamma-aminobutyric acid (GABA) administration in humans. Biofactors 26, 201–208 (2006).
[225] Yamatsu, A. et al. The Improvement of Sleep by Oral Intake of GABA and Apocynum venetum Leaf Extract. J. Nutr. Sci. Vitaminol. 61, 182–187 (2015).
[226] Ooi, S. L., Henderson, P. & Pak, S. C. Kava for Generalized Anxiety Disorder: A Review of Current Evidence. J. Altern. Complement. Med. 24, 770–780 (2018).
[227] Malsch, U. & Kieser, M. Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines. Psychopharmacology 157, 277–283 (2001).
[228] Dramard, V. et al. Effect of l-theanine tablets in reducing stress-related emotional signs in cats: an open-label field study. Ir. Vet. J. 71, 21 (2018).
[229] White, D. J. et al. Anti-Stress, Behavioural and Magnetoencephalography Effects of an L-Theanine-Based Nutrient Drink: A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial. Nutrients 8, (2016).
[230] Einöther, S. J. L., Martens, V. E. G., Rycroft, J. A. & De Bruin, E. A. L-theanine and caffeine improve task switching but not intersensory attention or subjective alertness. Appetite 54, 406–409 (2010).
[231] Nobre, A. C., Rao, A. & Owen, G. N. L-theanine, a natural constituent in tea, and its effect on mental state. Asia Pac. J. Clin. Nutr. 17 Suppl 1, 167–168 (2008).
[232] Smriga, M. et al. Oral treatment with L-lysine and L-arginine reduces anxiety and basal cortisol levels in healthy humans. Biomed. Res. 28, 85–90 (2007).
[233] Jezova, D., Makatsori, A., Smriga, M., Morinaga, Y. & Duncko, R. Subchronic treatment with amino acid mixture of L-lysine and L-arginine modifies neuroendocrine activation during psychosocial stress in subjects with high trait anxiety. Nutr. Neurosci. 8,
[234] Ooi, S. L., Henderson, P. & Pak, S. C. Kava for Generalized Anxiety Disorder: A Review of Current Evidence. J. Altern. Complement. Med. 24, 770–780 (2018).
[235] Malsch, U. & Kieser, M. Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines. Psychopharmacology 157, 277–283 (2001).
[236] Rafieian-Kopaei, M. & Movahedi, M. Systematic Review of Premenstrual, Postmenstrual and Infertility Disorders of Vitex Agnus Castus. Electron Physician 9, 3685–3689 (2017).
[237] Cerqueira, R. O., Frey, B. N., Leclerc, E. & Brietzke, E. Vitex agnus castus for premenstrual syndrome and premenstrual dysphoric disorder: a systematic review. Arch. Womens. Ment. Health 20, 713–719 (2017).
[238] Taksande, B. G. et al. Agmatine, an endogenous imidazoline receptor ligand modulates ethanol anxiolysis and withdrawal anxiety in rats. Eur. J. Pharmacol. 637, 89–101 (2010).
[239] Gibson, D. A. et al. Polyamines contribute to ethanol withdrawal-induced neurotoxicity in rat hippocampal slice cultures through interactions with the NMDA receptor. Alcohol. Clin. Exp. Res. 27, 1099–1106 (2003).
[240] Halaris, A. & Plietz, J. Agmatine : metabolic pathway and spectrum of activity in brain. CNS Drugs 21, 885–900 (2007).
[241] Xu, W., Gao, L., Li, T., Shao, A. & Zhang, J. Neuroprotective Role of Agmatine in Neurological Diseases. Curr. Neuropharmacol. 16, 1296–1305 (2018).
[242] Singh, N., Bhalla, M., de Jager, P. & Gilca, M. An overview on ashwagandha: a Rasayana (rejuvenator) of Ayurveda. Afr. J. Tradit. Complement. Altern. Med. 8, 208–213 (2011).
[243] Pratte, M. A., Nanavati, K. B., Young, V. & Morley, C. P. An alternative treatment for anxiety: a systematic review of human trial results reported for the Ayurvedic herb ashwagandha (Withania somnifera). J. Altern. Complement. Med. 20, 901–908 (2014).
