THE ENERGY BLUEPRINT

The Top Science-Backed Supplements To Boost Your Energy, Brain Performance, and Mood

by Ari Whitten

The Top Science-Backed Supplements To Boost Your Energy, Brain Performance and Mood

Boost Energy Levels

Fight Chronic Fatigue

Optimize Metabolic Health

Enhance Memory, Focus, and Attention

Improve Cognitive Function

Avert Neurodegeneration

Bolster Stress Resilience

The 25 Top Supplements For Energy and Mitochondrial Optimization

Virtually every biological process in your body requires energy to operate. And we can thank little organelles called *mitochondria* for generating the vast majority of this energy.

With very few exceptions, every type of cell in your body contains mitochondria responsible for producing virtually all the energy that your body uses on a daily basis. They are akin to the power plants that generate electricity for our cities — if they fail, dysfunction ensues.

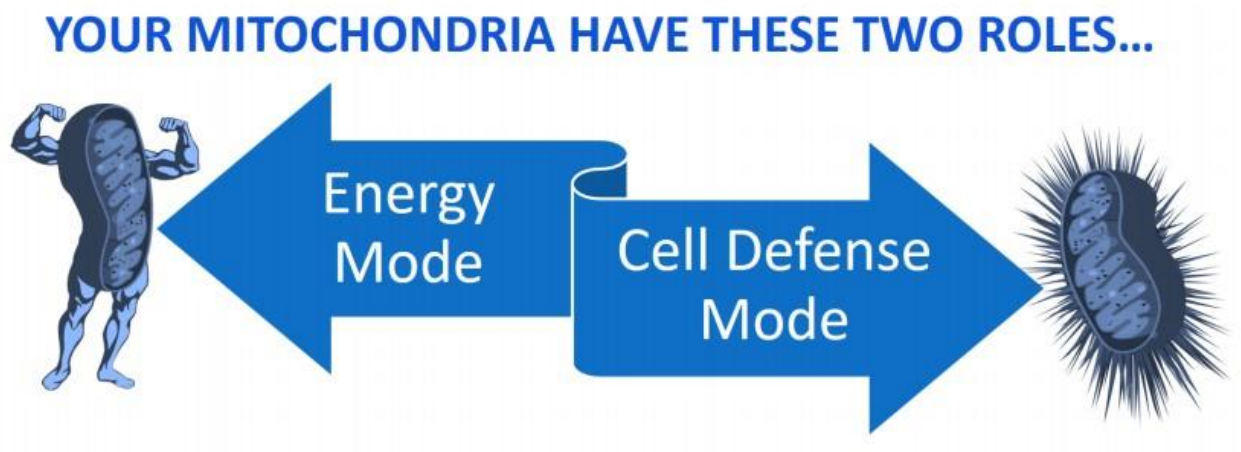
When our mitochondria are dysfunctional, so too is our metabolism.

Mitochondria sit at the central hub of our metabolism and function as gatekeepers of cell life and cell death [1]. They influence cell signaling, regulate cell death processes, impact cellular redox balance, and house important biosynthetic pathways [2].

When our mitochondria fail, we don't just lose our energy, we lose our health. There are many things that can cause mitochondria to fail — exposure to environmental toxicants (e.g. lead, pollutants, BPA, etc.) [3], chronic psychological stress [4], infections [5], smoking [6], and nutrient deficiencies [7], to name a few.

These chemical, physical, and biological threats cause oxidative stress and inflammation that damage our mitochondria and activate what's called the *Cell Danger Response* (CDR) [8], an evolutionarily conserved pathway where our mitochondria shift their resources away from energy production and towards cellular protection.

Mitochondria essentially function in two mutually exclusive modes: (1) the health-promoting energy production mode, and (2) the cell-protecting danger mode. The CDR cannot be "turned off" until the mitochondria give an "all-clear" signal, meaning they are free of harm.



So long as your mitochondria are damaged and dysfunctional, the CDR remains stuck in a repeating loop that blocks cellular healing in an attempt to eradicate perceived danger. The more your mitochondria go into danger mode, the less they can operate in energy mode, and the greater metabolic dysfunction and chronic fatigue you experience.

Over time, this metabolic dysfunction gives rise to the top killers and causes of disability in the developed world, *cardiometabolic diseases* — obesity, type 2 diabetes, heart disease, dyslipidemia, hypertension, fatty liver, renal failure, and more.

The supplements in this section all excel at helping our mitochondria shift from danger mode into energy mode by protecting them from damage, facilitating repair processes, and enhancing their ability to produce energy when under stress.

With time, your damaged and dysfunctional mitochondria will be replaced by an ever-growing number of strong and healthy mitochondria, leading to less fatigue, improved physical and mental performance, and better cardiometabolic health.

Comprehensive Vitamin and Mineral Formula

One of the best things you can do for mitochondrial health is take a highquality comprehensive vitamin and mineral formula (like *Energy Essentials and Superfoods*) that ensures you won't be running short on any of the essential nutrients that your mitochondria need to function.

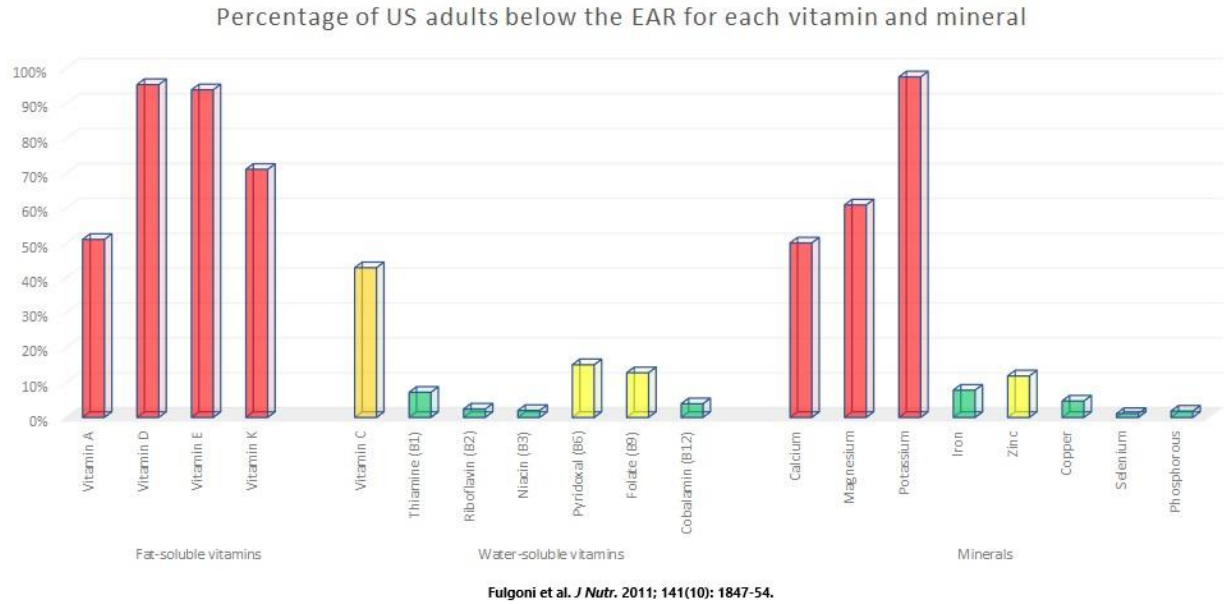
Think of it like a safety net.

Mitochondria require numerous vitamins and minerals to transform the carbohydrates, fatty acids, and amino acids we get from food into cellular energy, some of the most important being the B-vitamins, vitamin C, vitamin E, vitamin D, magnesium, and zinc [9].

The American biochemist Bruce Ames has conducted numerous studies looking at how nutrient insufficiencies over the lifetime contribute to mitochondrial decay and degenerative diseases, coining the term *Triage Theory* as a result [10,11]. Essentially, when nutrients are scarce, the body will prioritize their use for survival rather than long-term health.

Triage theory is distinctly different from clinical deficiencies. While most people consume enough of the vitamins and minerals to prevent overt signs of deficiency, they may not be consuming enough to sustain all healthpromoting functions within the body (triage theory), leading to covert signs and symptoms that manifest as degenerative diseases later in life.

Yet, more than half of Americans do not meet the estimated average requirement (EAR) for vitamins A, D, E, or K, calcium, magnesium, or potassium even after taking into account fortified foods [12], and 33–58% of adults have at least one biochemical vitamin or mineral deficiency when looking at diet alone [13].



Diets recommended by health organizations and professionals aren't much better. An analysis of 70 diet plans created for adults looking to improve their nutrient intake found 3–15 vitamin and mineral deficiencies per person [14]. In another study analyzing four popular diet plans (Atkins for Life diet, The South Beach Diet, the Best Life diet, and the DASH diet), a person would need to consume more than 18,000 calories per day to ensure an adequate intake of all essential micronutrients [15].

The solution is simple: *Take a high-quality vitamin and mineral supplement.*

Without doing expensive testing to look at what specific nutrients you may be low in, using a high-quality comprehensive vitamin and mineral formula is a powerful way to cover your nutritional bases and correct common nutritional deficiencies that frequently contribute to mitochondrial dysfunction, fatigue, and poor health.

Daily supplementation with a multivitamin has been shown to reduce fatigue by 35% and reduce sleep disturbances by 39% after two months in women with chronic fatigue [16]. Moreover, a meta-analysis of 13 primary prevention trials found that using a multivitamin for 1–11 years tended to reduce the risk of dying from any cause by 6% [17], likely through preventing clinical and subclinical deficiencies.

On a final note, you'll want to ensure that your multivitamin provides the right types of vitamins and minerals, as not all forms come equal when it comes to our health. For example, synthetic vitamin E (DL-alpha-tocopherol) not only has lower bioavailability than natural vitamin E (alpha-tocopherol), but may cause harm like liver damage and prostate cancer [18,19].

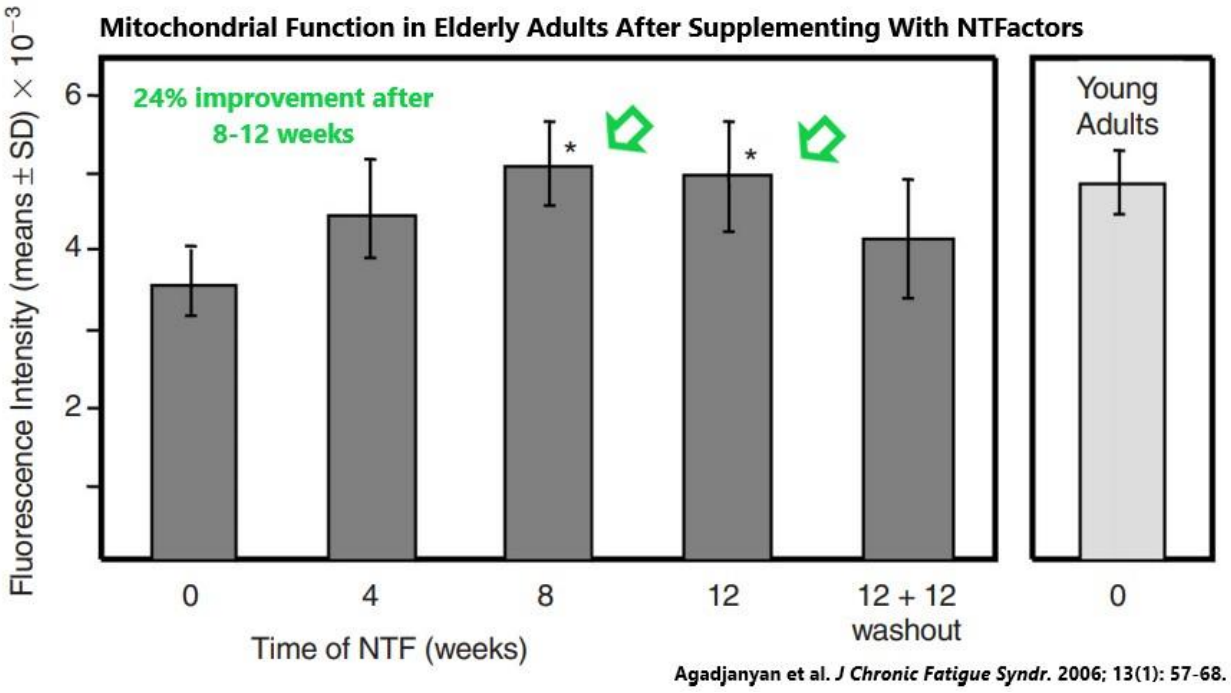
Recommended Dosing: Find a multivitamin that provides an array of biologically appropriate vitamins and minerals, rather than the typical cheap stuff you find in your local drug or health food store. (This is why we've formulated our own comprehensive vitamin, mineral, and superfood formula, *Energy Essentials & Superfoods.*)