[244] Elsas, S.-M. et al. Passiflora incarnata L. (Passionflower) extracts elicit GABA currents in hippocampal neurons in vitro, and show anxiogenic and anticonvulsant effects in vivo, varying with extraction method. Phytomedicine 17, 940–949 (2010).
[245] Akhondzadeh, S. et al. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J. Clin. Pharm. Ther. 26, 363–367 (2001).
[246] Krenn, L. [Passion Flower (Passiflora incarnata L.)--a reliable herbal sedative]. Wien. Med. Wochenschr. 152, 404–406 (2002).

[247] Kasper, S. & Dienel, A. Multicenter, open-label, exploratory clinical trial with extract in patients suffering from burnout symptoms. Neuropsychiatr. Dis. Treat. 13, 889–898 (2017).
[248] Anghelescu, I.-G., Edwards, D., Seifritz, E. & Kasper, S. Stress management and the role of Rhodiola rosea: a review. Int. J. Psychiatry Clin. Pract. 1–11 (2018).
[249] Coleman, C. I., Hebert, J. H. & Reddy, P. The effects of Panax ginseng on quality of life. J. Clin. Pharm. Ther. 28, 5–15 (2003).
[250] Kim, J.-H. Pharmacological and medical applications of and ginsenosides: a review for use in cardiovascular diseases. J. Ginseng Res. 42, 264–269 (2018).
[251] Lee, S.-T., Chu, K., Sim, J.-Y., Heo, J.-H. & Kim, M. Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer Dis. Assoc. Disord. 22, 222–226 (2008).
[252] Lho, S. K. et al. Effects of lifetime cumulative ginseng intake on cognitive function in late life. Alzheimers. Res. Ther. 10, 50 (2018).
[253] Blessing, E. M., Steenkamp, M. M., Manzanares, J. & Marmar, C. R. Cannabidiol as a Potential Treatment for Anxiety Disorders. Neurotherapeutics 12, 825–836 (2015).
[254] Gulluni, N. et al. Cannabis Essential Oil: A Preliminary Study for the Evaluation of the Brain Effects. Evid. Based. Complement. Alternat. Med. 2018, 1709182 (2018).
[255] Booz, G. W. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. Free Radic. Biol. Med. 51, 1054–1061 (2011).
[256] Ng, Q. X., Koh, S. S. H., Chan, H. W. & Ho, C. Y. X. Clinical Use of Curcumin in Depression: A Meta-Analysis. J. Am. Med. Dir. Assoc. 18, 503–508 (2017).
[257] Noorafshan, A., Vafabin, M., Karbalay-Doust, S. & Asadi-Golshan, R. Efficacy of Curcumin in the Modulation of Anxiety Provoked by Sulfite, a Food Preservative, in Rats. Prev Nutr Food Sci 22, 144–148 (2017).
[258] Hewlings, S. J. & Kalman, D. S. Curcumin: A Review of Its' Effects on Human Health. Foods 6, (2017).
[259] Jamwal, R. Bioavailable curcumin formulations: A review of pharmacokinetic studies in healthy volunteers. J. Integr. Med. 16, 367–374 (2018).
[260] McCarty, M. F. Clinical potential of Spirulina as a source of phycocyanobilin. J. Med. Food 10, 566–570 (2007).
[261] Zheng, J. et al. Phycocyanin and phycocyanobilin from Spirulina platensis protect against diabetic nephropathy by inhibiting oxidative stress. Am. J. Physiol. Regul. Integr. Comp. Physiol. 304, R110–20 (2013).
[262] Saha, S. K., Misbahuddin, M. & Ahmed, A. U. Comparison between the effects of alcohol and hexane extract of spirulina in arsenic removal from isolated tissues. Mymensingh Med. J. 19, 27–31 (2010).
[263] Saha, S. K., Misbahuddin, M., Khatun, R. & Mamun, I. R. Effect of hexane extract of spirulina in the removal of arsenic from isolated liver tissues of rat. Mymensingh Med. J. 14, 191–195 (2005).
[264] Panahi, Y., Darvishi, B., Jowzi, N., Beiraghdar, F. & Sahebkar, A. Chlorella vulgaris: A Multifunctional Dietary Supplement with Diverse Medicinal Properties. Curr. Pharm. Des. 22, 164–173 (2016).
[265] Parnetti, L., Mignini, F., Tomassoni, D., Traini, E. & Amenta, F. Cholinergic precursors in the treatment of cognitive impairment of vascular origin: ineffective approaches or need for re-evaluation? J. Neurol. Sci. 257, 264–269 (2007).
[266] Gatti, G. et al. A comparative study of free plasma choline levels following intramuscular administration of L-alpha-glycerylphosphorylcholine and citicoline in normal volunteers. Int. J. Clin. Pharmacol. Ther. Toxicol. 30, 331–335 (1992).
[267] Abbiati, G., Fossati, T., Lachmann, G., Bergamaschi, M. & Castiglioni, C. Absorption, tissue distribution and excretion of radiolabelled compounds in rats after administration of [14C]-L-alpha-glycerylphosphorylcholine. Eur. J. Drug Metab. Pharmacokinet.
[268] Hoffman, J. R. et al. The effects of acute and prolonged CRAM supplementation on reaction time and subjective measures of focus and alertness in healthy college students. J. Int. Soc. Sports Nutr. 7, 39 (2010).
[269] Di Perri, R. et al. A multicentre trial to evaluate the efficacy and tolerability of alpha-glycerylphosphorylcholine versus cytosine diphosphocholine in patients with vascular dementia. J. Int. Med. Res. 19, 330–341 (1991).
[270] De Jesus Moreno Moreno, M. Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomized, placebo-controlled trial. Clin. Ther. 25, 178–193 (200

[271] Parnetti, L., Amenta, F. & Gallai, V. Choline alphoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data. Mech. Ageing Dev. 122, 2041–2055 (2001).
[272] Parnetti, L. et al. Multicentre study of l-alpha-glyceryl-phosphorylcholine vs ST200 among patients with probable senile dementia of Alzheimer's type. Drugs Aging 3, 159–164 (1993).
[273] Ziegenfuss, T., Landis, J. & Hofheins, J. Acute supplementation with alpha-glycerylphosphorylcholine augments growth hormone response to, and peak force production during, resistance exercise. J. Int. Soc. Sports Nutr. 5, (2008).
[274] Bellar, D., LeBlanc, N. R. & Campbell, B. The effect of 6 days of alpha glycerylphosphorylcholine on isometric strength. J. Int. Soc. Sports Nutr. 12, 42 (2015).
[275] Marcus, L., Soileau, J., Judge, L. W. & Bellar, D. Evaluation of the effects of two doses of alpha glycerylphosphorylcholine on physical and psychomotor performance. J. Int. Soc. Sports Nutr. 14, 39 (2017).
[276] Pashkow, F. J., Watumull, D. G. & Campbell, C. L. Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. Am. J. Cardiol. 101, 58D–68D (2008).
[277] Goulinet, S. & Chapman, M. J. Plasma LDL and HDL subspecies are heterogenous in particle content of tocopherols and oxygenated and hydrocarbon carotenoids. Relevance to oxidative resistance and atherogenesis. Arterioscler. Thromb. Vasc. Biol. 17, 786–796
[278] Mashhadi, N. S. et al. Astaxanthin improves glucose metabolism and reduces blood pressure in patients with type 2 diabetes mellitus. Asia Pac. J. Clin. Nutr. 27, 341–346 (2018).
[279] Ito, N., Saito, H., Seki, S., Ueda, F. & Asada, T. Effects of Composite Supplement Containing Astaxanthin and Sesamin on Cognitive Functions in People with Mild Cognitive Impairment: A Randomized, Double-Blind, Placebo-Controlled Trial. J. Alzheimers. Dis
[280] Earnest, C. P., Lupo, M., White, K. M. & Church, T. S. Effect of astaxanthin on cycling time trial performance. Int. J. Sports Med. 32, 882–888 (2011).
[281] Liu, S. Z. et al. Building strength, endurance, and mobility using an astaxanthin formulation with functional training in elderly. J. Cachexia Sarcopenia Muscle 9, 826–833 (2018).