NTFactor® Phospholipid Complex

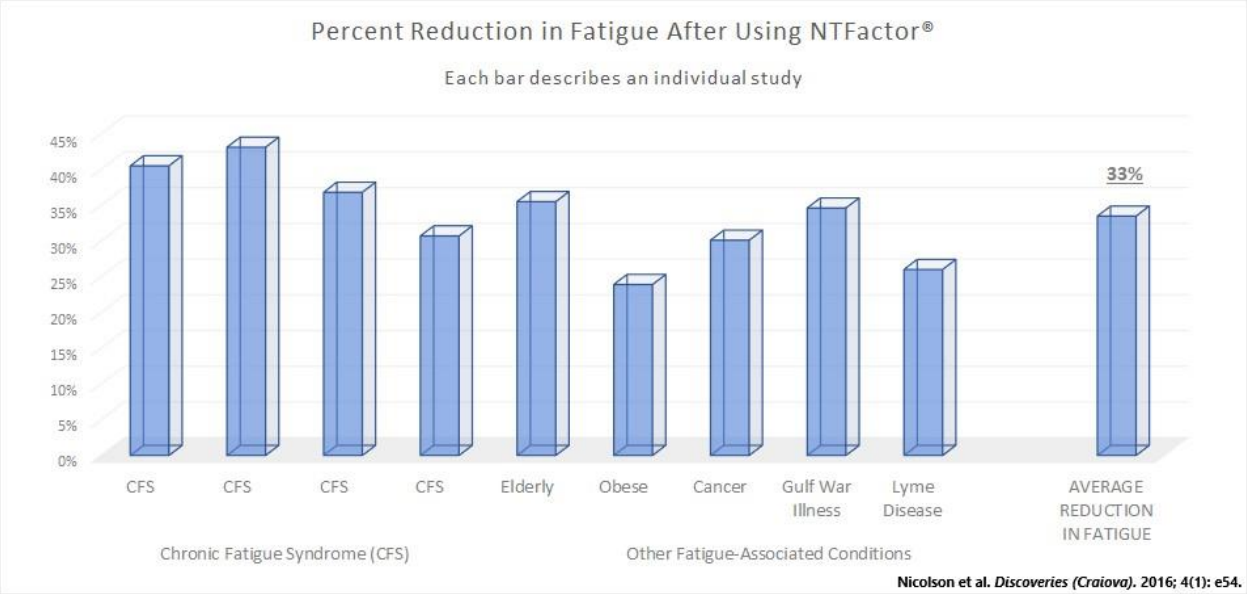
One of the primary determinants of whether mitochondria switch from energy mode to danger mode is the integrity of their membranes — damage to mitochondrial membranes signals danger and a need to shift resources away from energy production.

NTFactor® is a phospholipid complex capable of surviving digestion and supplying mitochondria with a supply of bioactive phospholipids that naturally replace damaged mitochondrial membrane components, leading to a regeneration of dysfunctional mitochondria, a process called lipid replacement therapy [20].

After just 3 months of supplementation, NTFactor has been shown to restore the mitochondrial function of chronically fatigued elderly adults to a level seen in healthy 29 year-olds [21]. This improvement was associated with a 33% reduction in fatigue severity.



Numerous other studies have also shown that supplementing with 1–3 grams of NTFactor® reduces fatigue by 24–43% among those with chronic fatigue syndrome or conditions associated with fatigue, like general aging, obesity, lyme disease, and Gulf War Illness — all after just several months of daily use [22].



Recommended Dosing: Supplement with 1–3 grams of NTFactor® per day.

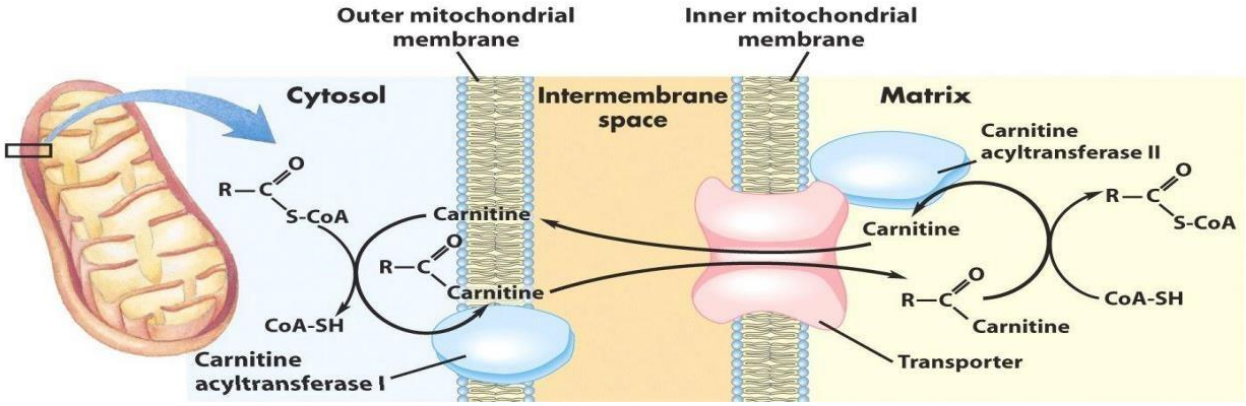
Acetyl-L-Carnitine

Consider this little thought experiment: what do you think would happen if a delivery of wood never made it to a chair factory that turns wood into chairs? The factory was running at full capacity, all of the machines were operating perfectly, and every worker that needed to be there was present — the wood just never showed up.

Nothing would be made, right?

You can't make wooden chairs out of nothing, and if there was never a delivery of wood, then it doesn't matter how efficient the factory was, it may as well shut down for the day.

Now pretend this factory was your mitochondria — they don't make energy out of nothing, and our body uses intricate transport systems to get raw materials inside of them to be used for energy production. One of those transport systems is called the carnitine shuttle system, which is essential for bringing fatty acids inside mitochondria.



If you don't have enough carnitine, you won't be burning fat and your mitochondria are going to have one hell of a time making energy. Even if everything else about them is functioning optimally, a lack of carnitine will cause your mitochondria to act as if they are damaged and dysfunctional.

At the extreme end of this situation, where there is a genetic deficit in carnitine biosynthesis, some nasty stuff happens without carnitine supplementation [23]:

- Liver damage and dysfunction
- Brain damage
- Muscle weakness
- Lethargy
- Exercise intolerance

Yet, there can also be situations of mild deficiency where these overt signs aren't present. Dysfunctional carnitine status is consistently observed in those with chronic fatigue and correlates to fatigue severity despite no signs of clinical deficiency [24].

We also see problems in the carnitine system with metabolic dysfunction — carnitine levels are reduced in rats that develop insulin resistance regardless of whether the insulin resistance is brought about from diet-induced obesity, genetic alterations, or simple aging [25]. Yet, **carnitine supplementation greatly offsets the metabolic perturbations and restores mitochondrial function.**

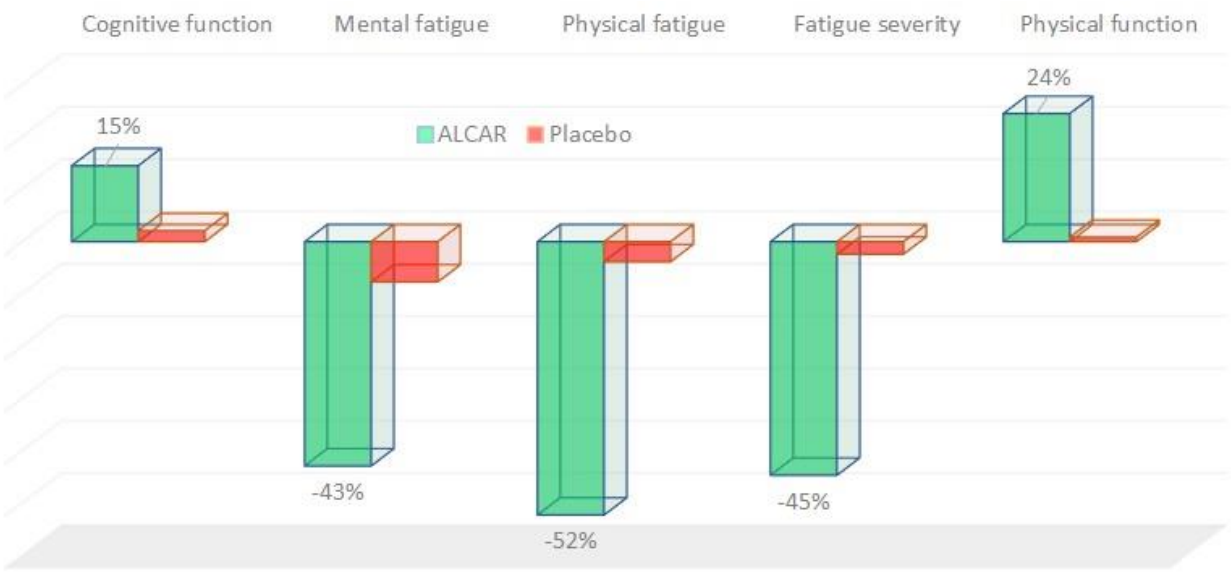
In humans, meta-analyses of intervention **studies using carnitine have documented reductions in body weight and fat mass in overweight and obese adults** [26]**, as well as markers of systemic inflammation**, including C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) [27,28].

Or maybe you're healthy, but you're aging. Carnitine levels and the ability to synthesize carnitine decline as we age [29], which may help explain why energy levels tend to dip and metabolic health tends to decline as we get older, even if all else remains pretty stable.

Thankfully, the solution is pretty simple: supplement carnitine. And if you're going to do that, then you might as well optimize the form you take. AcetylL-carnitine (ALCAR) has been called a "mitochondrial rejuvenator" because it not only supplies the carnitine that our mitochondria need to produce energy from fatty acids, but also supplies an acetyl moiety that mitochondria use to remain youthful and healthy [30].

Over 20% of mitochondrial proteins rely on acetyl moieties to function properly, including those involved in antioxidant defenses and energy production [31,32], and one of the key changes in physiology associated with longevity is an increased acetylation of mitochondrial proteins [33].

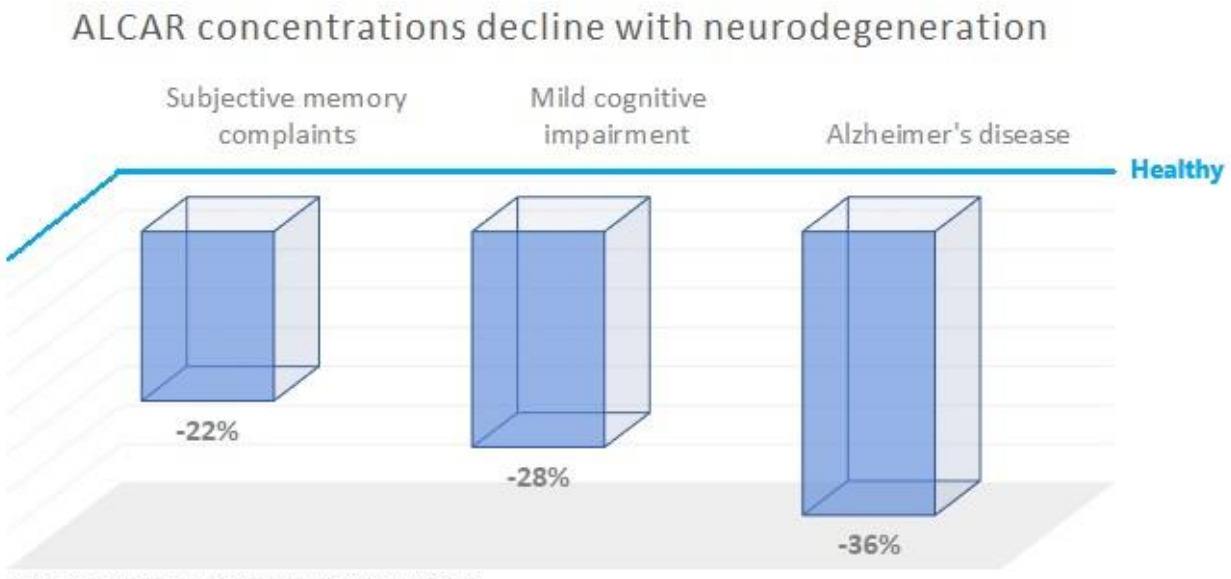
Supplementing with 4 grams of ALCAR has been shown to improve physical function by 24% and reduce mental fatigue, physical fatigue, and overall fatigue severity by 43–52% after just six months of daily use in chronically fatigued older adults [34]. Their cognitive function also improved by 15%.



Malaguarnera et al. *Arch Gerontol Geriatr.* 2008; 46(2): 181-90.

One of the best-investigated areas of research involving ALCAR's benefits for mitochondrial function is within the brain, making it a powerful nootropic ally against neurodegeneration and cognitive decline with aging [35].

ALCAR concentrations slowly decline as cognitive impairment progresses, being 22% lower than normal in those with subjective memory complaints, 28% lower in those with mild cognitive impairment, and 36% lower in Alzheimer's disease patients [36].

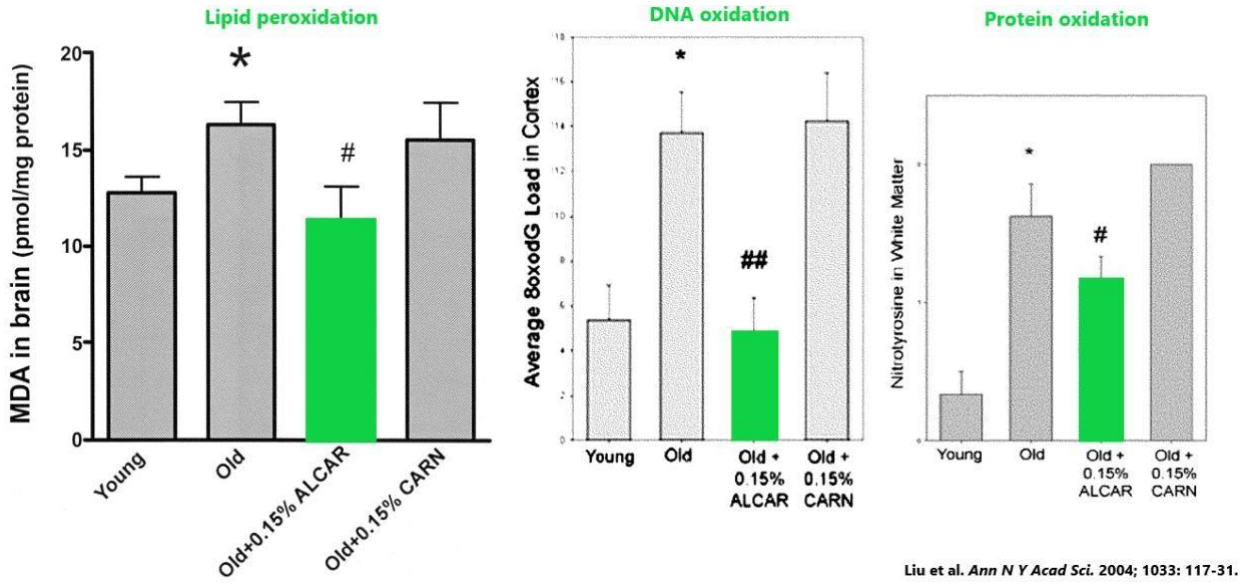


Cristofano et al. *PLoS One.* 2016; 11(5): e0155694.

Yet, supplementation has been shown to have several brain health benefits:

- Improves mitochondrial function within brain cells [37,38].
- Increases acetylcholine signaling and improves learning capacity [39,40].
- Increases brain energy availability [41].
- Protects against β-amyloid neurotoxicity and reduces oxidative stress [42,43].

And no, regular carnitine cannot accomplish these same things. In a headto-head comparison trial pitting ALCAR against carnitine, **only ALCAR reduced several biomarkers of oxidative stress within the brain, including those for lipid peroxidation, DNA oxidation, and protein oxidation** [43]**.**



Liu et al. *Ann N Y Acad Sci.* 2004; 1033: 117-31.

Both were able to similarly increase total-body and brain-specific concentrations of carnitine, so we know that this didn't play a role in reducing oxidative stress. Rather, ALCAR's ability to increase mitochondrial acetylation was likely the reason behind its benefits.

A meta-analysis of 21 randomized, double-blind, placebo-controlled trials reported that 1.5–3 grams of ALCAR per day significantly improved cognitive function in older adults with mild cognitive impairment or early Alzheimer's disease, with benefits seen as early as 3 months after starting supplementation [44].

Other studies have documented cognitive improvements from ALCAR supplementation in those with vascular dementia [45], those who recently suffered a stroke [46], and those with hepatic encephalopathy [47,48].

It can also be a powerful ally against mood disorders like depression. A meta-analysis of 12 randomized controlled trials showed that ALCAR significantly reduced depressive symptoms with an efficacy similar to antidepressant medications, but with less side-effects [49].

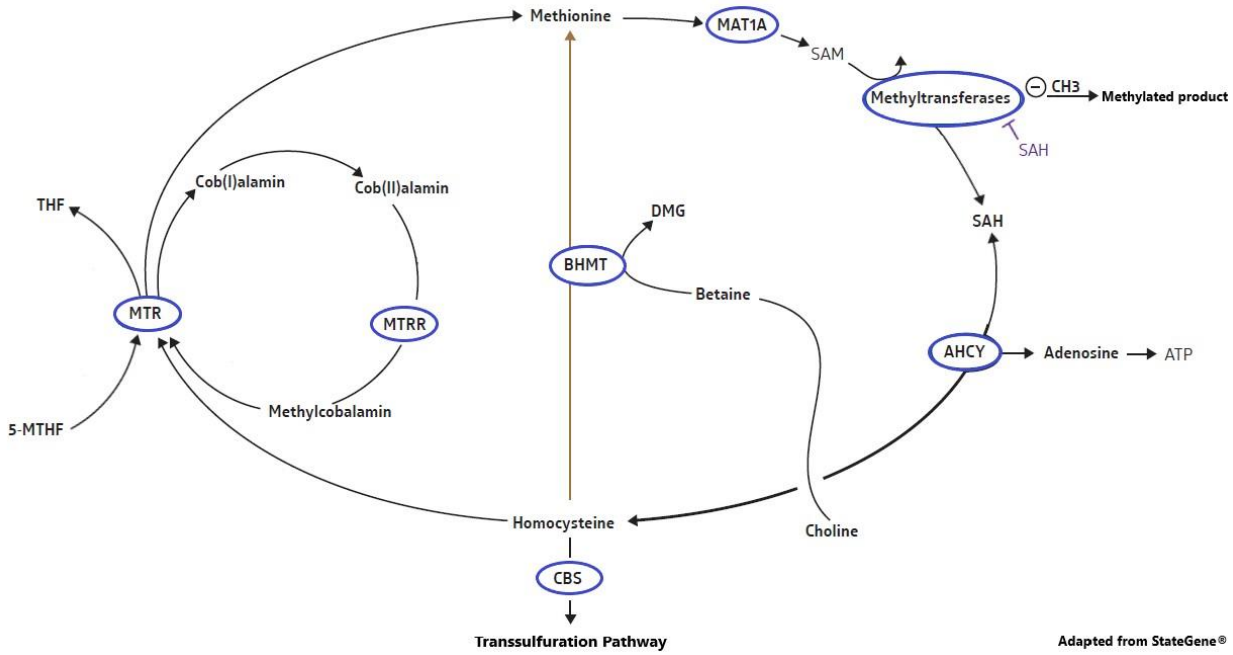
Recommended Dosing: Supplement 500–5000 mg of ALCAR per day.

Methylation Support

One of the most basic compounds in biochemistry is a methyl group — it's just a single carbon bound to three hydrogen atoms. Yet, this simple molecule could be the determining factor in whether you get cancer [50,51], whether your genetics express themselves [52], or whether the countless proteins in your body function properly [53,54].

The transfer of methyl groups to things that need them — be it your DNA, a protein, or a neurotransmitter — is called methylation, and it's a carefully orchestrated enzymatic reaction that we need not just for our survival, but also for obtaining optimal health and energy levels.

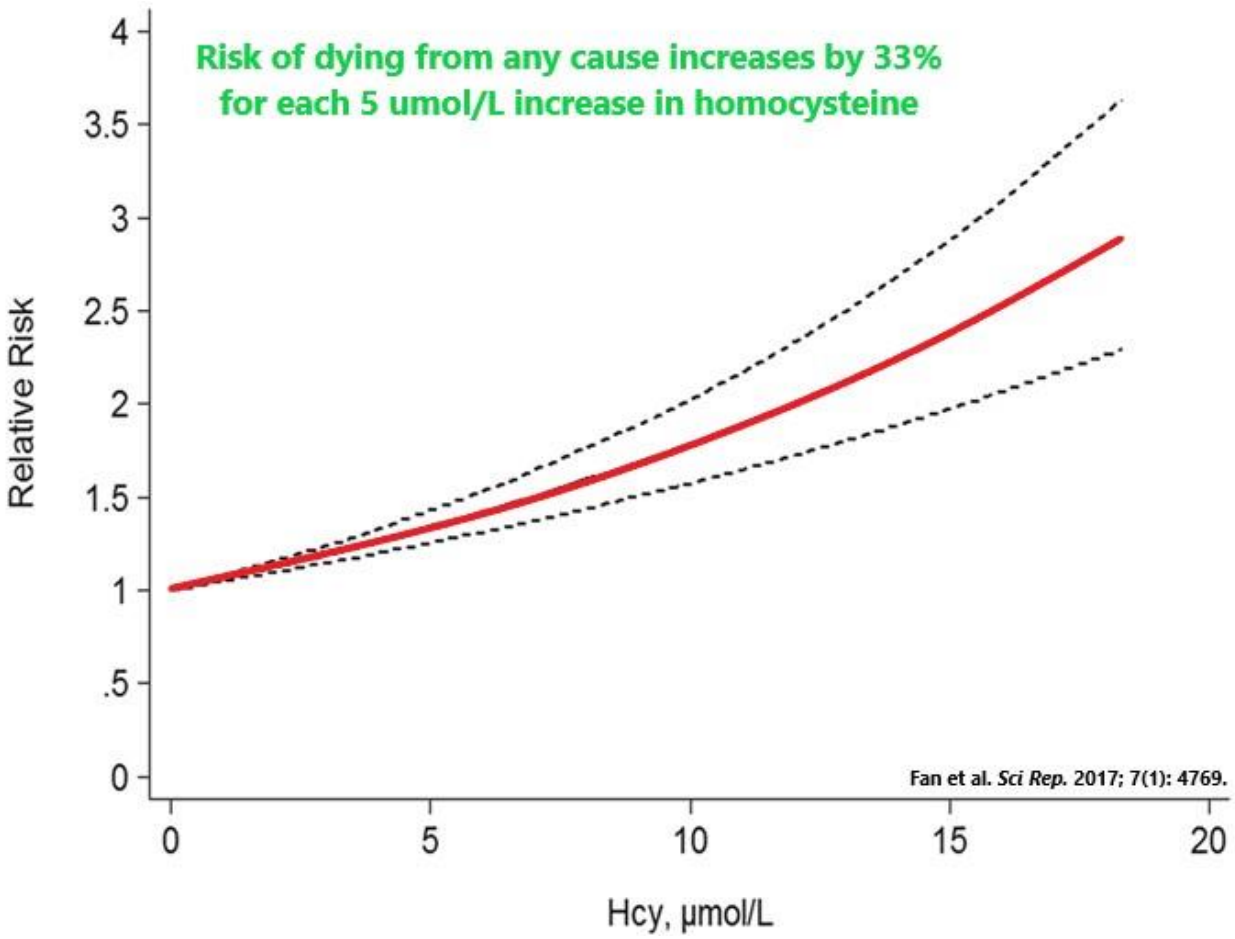
This entire process is based around the *methionine-homocysteine cycle*. The body's universal methyl donor, *S-adenosyl-methionine* (SAM) [55], is created from the essential amino acid methionine, transformed into *Sadenosyl-homocysteine* (SAH) upon methylating something, and then further metabolized into *homocysteine*, which is either recycled back into methionine or used in the transsulfuration pathway.



Several nutrients are required to ensure that the methionine-homocysteine cycle runs smoothly, and insufficiencies in any of them, or certain genetic polymorphisms that affect how the nutrients are used, can lead to toxic elevations in homocysteine.