[282] Ueland, P. M., Holm, P. I. & Hustad, S. Betaine: a key modulator of one-carbon metabolism and homocysteine status. Clin. Chem. Lab. Med. 43, 1069–1075 (2005).
[283] Trepanowski, J. F. et al. The effects of chronic betaine supplementation on exercise performance, skeletal muscle oxygen saturation and associated biochemical parameters in resistance trained men. J. Strength Cond. Res. 25, 3461–3471 (2011).
[284] Cholewa, J. M. et al. The effects of chronic betaine supplementation on body composition and performance in collegiate females: a double-blind, randomized, placebo controlled trial. J. Int. Soc. Sports Nutr. 15, 37 (2018).
[285] Cholewa, J. M. et al. Effects of betaine on body composition, performance, and homocysteine thiolactone. J. Int. Soc. Sports Nutr. 10, 39 (2013).
[286] Pryor, J. L., Craig, S. A. & Swensen, T. Effect of betaine supplementation on cycling sprint performance. J. Int. Soc. Sports Nutr. 9, 12 (2012).
[287] Ueland, P. M. Choline and betaine in health and disease. J. Inherit. Metab. Dis. 34, 3–15 (2011).
[288] Holm, P. I. et al. Betaine and folate status as cooperative determinants of plasma homocysteine in humans. Arterioscler. Thromb. Vasc. Biol. 25, 379–385 (2005).
[289] Di Pierro, F., Orsi, R. & Settembre, R. Role of betaine in improving the antidepressant effect of S-adenosyl-methionine in patients with mild-to-moderate depression. J. Multidiscip. Healthc. 8, 39–45 (2015).
[290] Courtenay, E. S., Capp, M. W., Anderson, C. F. & Record, M. T., Jr. Vapor pressure osmometry studies of osmolyte-protein interactions: implications for the action of osmoprotectants in vivo and for the interpretation of 'osmotic stress' experiments in vit
[291] Burg, M. B. & Ferraris, J. D. Intracellular organic osmolytes: function and regulation. J. Biol. Chem. 283, 7309–7313 (2008).
[292] Ochiai, M. et al. Short-term effects of L-citrulline supplementation on arterial stiffness in middle-aged men. Int. J. Cardiol. 155, 257–261 (2012).
[293] Orozco-Gutiérrez, J. J. et al. Effect of L-arginine or L-citrulline oral supplementation on blood pressure and right ventricular function in heart failure patients with preserved ejection fraction. Cardiol. J. 17, 612–618 (2010).

[294] Ochiai, M. et al. Short-term effects of L-citrulline supplementation on arterial stiffness in middle-aged men. Int. J. Cardiol. 155, 257–261 (2012).
[295] Orozco-Gutiérrez, J. J. et al. Effect of L-arginine or L-citrulline oral supplementation on blood pressure and right ventricular function in heart failure patients with preserved ejection fraction. Cardiol. J. 17, 612–618 (2010).
[296] Figueroa, A., Trivino, J. A., Sanchez-Gonzalez, M. A. & Vicil, F. Oral L-citrulline supplementation attenuates blood pressure response to cold pressor test in young men. Am. J. Hypertens. 23, 12–16 (2010).
[297] Wax, B., Kavazis, A. N. & Luckett, W. Effects of Supplemental Citrulline-Malate Ingestion on Blood Lactate, Cardiovascular Dynamics, and Resistance Exercise Performance in Trained Males. J. Diet. Suppl. 13, 269–282 (2016).
[298] Wax, B., Kavazis, A. N., Weldon, K. & Sperlak, J. Effects of supplemental citrulline malate ingestion during repeated bouts of lower-body exercise in advanced weightlifters. J. Strength Cond. Res. 29, 786–792 (2015).
[299] Pérez-Guisado, J. & Jakeman, P. M. Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. J. Strength Cond. Res. 24, 1215–1222 (2010).
[300] Glenn, J. M. et al. Acute citrulline malate supplementation improves upper- and lower-body submaximal weightlifting exercise performance in resistance-trained females. Eur. J. Nutr. 56, 775–784 (2017).
[301] Butts, J., Jacobs, B. & Silvis, M. Creatine Use in Sports. Sports Health 10, 31–34 (2018).