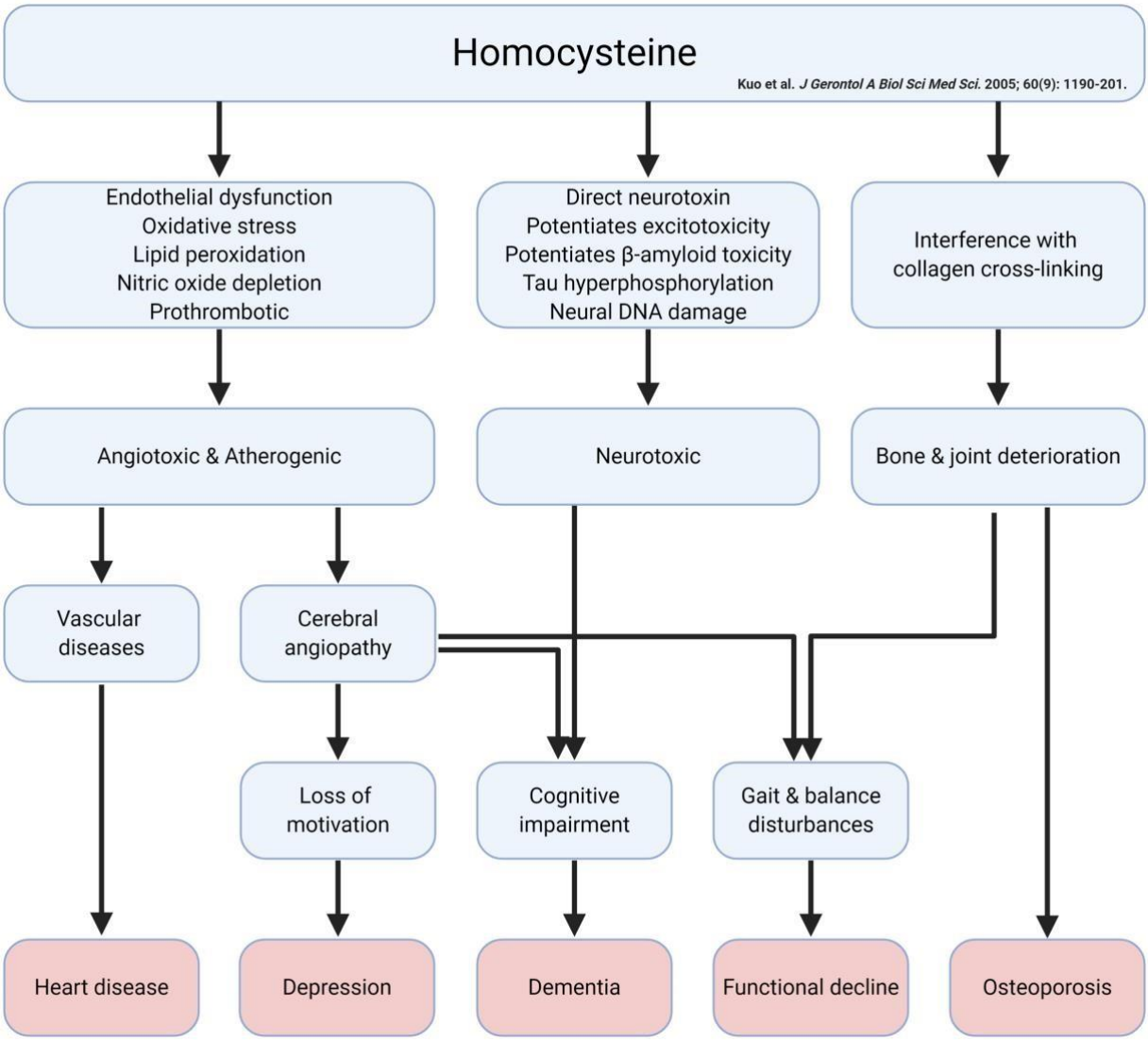
First and foremost, the buildup of homocysteine causes a backlog of SAH, which binds to and blocks the action of methyltransferase enzymes that would otherwise use SAM to methylate things [56,57]. The result is a global down-regulation of methylation that leads to unstable DNA, altered gene expression, and dysfunctional proteins both within the cell and the mitochondria.

Second, homocysteine itself has a diversity of harmful effects when concentrations become too high. In a dose-response meta-analysis of six studies involving over 18,000 adults who were followed for 3–11 years, every 5 µmol/L increase in homocysteine was associated with a 33% greater risk of dying from any cause [58].



A separate meta-analysis found that every 5 µmol/L increase in homocysteine was associated with a 27% increased risk of dying from any cause, a 32% increased risk of dying from cardiovascular diseases, and a 52% increased risk of dying from coronary heart disease [59].

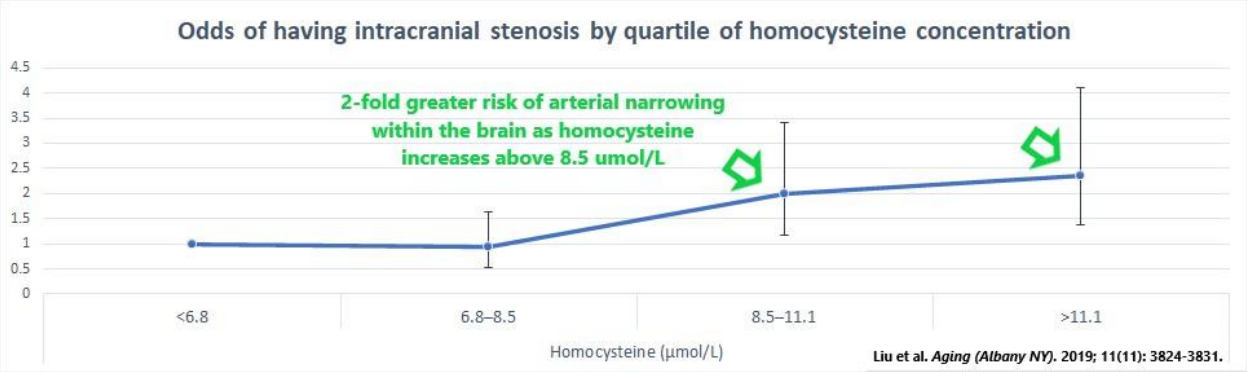
Part of this association is likely explained by homocysteine's effects on mitochondria, where it interferes with the activity of complexes II, III, and IV in the electron transport chain, impairs mitochondrial membrane integrity, reduces energy production, and promotes cell death processes [60]. The other part of this association is likely explained by noxious effects on the cardiovascular, nervous, and skeletal systems [61].



High levels of homocysteine wreck havoc on the cardiovascular system by causing blood vessel damage and dysfunction, reducing the flexibility of blood vessels, and impairing processes involved in regulating blood fluidity [62,63]. Dysfunctional blood vessels means less oxygen and nutrient delivery throughout the body and brain.

A meta-analysis of 21 studies found that every 5 μmol/L increase in homocysteine was associated with a 20% increased risk of developing heart disease, even after adjusting for traditional risk factors like smoking, physical activity, and high blood pressure [64]. Another study found that every 5 μmol/L

increase was associated with a 40% increased risk of having narrow arteries within the brain, something called intracranial stenosis [65].



The vascular effects of homocysteine, combined with the fact that it's a neurotoxin, also make it a strong risk factor for neurodegenerative diseases, dementia, and mood disorders [66]. If you currently don't have any form of cognitive impairment, then you can expect your risk of cognitive decline, dementia, and Alzheimer's disease to increase over the next decade of life if you have high homocysteine concentrations [67].

Increased risk of cognitive decline per 5 µmol/L increase in homocysteine

All types of dementia	Alzheimer's disease	Vascular dementia	Cognitive impairment
12%	**15%**	**32%**	**6%**

Mechanistic, clinical, and observational evidence all converge to show that even just a moderately elevated homocysteine level is causal for cognitive decline and Alzheimer's disease, and that lowering homocysteine levels in the elderly population could prevent 12–30% of all dementia and Alzheimer's disease cases [68].

Lastly, homocysteine directly interferes with collagen formation, which can have severe long-term consequences on bone and joint health, particularly when combined with impaired blood flow from vascular complications [69,70]. As a result, elevated homocysteine levels have been linked to an increased risk for fractures [71], physical limitations [72–74], and low muscle strength [73,74].

Ideally, you want your homocysteine level to be 5–7 μmol/L, since it's above this range that the harmful effects start to appear. You don't want your homocysteine too low because it's one of the primary sources of glutathione via the aforementioned transsulfuration pathway (about half of the liver's glutathione concentration comes from homocysteine [75]), and having concentrations less than 5 μmol/L could predispose you to oxidative stress [76].

Ensuring that we keep our homocysteine in the optimal range requires four nutrients:

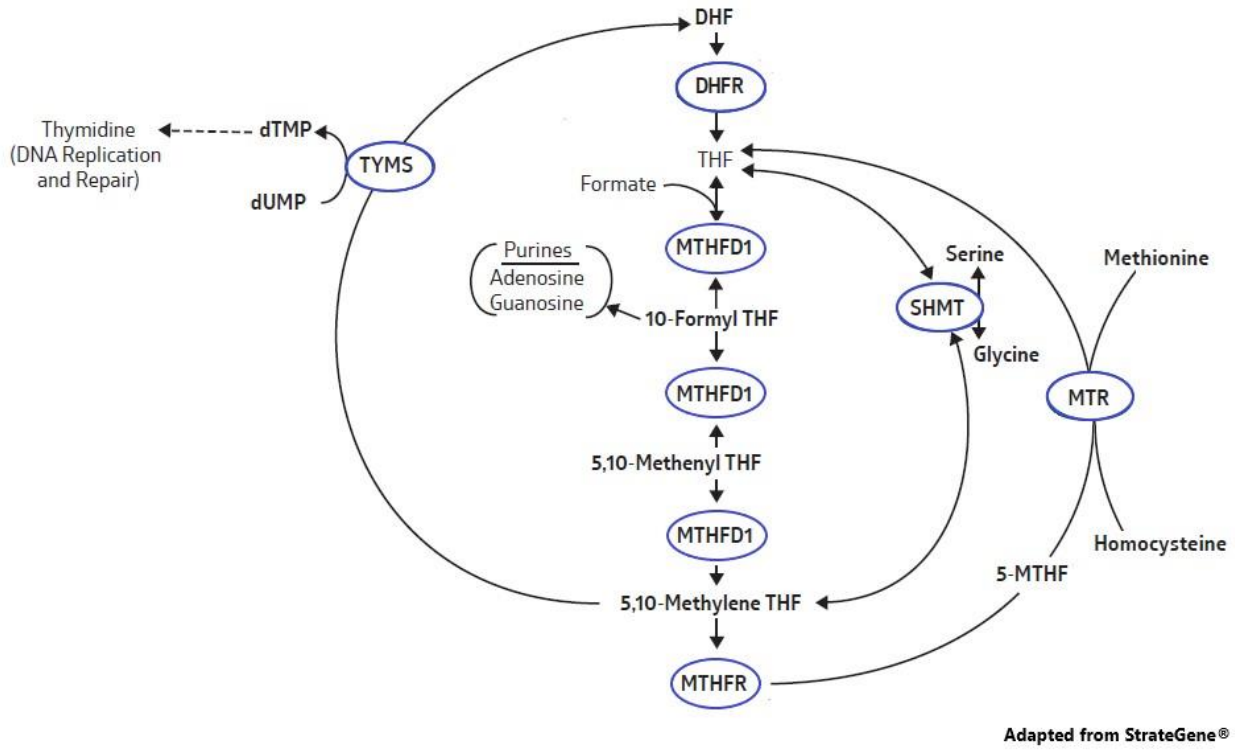
1) **Folate and Vitamin B12** for remethylation into methionine via methionine synthase (MTR), which is the primary route of recycling homocysteine.

2) **Betaine** for remethylation into methionine via betaine-homocysteine methyltransferase (BHMT), which is a secondary route of recycling homocysteine.

3) **Vitamin B6** for transformation into cysteine via cystathionine-βsynthase (CBS) and entrance into the transsulfuration pathway.

Folate

Of all the nutrients involved in homocysteine metabolism, folate is the most well-investigated and nuanced, the reason being the complexity of folate metabolism itself. When dealing with methylation, we require a form of folate called 5-methyl-tetrahydrofolate (5-MTHF), or methyl-folate for short.



Methyl-folate makes up over half of the folate you get from plants [77], so a diet rich in fibrous vegetables and legumes is a great way to help maintain healthy homocysteine levels, but many individuals do require folate supplements, in which case it is prudent to use methyl-folate.

The only way we can make methyl-folate from other forms is through the enzyme methylene-tetrahydrofolate reductase (MTHFR). Yet, many people have single-nucleotide polymorphisms (SNPs) that impair the ability of this enzyme to function.

The two most common polymorphisms are 677C→T and 1298A→C, both of which reduce MTHFR function to varying degrees [78–80]. For example, if having zero SNPs represents a completely functional enzyme, then being 677 TT can reduce enzymatic function by 70–80%, while being 1298 CC can reduce function by 40–50%.

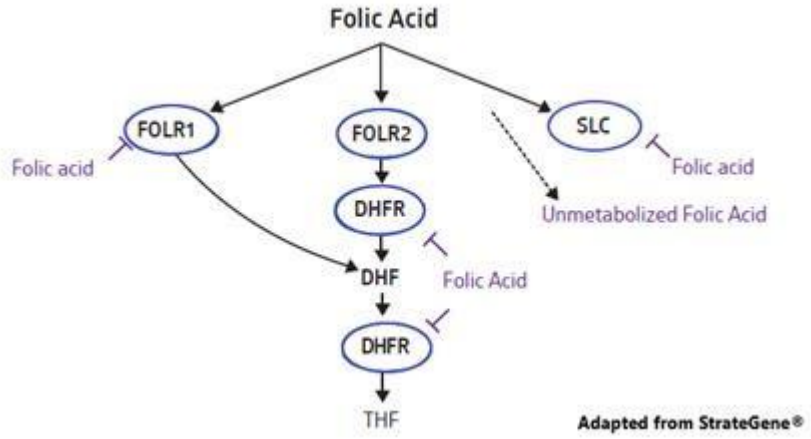
GENOTYPE	677 CC (normal)	677 CT (heterozygous)	677 TT (homozygous)
1298 AA (normal)	100%	50–75%	20–30%

1298 AC (heterozygous)	60–90%	35–60%	—
1298 CC (homozygous)	50–60%	—	—
The dashes (—) represent a lack of data due to the extreme rarity of these combinations.			

If you have any of these mutations, then you're going to have difficulty recycling homocysteine unless you directly consume methyl-folate to bypass this bottleneck process.