[302] Dempsey, R. L., Mazzone, M. F. & Meurer, L. N. Does oral creatine supplementation improve strength? A meta-analysis. J. Fam. Pract. 51, 945–951 (2002).
[303] Chilibeck, P. D., Kaviani, M., Candow, D. G. & Zello, G. A. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. Open Access J Sports Med 8, 213–226 (2017).
[304] Ainsley Dean, P. J., Arikan, G., Opitz, B. & Sterr, A. Potential for use of creatine supplementation following mild traumatic brain injury. Concussion 2, CNC34 (2017).
[305] Korpacheva, O. V., Dolgikh, V. T., Shikunova, L. G. & Zolotov, A. N. [Cardioprotective effect of exogenous creatine phosphate in acute hemorrhage]. Anesteziol. Reanimatol. 13–16 (2002).
[306] Avgerinos, K. I., Spyrou, N., Bougioukas, K. I. & Kapogiannis, D. Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review of randomized controlled trials. Exp. Gerontol. 108, 166–173 (2018).
[307] Rawson, E. S. & Venezia, A. C. Use of creatine in the elderly and evidence for effects on cognitive function in young and old. Amino Acids 40, 1349–1362 (2011).
[308] Bondonno, C. P., Croft, K. D. & Hodgson, J. M. Dietary Nitrate, Nitric Oxide, and Cardiovascular Health. Crit. Rev. Food Sci. Nutr. 56, 2036–2052 (2016).
[309] Bondonno, C. P. et al. Vegetable-derived bioactive nitrate and cardiovascular health. Mol. Aspects Med. 61, 83–91 (2018).
[310] Stanaway, L., Rutherfurd-Markwick, K., Page, R. & Ali, A. Performance and Health Benefits of Dietary Nitrate Supplementation in Older Adults: A Systematic Review. Nutrients 9, (2017).
[311] Jones, A. M., Thompson, C., Wylie, L. J. & Vanhatalo, A. Dietary Nitrate and Physical Performance. Annu. Rev. Nutr. 38, 303–328 (2018).
[312] Demura, S., Yamada, T., Yamaji, S., Komatsu, M. & Morishita, K. The effect of L-ornithine hydrochloride ingestion on performance during incremental exhaustive ergometer bicycle exercise and ammonia metabolism during and after exercise. Eur. J. Clin. Nutr.
[313] Demura, S., Morishita, K., Yamada, T., Yamaji, S. & Komatsu, M. Effect of L-ornithine hydrochloride ingestion on intermittent maximal anaerobic cycle ergometer performance and fatigue recovery after exercise. Eur. J. Appl. Physiol. 111, 2837–2843 (2011).
[314] Sugino, T., Shirai, T., Kajimoto, Y. & Kajimoto, O. L-ornithine supplementation attenuates physical fatigue in healthy volunteers by modulating lipid and amino acid metabolism. Nutr. Res. 28, 738–743 (2008).
[315]Miyake, M. et al. Randomised controlled trial of the effects of L-ornithine on stress markers and sleep quality in healthy workers. Nutr. J. 13, 53 (2014).
[316] Mahoney, D. E. et al. Understanding D-Ribose and Mitochondrial Function. Adv Biosci Clin Med 6, 1–5 (2018).

[317] Omran, H., Illien, S., MacCarter, D., St Cyr, J. & Lüderitz, B. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. Eur. J. Heart Fail. 5, 615–619 (2003).
[318] MacCarter, D. et al. D-ribose aids advanced ischemic heart failure patients. Int. J. Cardiol. 137, 79–80 (2009).
[319] Pliml, W. et al. Effects of ribose on exercise-induced ischaemia in stable coronary artery disease. Lancet 340, 507–510 (1992).
[320] Hellsten, Y., Skadhauge, L. & Bangsbo, J. Effect of ribose supplementation on resynthesis of adenine nucleotides after intense intermittent training in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 286, R182–8 (2004).
[321] Seifert, J. G., Brumet, A. & St Cyr, J. A. The influence of D-ribose ingestion and fitness level on performance and recovery. J. Int. Soc. Sports Nutr. 14, 47 (2017).
[322] Teitelbaum, J. E., Johnson, C. & St Cyr, J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. J. Altern. Complement. Med. 12, 857–862 (2006).
[323] Gebhart, B. & Jorgenson, J. A. Benefit of ribose in a patient with fibromyalgia. Pharmacotherapy 24, 1646–1648 (2004).
[324] Nielsen, H. B., Hein, L., Svendsen, L. B., Secher, N. H. & Quistorff, B. Bicarbonate attenuates intracellular acidosis. Acta Anaesthesiol. Scand. 46, 579–584 (2002).
[325] Heibel, A. B., Perim, P. H. L., Oliveira, L. F., McNaughton, L. R. & Saunders, B. Time to Optimize Supplementation: Modifying Factors Influencing the Individual Responses to Extracellular Buffering Agents. Front Nutr 5, 35 (2018).
[326] Carr, A. J., Hopkins, W. G. & Gore, C. J. Effects of acute alkalosis and acidosis on performance: a meta-analysis. Sports Med. 41, 801–814 (2011).
[327] Krustrup, P., Ermidis, G. & Mohr, M. Sodium bicarbonate intake improves high-intensity intermittent exercise performance in trained young men. J. Int. Soc. Sports Nutr. 12, 25 (2015).
[328] Freis, T., Hecksteden, A., Such, U. & Meyer, T. Effect of sodium bicarbonate on prolonged running performance: A randomized, double-blind, cross-over study. PLoS One 12, e0182158 (2017).
[329] Ripps, H. & Shen, W. Review: taurine: a 'very essential' amino acid. Mol. Vis. 18, 2673–2686 (2012).
[330] Scicchitano, B. M. & Sica, G. The Beneficial Effects of Taurine to Counteract Sarcopenia. Curr. Protein Pept. Sci. 19, 673–680 (2018).
[331] Schaffer, S. & Kim, H. W. Effects and Mechanisms of Taurine as a Therapeutic Agent. Biomol. Ther. 26, 225–241 (2018).
[332] Jong, C. J., Ito, T., Prentice, H., Wu, J.-Y. & Schaffer, S. W. Role of Mitochondria and Endoplasmic Reticulum in Taurine-Deficiency-Mediated Apoptosis. Nutrients 9, (2017).
[333] Waldron, M., Patterson, S. D., Tallent, J. & Jeffries, O. The Effects of an Oral Taurine Dose and Supplementation Period on Endurance Exercise Performance in Humans: A Meta-Analysis. Sports Med. 48, 1247–1253 (2018).
[334] Veronese, N. et al. Acetyl-L-Carnitine Supplementation and the Treatment of Depressive Symptoms: A Systematic Review and Meta-Analysis. Psychosom. Med. 80, 154–159 (2018).
[335] Rump, T. J. et al. Acetyl-L-carnitine protects neuronal function from alcohol-induced oxidative damage in the brain. Free Radic. Biol. Med. 49, 1494–1504 (2010).
[336] Scafidi, S., Racz, J., Hazelton, J., McKenna, M. C. & Fiskum, G. Neuroprotection by acetyl-L-carnitine after traumatic injury to the immature rat brain. Dev. Neurosci. 32, 480–487 (2010).
[337] Nicassio, L. et al. Dietary supplementation with acetyl-l-carnitine counteracts age-related alterations of mitochondrial biogenesis, dynamics and antioxidant defenses in brain of old rats. Exp. Gerontol. 98, 99–109 (2017).
[338] Patel, S. P., Sullivan, P. G., Lyttle, T. S. & Rabchevsky, A. G. Acetyl-L-carnitine ameliorates mitochondrial dysfunction following contusion spinal cord injury. J. Neurochem. 114, 291–301 (2010).
[339] Rosca, M. G., Lemieux, H. & Hoppel, C. L. Mitochondria in the elderly: Is acetylcarnitine a rejuvenator? Adv. Drug Deliv. Rev. 61, 1332–1342 (2009).
[340] Rai, G. et al. Double-blind, placebo controlled study of acetyl-l-carnitine in patients with Alzheimer's dementia. Curr. Med. Res. Opin. 11, 638–647 (1990).