Another form of folate to be aware of is folinic acid, which is capable of becoming the core tetrahydrofolate (THF) molecule in folate metabolism without any enzymatic conversion. While it cannot bypass issues with MTHFR activity, it can effectively support overall folate requirements by the body, particularly those involved in DNA repair and replication [81].

Lastly, it's important to note that most folate supplements do not include any folate, instead opting for folic acid, a cheap and synthetic form of folate with zero biological activity within the body. To be usable, it needs to be converted twice by the enzyme dihydrofolate reductase (DHFR).



DHFR was designed by nature to deal with dihydrofolate (DHF), not the synthetic folic acid. As a result, enzymatic transformation of folic acid is incredibly slow, about 1300 times slower than the enzymatic transformation of DHF [82],

meaning that the ability to create biologically active forms of folate are greatly impaired with folic acid.

To add insult to injury, the slow metabolism of folic acid causes it to backlog, leading to a buildup of unmetabolized folic acid that interferes with other aspects of folate metabolism [83]:

- Binds to folate receptors (FOLR) and transporters (SLC) [84–86], thereby blocking biologically active forms of folate from being able to enter cells and circulate through the body.

- Competitively inhibits the ability of DHFR from metabolizing DHF [82], further inhibiting the creation of biologically active folates.

- Can reduce the activity of the MTHFR enzyme, thereby reducing the ability to create methyl-folate and recycle homocysteine [87,88].

While negative effects are unlikely with small amounts of folic acid, consuming 5 mg per day from fortified foods and supplements has been documented to cause a pseudo methyl-folate deficiency in someone who didn't have any MTHFR polymorphisms [89].

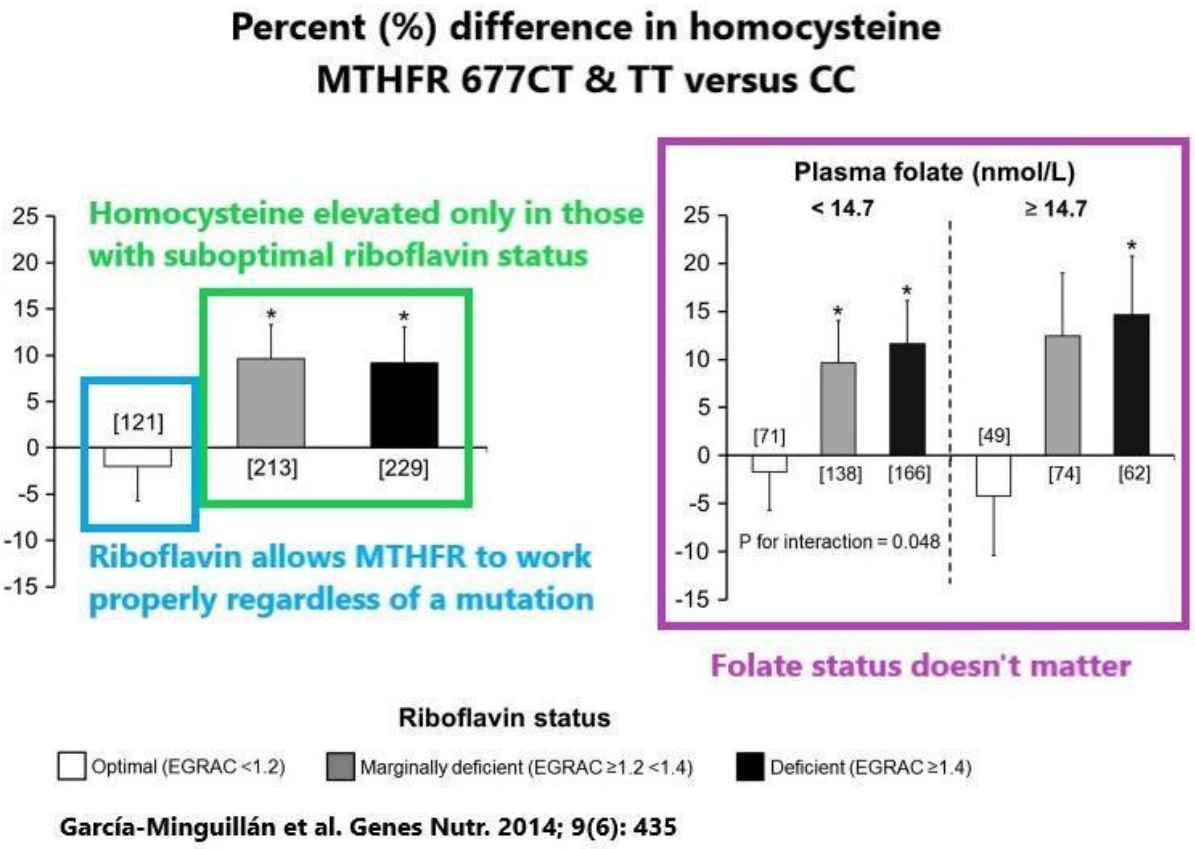
Recommended Dosing: The amount of folate needed to support maintaining healthy levels of homocysteine is variable between individuals, but you want to ensure you are getting at least 400 mcg per day of methylfolate. Taking additional folinic acid can help optimize folate status, but is not necessary. *Folic acid should be avoided.*

Riboflavin

While not involved in homocysteine metabolism per se, riboflavin is necessary to optimize the function of the MTHFR enzyme involved in creating methyl-folate. Specifically, the 677C→T SNP reduces enzyme activity by reducing the binding affinity of MTHFR to riboflavin, which is required for MTHFR to function [90,91].

A reduced binding affinity simply means that more riboflavin is necessary for the enzyme to function normally, and saturating riboflavin stores can actually restore mostly normal function of this enzyme in those who have the SNP.

This was beautifully demonstrated in a study by researchers from Spain, who looked at the relationship between homocysteine, MTHFR polymorphisms, and riboflavin status [92]. They found that individuals with MTHFR polymorphisms had elevated homocysteine concentrations only when riboflavin status was suboptimal, and that this relationship held regardless of how much folate was available.



Since you need methyl-folate around the clock, it's sensible to saturate riboflavin stores and ensure MTHFR functions properly. Although people tend to see improvements in their riboflavin status from supplementing with just 2–5 mg per day [93], intestinal absorption for a single dose maxes out at around 27 mg [94], and at least one study has shown that supplementing 25 mg improves riboflavin status more than supplementing 2 mg [95].

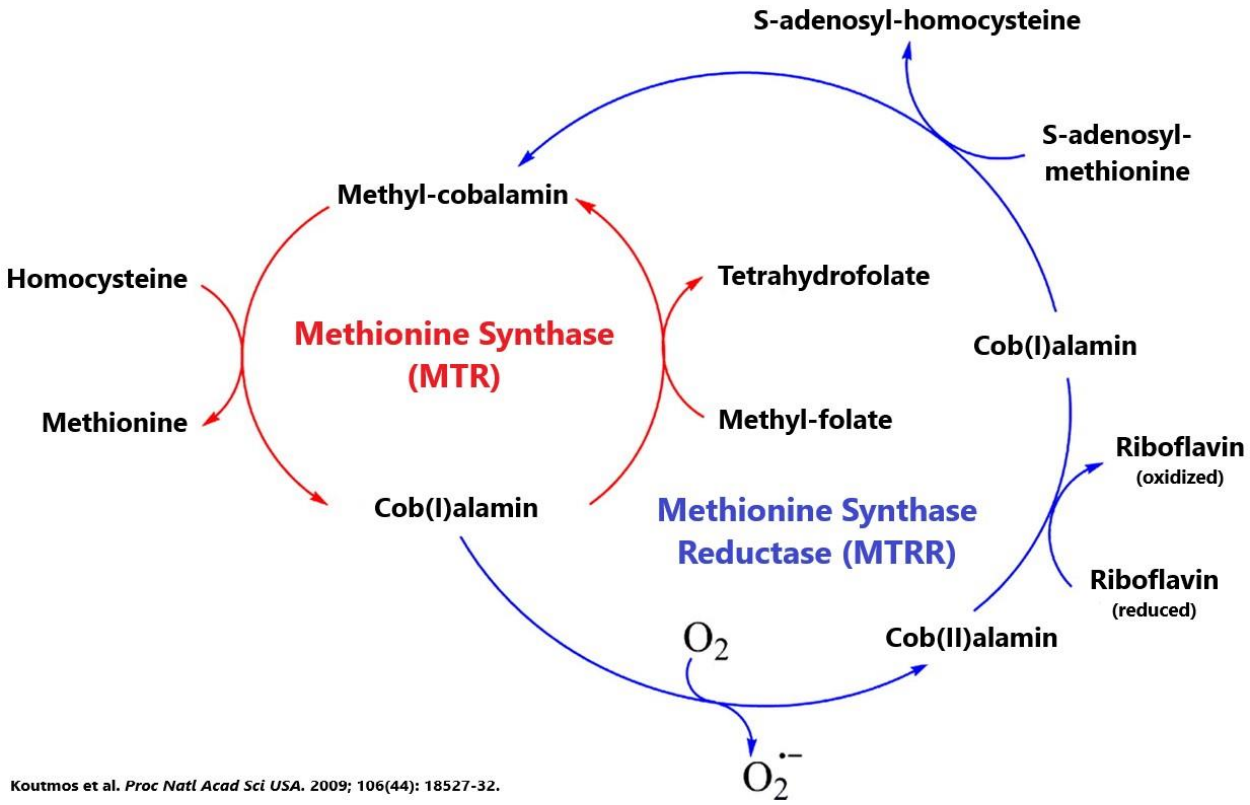
Recommended Dosing: Supplement with 25 mg of riboflavin per day.

Vitamin B12

Vitamin B12, also known as cobalamin, is required alongside folate for turning homocysteine back into methionine. Methyl-folate donates its methyl group to vitamin B12, forming methyl-B12 that passes the methyl group to homocysteine, forming methionine.

The methionine synthase reaction repeats indefinitely provided there is enough vitamin B12 and methyl-folate to support it. However, every 2000 reactions or so, B12 becomes oxidized and unusable, which requires fixing by methionine synthase reductase (MTRR) [96].

MTRR is basically a giant enzyme that latches onto methionine synthase and helps repair the B12 with the use of riboflavin and SAM. If MTRR didn't exist to perform this function, then methionine synthase enzymes couldn't function due to the accumulation of oxidized B12.



Koutmos et al. *Proc Natl Acad Sci USA.* 2009; 106(44): 18527-32.

Just like with MTHFR, there are SNPs in the MTRR enzyme that reduce its functional ability. The most common are the SNPs 66A→G and 524C→T, which reduce the affinity of MTRR for MTR by more than 3-fold, meaning that more

oxidized B12 and dysfunctional MTR enzymes need to accumulate before MTRR starts working optimally [97].

To circumvent this problem, you'll simply want to optimize your vitamin B12 status, which will ensure a fresh supply of non-oxidized B12 is available to be used on-demand, even if the repair processes take longer to work.

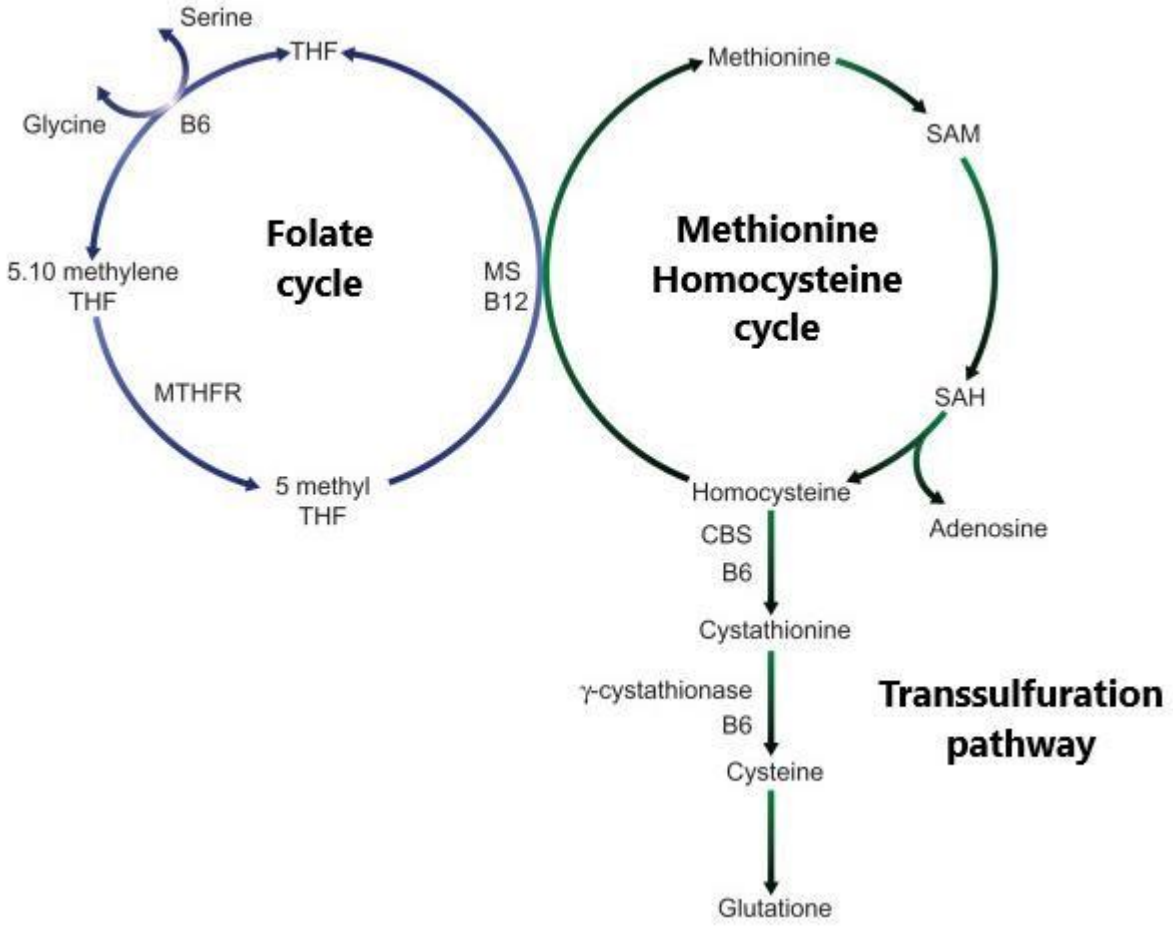
Ultimately, all supplemental forms of vitamin B12 are capable of supplying bioavailable B12 preventing a deficiency [98]. However, some studies have suggested that retention rates with methyl- and hydroxy- B12 are greater than that of cyano-B12, largely due to lower excretion [99,100].

If we combine that with the fact that there could be yet unidentified SNPs in B12 receptors and transporters that impact how someone responds to specific forms of B12 supplements, then it makes sense to supplement with a combination of the methyl-, adenosyl-, and hydroxy- forms of B12 — the forms that we naturally obtain in our diet.

Recommended Dosing: With daily requirements for vitamin B12 being incredibly low (<3 mcg), and with no known upper limit for toxicity, virtually all supplements provide more than enough vitamin B12 to be taken on a daily basis. Instead of dose, focus on looking for methyl-, adenosyl-, or hydroxy forms.

Vitamin B6

Vitamin B6 is required for the function of cystathionine-β-synthase (CBS) that enters homocysteine into the transsulfuration pathway. This is a critically important pathway because one of the primary end-products is glutathione, our body's master antioxidant.



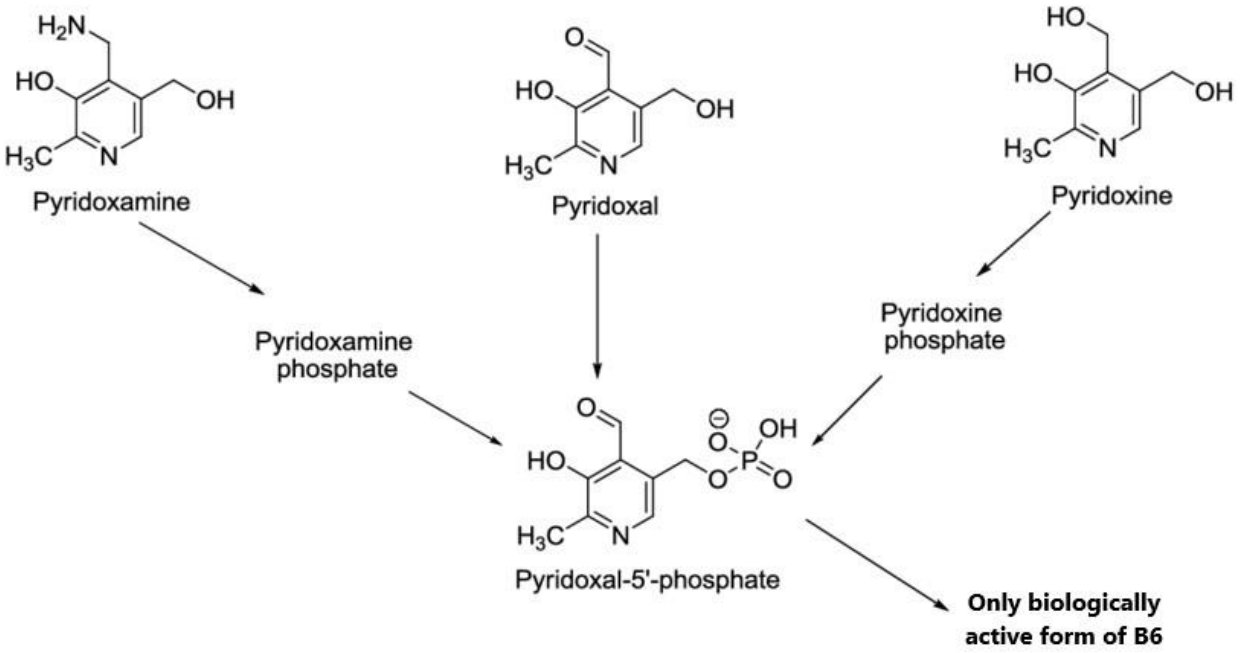
Your body is smart enough to have evolved regulatory mechanisms whereby high levels of oxidative stress impair the enzymes involved in recycling homocysteine back into methionine, while simultaneously upregulating the activity of CBS, so that more homocysteine becomes available to enter into the transsulfuration pathway and create glutathione [75,101,102].

There are three naturally occurring forms of vitamin B6 that we can get in the diet:

- Pyridoxal
- Pyridoxamine
- Pyridoxine

The first two are found in animal products while the latter comes from plants. However, only pyridoxal has biological activity in the body, meaning that all

forms must be turned into it to be usable. Specifically, they need to become pyridoxal-5-phosphate (P5P).



Regardless of the form you take, most of the B6 will be turned into P5P within intestinal cells and the liver [103,104], similar to how all forms of vitamin B12 are turned into a basic B12 molecule. However, there could be yet unknown polymorphisms in the enzymes involved in these interconversion processes that impair our ability to make P5P from other forms of B6.

For example, research in children with epilepsy has suggested that P5P is more effective at managing seizures than pyridoxine in some children [105], indicating there could be yet-unknown differences in the ability to interconvert the B6 forms.

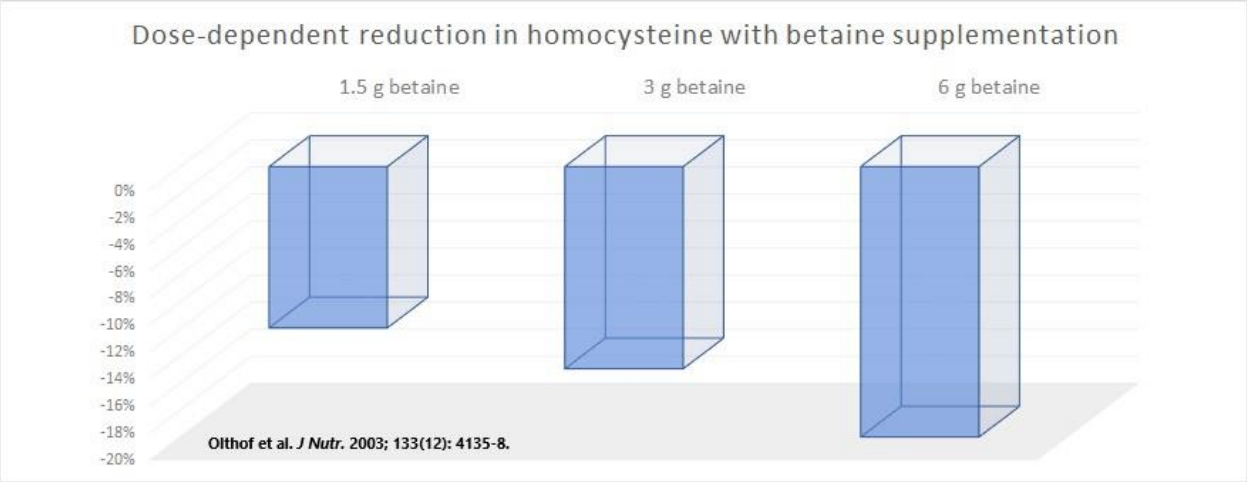
Another potential reason to favor P5P supplements over pyridoxine is because the latter has been linked to the development of peripheral neuropathy in people supplementing more than 25 mg per day for months to years [106]. While the exact mechanism isn't known, the most likely scenario is that pyridoxine competes with P5P for enzymes that need P5P to function, rendering them useless [107].

Recommended Dosing: Supplement with 5–10 mg of pyridoxal-5phosphate.

Betaine

Betaine, also known as trimethylglycine, can help recycle homocysteine back into methionine by donating one of its methyl groups, thereby providing an alternative route of homocysteine metabolism that does not require folate or vitamin B12.

Several studies have shown that betaine supplementation reduces homocysteine levels in a dose-dependent manner, where higher doses lead to greater reductions [108–110]. These studies used upwards of 6 grams per day without harm, suggesting this is a safe upper limit to work towards. However, even amounts of 100–200 mg will support homocysteine metabolism.



While we can make betaine within our body from choline, it makes more sense to simply supplement betaine, since that frees up choline to create phospholipids and neurotransmitters that require it.

Recommended Dosing: Supplement with at least 100–200 mg of betaine (trimethylglycine) daily, going up to 6 grams per day if homocysteine levels remain elevated.

Creatine Monohydrate

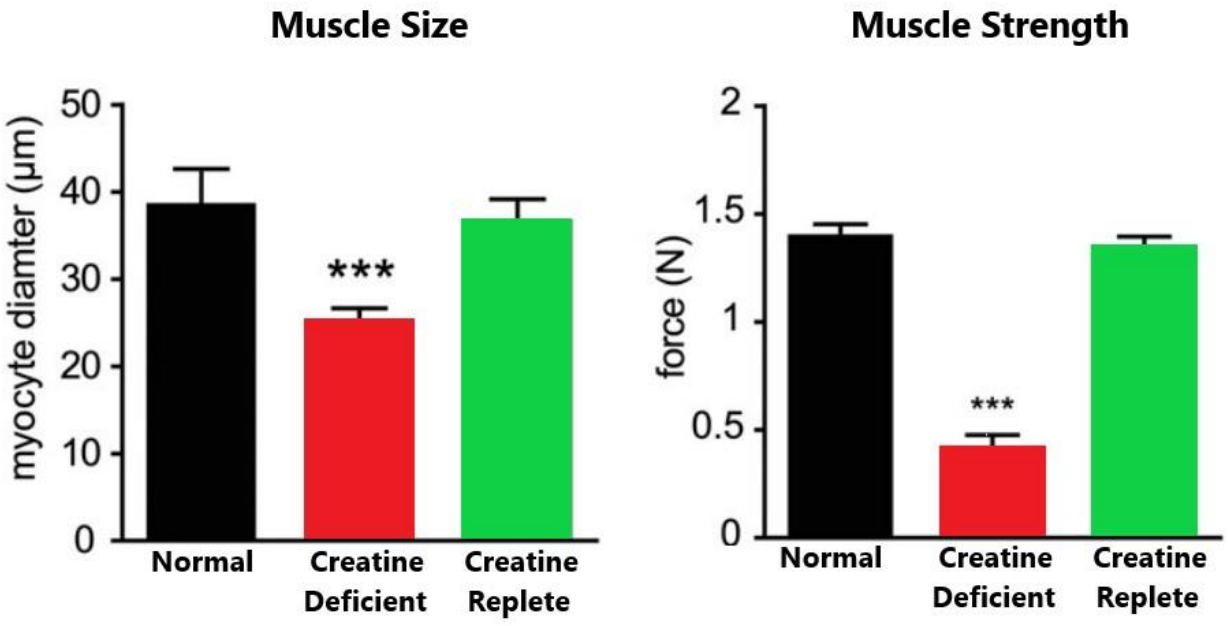
Although mitochondria produce most of the energy our body needs on a daily basis, certain activities require more energy than what's available for use. Since our cells store very little cellular energy (ATP), the body relies on a molecule

called *phosphocreatine* to near-instantly regenerate ATP when other methods of energy production can't keep up with demands.

The ability to replenish ATP is so efficient that intramuscular ATP concentrations remain almost unchanged during the first 10 seconds of allout exertion [111,112]. Phosphocreatine produces energy 12 times faster than mitochondria [113], and the depletion of phosphocreatine is the entire reason your speed slows down and your strength declines after 5–10 seconds of going all-out.

Creatine supplementation works through saturating phosphocreatine stores, making more of it available for use when needed. This is why creatine is such a heavily researched ergogenic supplement for bolstering exercise performance, and meta-analyses of randomized controlled trials unambiguously report that creatine supplementation increases muscle strength, power output, and lean body mass in both younger and older adults [114–118].

Cellular growth and repair processes also require creatine to support their energy demands, such as when your muscles become damaged from exercise [119,120]. If you genetically alter mice to lack creatine, they experience substantial reductions in muscle size and strength compared to normal mice, effects that are completely reversed with creatine supplementation [121].