[341] Passeri, M. et al. Acetyl-L-carnitine in the treatment of mildly demented elderly patients. Int. J. Clin. Pharmacol. Res. 10, 75–79 (1990).

[342] Thal, L. J. et al. A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. Neurology 47, 705–711 (1996).
[343] Tomassini, V. et al. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. J. Neurol. Sci. 218, 103–108 (2004).
[344] Plioplys, A. V. & Plioplys, S. Amantadine and L-carnitine treatment of Chronic Fatigue Syndrome. Neuropsychobiology 35, 16–23 (1997).
[345] Xu, Y. et al. L-carnitine treatment of insulin resistance: A systematic review and meta-analysis. Adv. Clin. Exp. Med. 26, 333–338 (2017).
[346] Song, X. et al. Efficacy and Safety of L-Carnitine Treatment for Chronic Heart Failure: A Meta-Analysis of Randomized Controlled Trials. Biomed Res. Int. 2017, 6274854 (2017).
[347] Shang, R., Sun, Z. & Li, H. Effective dosing of L-carnitine in the secondary prevention of cardiovascular disease: a systematic review and meta-analysis. BMC Cardiovasc. Disord. 14, 88 (2014).
[348] Cordero, M. D. et al. Coenzyme Q10 distribution in blood is altered in patients with fibromyalgia. Clin. Biochem. 42, 732–735 (2009).
[349] Di Pierro, F., Rossi, A., Consensi, A., Giacomelli, C. & Bazzichi, L. Role for a water-soluble form of CoQ10 in female subjects affected by fibromyalgia. A preliminary study. Clin. Exp. Rheumatol. 35 Suppl 105, 20–27 (2017).
[350] Cordero, M. D. et al. Can coenzyme q10 improve clinical and molecular parameters in fibromyalgia? Antioxid. Redox Signal. 19, 1356–1361 (2013).
[351] Jafari, M., Mousavi, S. M., Asgharzadeh, A. & Yazdani, N. Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews. Indian Heart J. 70 Suppl 1, S111–S117 (2018).
[352] DiNicolantonio, J. J., Bhutani, J., McCarty, M. F. & O'Keefe, J. H. Coenzyme Q10 for the treatment of heart failure: a review of the literature. Open Heart 2, e000326 (2015).
[353] 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. 19, 138–143 (2016).
[354] Sanoobar, M. et al. Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. Nutr. Neurosci. 18, 169–176 (2015).
[355] Lafuente, R. et al. Coenzyme Q10 and male infertility: a meta-analysis. J. Assist. Reprod. Genet. 30, 1147–1156 (2013).
[356] Xu, Y. et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reprod. Biol. Endocrinol. 16, 29 (2018).
[357] Ben-Meir, A. et al. Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging. Aging Cell 14, 887–895 (2015).
[358] Shoeibi, A. et al. Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled trial. Acta Neurol. Belg. 117, 103–109 (2017).
[359] Sándor, P. S. et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology 64, 713–715 (2005).
[360] Deichmann, R., Lavie, C. & Andrews, S. Coenzyme q10 and statin-induced mitochondrial dysfunction. Ochsner J. 10, 16–21 (2010).
[361] Skarlovnik, A., Janić, M., Lunder, M., Turk, M. & Šabovič, M. Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: a randomized clinical study. Med. Sci. Monit. 20, 2183–2188 (2014).
[362] Mitchell, D. C., Knight, C. A., Hockenberry, J., Teplansky, R. & Hartman, T. J. Beverage caffeine intakes in the U.S. Food Chem. Toxicol. 63, 136–142 (2014).
[363] Martyn, D., Lau, A., Richardson, P. & Roberts, A. Temporal patterns of caffeine intake in the United States. Food Chem. Toxicol. 111, 71–83 (2018).
[364] Tarnopolsky, M. & Cupido, C. Caffeine potentiates low frequency skeletal muscle force in habitual and nonhabitual caffeine consumers. J. Appl. Physiol. 89, 1719–1724 (2000).
[365] Astorino, T. A., Rohmann, R. L. & Firth, K. Effect of caffeine ingestion on one-repetition maximum muscular strength. Eur. J. Appl. Physiol. 102, 127–132 (2008).