Moreover, creatine has been shown to protect muscle fibers from high levels of oxidative stress and preserve their ability to grow and differentiate under these harsh conditions [122], effects that were determined to be through several converging mechanisms [123]:

- Direct antioxidant activity
- Increased growth factor signaling
- Enhanced energy availability
- Mitochondrial protection

The impact of creatine on mitochondria may be one of its most underappreciated benefits. Not only does creatine increase mitochondrial biogenesis, structural integrity, and function [124], it helps transport energy out of mitochondria and sensitize mitochondrial energy production to cellular energy requirements [125,126].

Collectively, these benefits for cellular repair and mitochondrial function explain why creatine supplementation speeds recovery after muscledamaging exercise, reduces the extent of muscle damage, and lessens the inflammatory fallout from a hard training session [127–129].

But muscles aren't the only tissue reliant on creatine. The neurons in our brain and throughout the body require creatine to support their intense and fluctuating bursts of communication, with impairments in creatine metabolism linked to neurodegeneration [130,131].

Just like with our muscles, creatine supplementation increases brain creatine stores by 5–15% depending on concentrations before supplementation and the size of the person supplementing [132–134]. Some evidence suggests that supplementation may improve short-term memory, intelligence, and reasoning ability among otherwise healthy adults, particularly in those with a low dietary intake (found only in meat) [135,136].

Lastly, creatine synthesis uses 40% of all S-adenosyl-methionine (SAM) within the liver [137], making it an appreciable burden on our methylation system (see our prior discussion on supplements for methylation support). Supplementation can, therefore, free up significant amounts of SAM to methylate other molecules by inhibiting the body's creatine synthesis.

There is no benefit from using forms of creatine other than monohydrate, as this is the form used in virtually all research on creatine to date. Research comparing monohydrate to other forms advertised as being superior have found no differences (such is the case for the buffered creatine known as Kre-Alkalyn® [138] and creatine ethyl ester [139]).

Recommended Dosing: Supplement with 500–5000 mg of creatine monohydrate per day.

Taurine

Taurine is an omnipresent amino acid within the body, essential for the development and function of our cardiovascular, muscular, nervous, and ocular systems [140]. It's required to regulate water balance, for cell signaling, to make bile and excrete toxicants, and, most importantly, it's required for mitochondrial function and energy production.

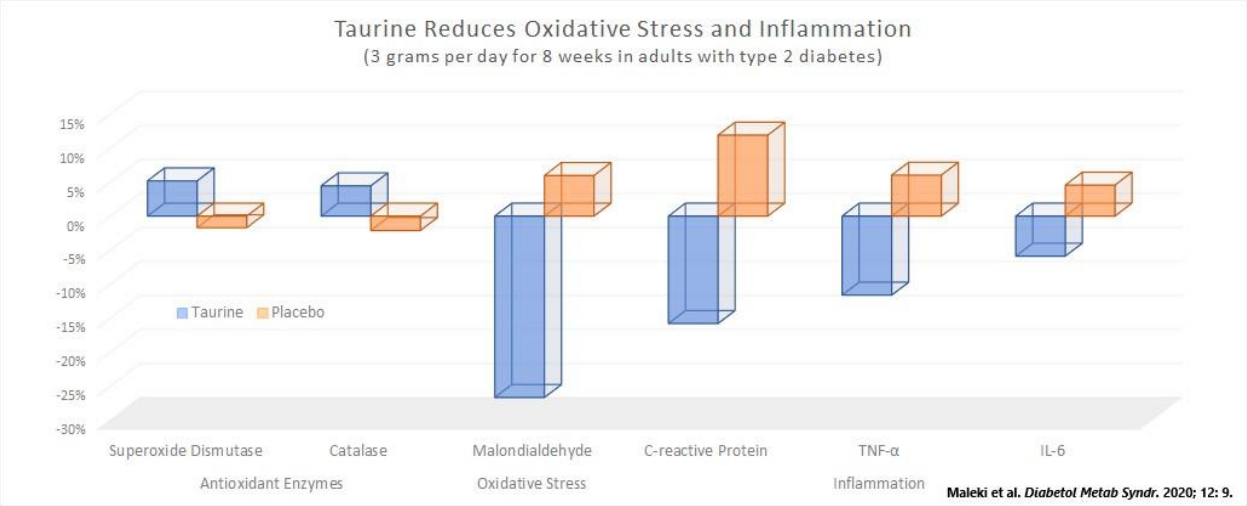
As such, it should be no surprise that taurine deficiencies are implicated in numerous chronic disease states [141,142].

- Neurodegeneration
- Stroke
- Macular degeneration and cataracts
- Metabolic dysfunction
- Heart failure
- High blood pressure
- Atherosclerosis
- Muscular dystrophy
- Sarcopenia

The highest amounts of taurine are in tissues with huge energy requirements and a lot of mitochondria, such as the retina, nerves, kidney, heart, and skeletal muscle [143]. There's two primary reasons for this:

1) Taurine is essential for mitochondrial protein synthesis [144].
2) Taurine stabilizes the mitochondrial pH gradient necessary for mitochondrial enzyme activity and energy production [145].

If mitochondria don't have enough taurine, energy production decreases and oxidative stress increases [146]. Several clinical trials have shown that supplementing with 3 grams of taurine per day reduces biomarkers of oxidative stress and inflammation in those with metabolic dysfunction [147– 149].



Over time, the build-up of oxidative stress causes mitochondria to simply terminate their lives and the life of the cell containing them [150]. The reduction in mitochondrial energy production and increase in cell death as a result of taurine deficiency is an established cause of heart failure and other cardiovascular diseases [151,152].

Taurine is also being heavily investigated for its ability to help offset sarcopenia and other diseases of muscle wasting [153,154]. In mice lacking the ability to uptake taurine into their skeletal muscle, exercise capacity is reduced by over 80% [155], whereas supplementing taurine into the diets of mice undergoing an exercise program enhanced mitochondrial function, energy production, and muscular strength [156].

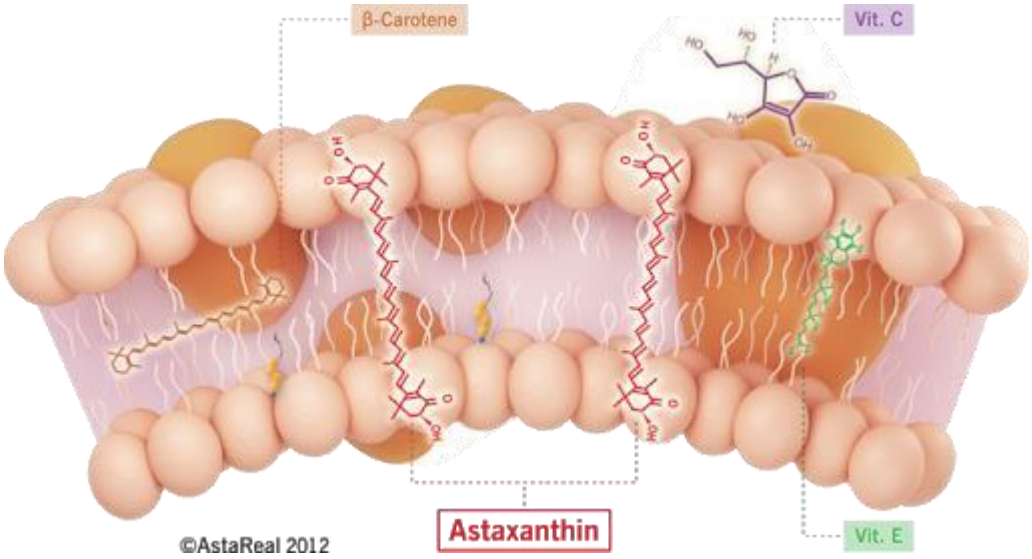
Additionally, a meta-analysis of 10 studies involving mostly young and healthy adults reported that 1–6 grams of taurine improved endurance exercise performance, particularly power output and the amount of time that people could run before exhaustion [157].

Recommended Dosing: Supplement with 1–6 grams of taurine per day.

Astaxanthin

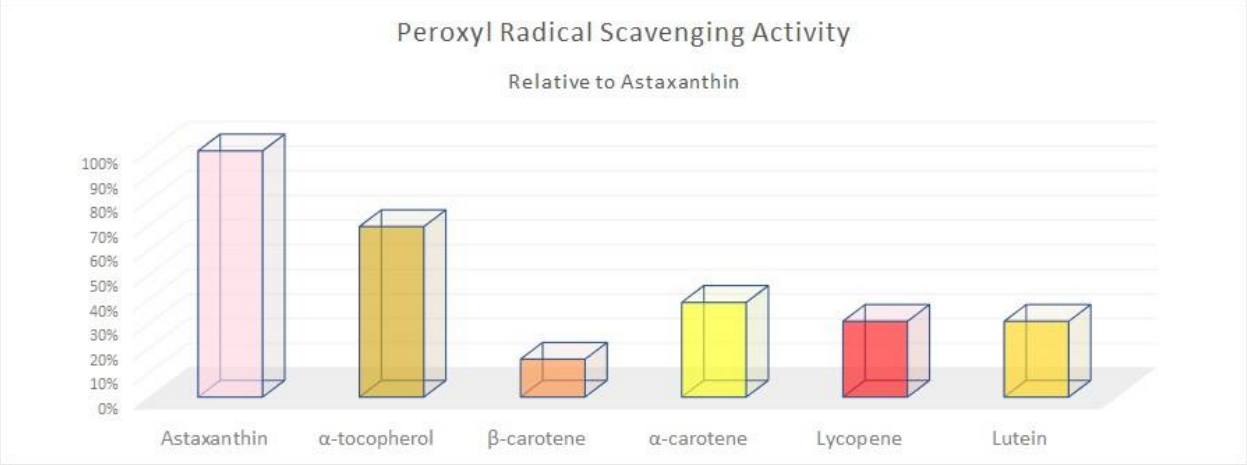
Astaxanthin is a carotenoid produced by the microalgae *Haematococcus pluvialis* as protection for its cells against oxidative stress [158]. You've likely seen it in the many creatures that eat it — krill, shrimp, crab, and salmon are all rich sources of astaxanthin that pigments their flesh and shells with a red-orange hue.

Humans also make use of it, as we've developed an effective system of incorporating dietary carotenoids directly into cell membranes as a means of preventing membrane oxidation and increasing membrane fluidity [159]. Astaxanthin is particularly good at this because of its unique polar structure that allows it to cross the entire cell membrane [160].



While other types of antioxidant molecules generally act either inside or outside the membrane, astaxanthin's structure allows it to do both, thereby helping stabilize membranes and protect them from oxidative damage, both for the cell itself and the mitochondria within [161–163].

Astaxanthin is also a far more potent antioxidant molecule than vitamin E and other carotenoids like β-carotene, lycopene, and lutein, which have only 15–69% of astaxanthin's ability to prevent membrane peroxidation [164]. Just three weeks of supplementing with 5 mg of astaxanthin per day reduced oxidative stress and increased antioxidant status in individuals carrying around too much body fat to levels seen in those at a normal body weight [165].



Naguib YM. *J Agric Food Chem.* 2000; 48(4): 1150-4.

The structural polarity and antioxidant properties of astaxanthin have afforded it a powerful ability to prevent mitochondrial dysfunction and help reverse the mitochondrial dysfunction associated with aging [166,167], leading some researchers to call it a "mitochondria-targeted antioxidant" [168].

In fatigued elderly adults, four months of supplementation with 12 mg of astaxanthin increased maximal strength by 14%, muscle size by 3%, and force production by 12% compared to a placebo [169].

In recreationally active college students, six months of supplementation with 4 mg of astaxanthin per day increased muscular endurance by 3-fold compared to a placebo group [170].

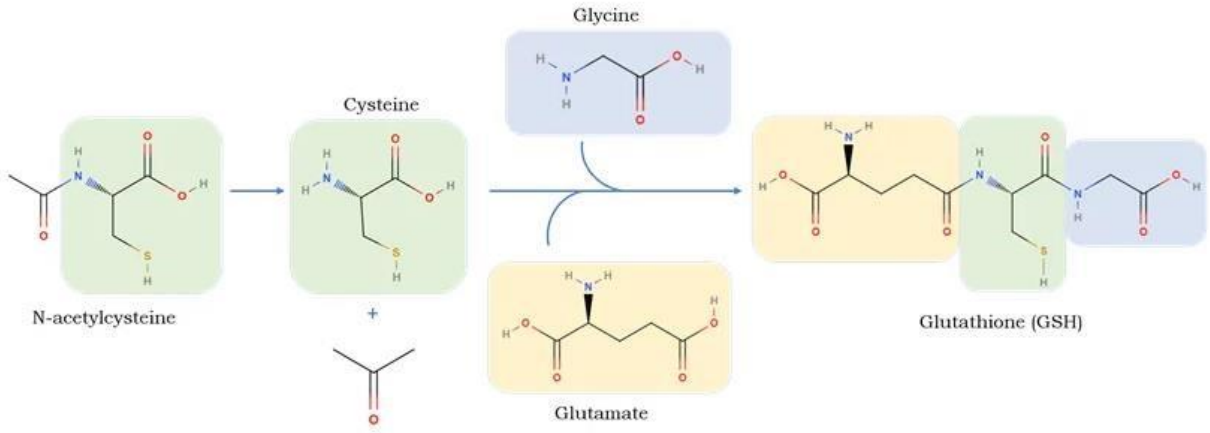
Other studies have found that astaxanthin helps prevent the decrease in antioxidant defenses that occur from prolonged endurance exercise in elitelevel soccer players and helps improve endurance exercise recovery in recreational athletes [171,172].