[366] Bell, D. G. & McLellan, T. M. Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers. J. Appl. Physiol. 93, 1227–1234 (2002).
[367] Bell, D. G. & McLellan, T. M. Effect of repeated caffeine ingestion on repeated exhaustive exercise endurance. Med. Sci. Sports Exerc. 35, 1348–1354 (2003).
[368] Acheson, K. J., Zahorska-Markiewicz, B., Pittet, P., Anantharaman, K. & Jéquier, E. Caffeine and coffee: their influence on metabolic rate and substrate utilization in normal weight and obese individuals. Am. J. Clin. Nutr. 33, 989–997 (1980).
[369] Ribeiro, J. A. & Sebastião, A. M. Caffeine and adenosine. J. Alzheimers. Dis. 20 Suppl 1, S3–15 (2010).
[370] Childs, E. & de Wit, H. Subjective, behavioral, and physiological effects of acute caffeine in light, nondependent caffeine users. Psychopharmacology 185, 514–523 (2006).
[371] Murphy, J. A., Deurveilher, S. & Semba, K. Stimulant doses of caffeine induce c-FOS activation in orexin/hypocretin-containing neurons in rat. Neuroscience 121, 269–275 (2003).
[372] Boulenger, J. P., Patel, J., Post, R. M., Parma, A. M. & Marangos, P. J. Chronic caffeine consumption increases the number of brain adenosine receptors. Life Sci. 32, 1135–1142 (1983).
[373] Newland, M. C. & Brown, K. Behavioral characterization of caffeine and adenosine agonists during chronic caffeine exposure. Behav. Pharmacol. 8, 17–30 (1997).
[374] Blanchard, J. & Sawers, S. J. Comparative pharmacokinetics of caffeine in young and elderly men. J. Pharmacokinet. Biopharm. 11, 109–126 (1983).
[375] Blanchard, J. & Sawers, S. J. The absolute bioavailability of caffeine in man. Eur. J. Clin. Pharmacol. 24, 93–98 (1983).
[376] Dani, J. A. Neuronal Nicotinic Acetylcholine Receptor Structure and Function and Response to Nicotine. Int. Rev. Neurobiol. 124, 3–19 (2015).
[377] Pasumarthi, R. K., Reznikov, L. R. & Fadel, J. Activation of orexin neurons by acute nicotine. Eur. J. Pharmacol. 535, 172–176 (2006).
[378] Andersson, K., Eneroth, P. & Arner, P. Changes in circulating lipid and carbohydrate metabolites following systemic nicotine treatment in healthy men. Int. J. Obes. Relat. Metab. Disord. 17, 675–680 (1993).
[379] Jessen, A. B., Toubro, S. & Astrup, A. Effect of chewing gum containing nicotine and caffeine on energy expenditure and substrate utilization in men. Am. J. Clin. Nutr. 77, 1442–1447 (2003).
[380] Haaz, S. et al. Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update. Obes. Rev. 7, 79–88 (2006).
[381] Stohs, S. J. et al. Effects of p-synephrine alone and in combination with selected bioflavonoids on resting metabolism, blood pressure, heart rate and self-reported mood changes. Int. J. Med. Sci. 8, 295–301 (2011).
[382] Feduccia, A. A. et al. Locomotor activation by theacrine, a purine alkaloid structurally similar to caffeine: involvement of adenosine and dopamine receptors. Pharmacol. Biochem. Behav. 102, 241–248 (2012).
[383] Taylor, L. et al. Safety of TeaCrine®, a non-habituating, naturally-occurring purine alkaloid over eight weeks of continuous use. J. Int. Soc. Sports Nutr. 13, 2 (2016).
[384] Taylor, L. et al. Safety of TeaCrine®, a non-habituating, naturally-occurring purine alkaloid over eight weeks of continuous use. J. Int. Soc. Sports Nutr. 13, 2 (2016).
[385] Kuhman, D. J., Joyner, K. J. & Bloomer, R. J. Cognitive Performance and Mood Following Ingestion of a Theacrine-Containing Dietary Supplement, Caffeine, or Placebo by Young Men and Women. Nutrients 7, 9618–9632 (2015).