Recommended Dosing: Take 4–12 mg of astaxanthin per day.

N-Acetyl-Cysteine

Glutathione is an omnipresent molecule required for direct antioxidant activity, recycling other antioxidants, detoxifying and excreting toxins, and maintaining mitochondrial function [173]. Our body relies on glutathione so heavily that virtually every cell in the body has stores of it similar in size to some of the most important nutrients for energy and cellular function, like glucose, potassium, and cholesterol.

The synthesis of glutathione requires three amino acids: cysteine, glycine, glutamate, and glycine. Cysteine is the rate-limiting amino acid, meaning that cysteine concentrations are what determine how much glutathione can be made. N-Acetyl-Cysteine (NAC) supplementation is an effective means of increasing glutathione concentrations because it supplies the cysteine that our body needs to make glutathione [174,175].



For instance, acetaminophen (Tylenol) toxicity causes liver damage by depleting the liver of glutathione, and the standard of care medical treatment is simply providing patients with NAC to replenish glutathione reserves in the liver, which quells the oxidative stress and maintains mitochondrial energy production [176].

Through helping to sustain optimal glutathione concentrations, NAC has been demonstrated to reduce mitochondrial oxidative damage and preserve cellular life in the face of genetic mitochondrial mutations or toxic conditions that directly damage mitochondria [177–180].

Moreover, by serving as an antioxidant precursor rather than an antioxidant itself, NAC shows greater promise than other antioxidant compounds for

supporting mitohormesis [181], a process whereby the mitochondria adapt to stress by growing bigger and stronger. That’s because it doesn't directly interfere with oxidative stress, but rather gives the body the tools it needs to deal with it itself.

A meta-analysis of 28 clinical trials found that supplementing with 600–2000 mg of NAC per day significantly reduced biomarkers of oxidative stress and inflammation [182]. A separate meta-analysis of 24 randomized controlled trials also reported that 400–2000 mg of NAC per day reduced inflammatory biomarkers [183].

Lastly, glutathione is essential for the proliferation of white blood cells and overall immune function [184,185]. One potential contributor to chronic fatigue is an overactive immune system “stealing” NAC from muscle tissue to satisfy its own glutathione needs, thereby limiting energy production and antioxidant protection in muscle tissues [186].

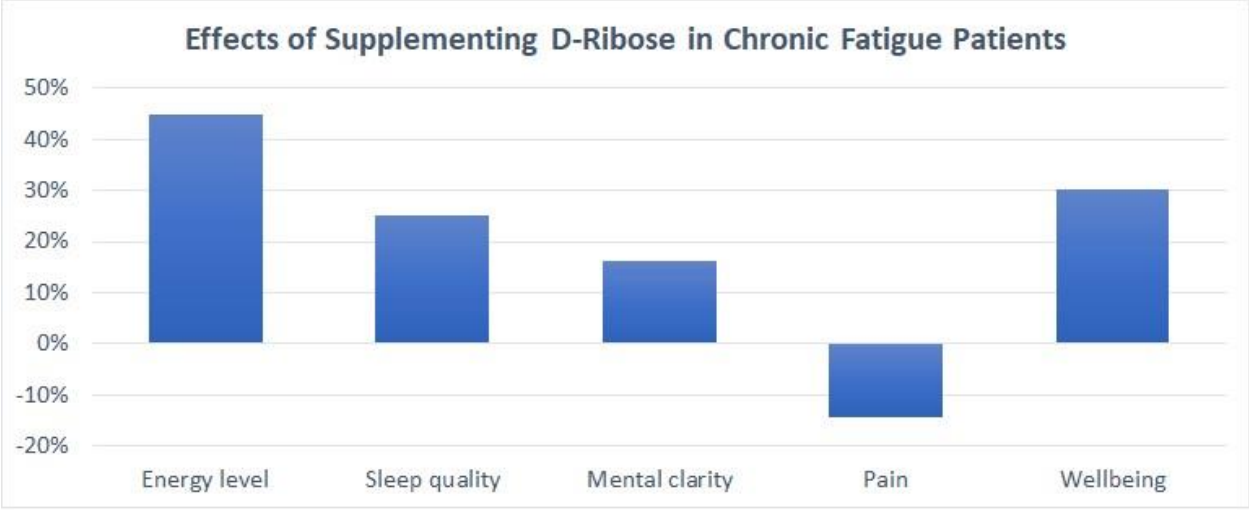
Recommended Dosing: Supplement 200–2000 mg of NAC per day.

D-Ribose

D-ribose is a naturally occurring sugar molecule that assists in the production of cellular energy by virtue of being a necessary component of ATP, DNA, and RNA [187]. In particular, D-ribose is the product of a ratelimiting step in ATP production within mitochondria and supplementation directly bypasses this bottleneck to increase energy production [188].

Accordingly, 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 [189–191], or people engaging in regular intense exercise [192,193].

In adults with chronic fatigue, supplementing with 5 grams of D-ribose three times per day (15 grams per day in total) led to 45% greater energy levels, 25% better sleep quality, 16% more mental clarity, 14% less pain, and 30% greater overall wellbeing [194]. Another study reported similar findings after using 10 grams per day, with all benefits disappearing within a week of stopping supplementation [195].

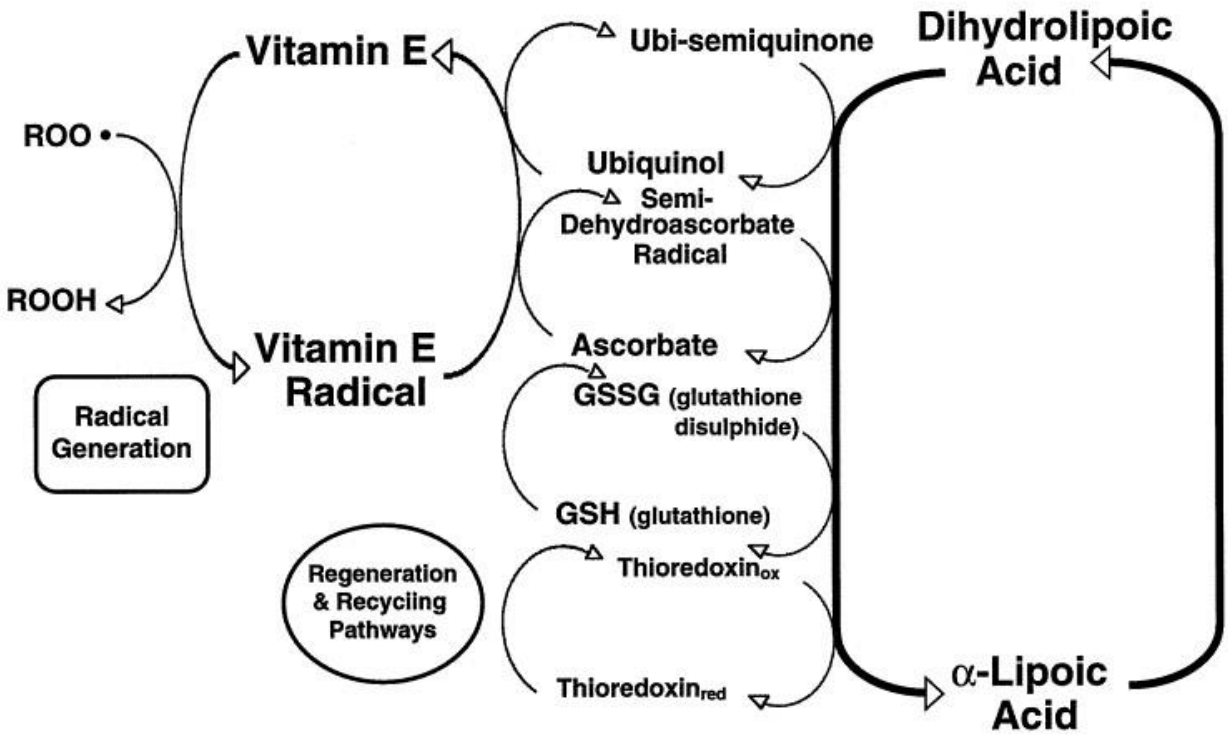


Teitelbaum & Cyr. *J Altern Complement Med.* 2006; 12(9): 857-62.

Recommended Dosing: Supplement with at least 500 mg of D-ribose per day to support mitochondrial energy production, and up to 15 grams per day as necessary.

Alpha-Lipoic Acid (Ideally R-ALA)

Alpha-lipoic acid (ALA) is a mitochondrial molecule involved in energy metabolism and the antioxidant system. It is not only essential for mitochondria to create cellular energy, but also serves to function as an antioxidant, replenish other antioxidants, and stimulate the production of antioxidant enzymes like glutathione [196].



ALA is being heavily investigated as a mitochondrial rejuvenator, able to help reverse age-related declines in mitochondrial energy production [197], particularly within the brain [198,199]. One case study of a woman suffering from mitochondrial disease found that daily supplementation with 600 mg of ALA increased brain energy availability and her ability to be active [200].

Other research has suggested that ALA benefits neurodegenerative disorders and age-related cognitive decline [201,202]. ALA accumulates in various brain regions as soon as an hour after ingestion [203,204], and it has been shown to protect against neuronal cell death [205]. In patients with Alzheimer's disease, supplementing with 600 mg of ALA per day alongside fish oil prevented a decline in cognitive function over one year compared to both fish oil alone and a placebo [206].

Lastly, the mitochondrial benefits of ALA supplementation seem to extend to metabolic health as well [207,208]. Several studies have shown that supplementing with 800–2000 mg per day facilitates weight loss and reductions in waist circumference among both men and women using it for several months [209–211].

As an aside, ALA exists as either an S or R isomer, with unspecified ALA being a 50-50 'racemic' solution of both. Most studies use the racemic solution, but only R-ALA has biological activity in the body and is more bioavailable [212].

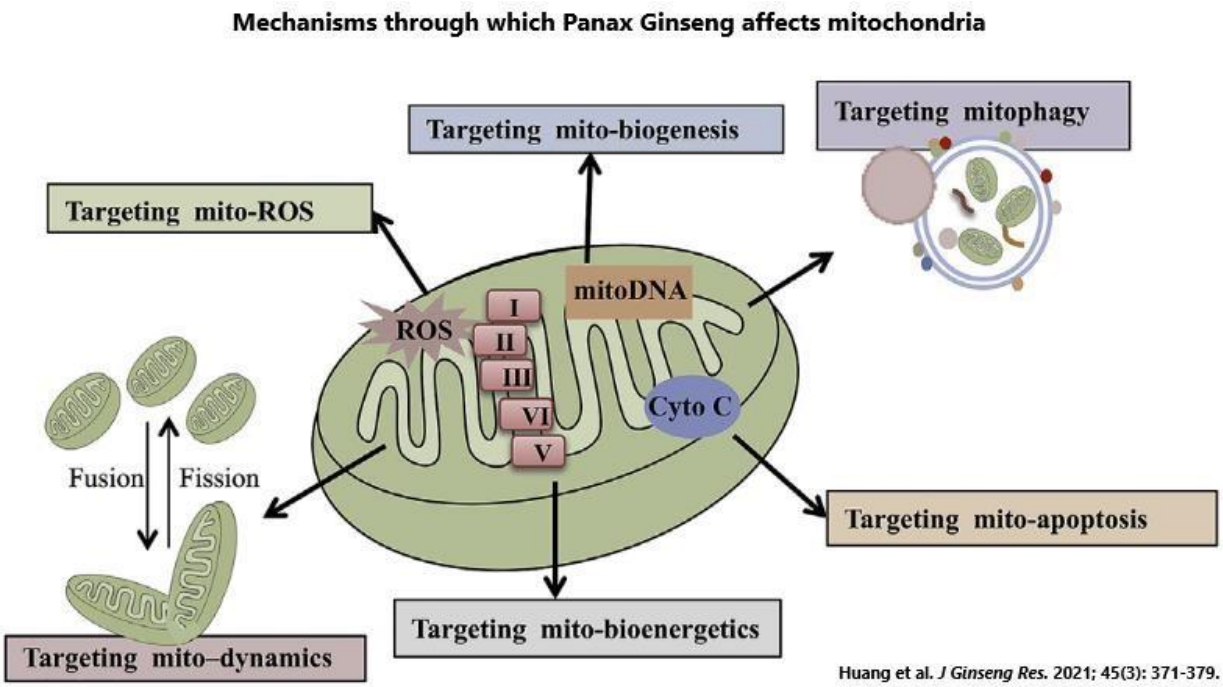
Recommended Dosing: Supplement with at least 50 mg of R-ALA per day to support mitochondrial function and upwards of 600 mg to support brain health. (Note: If using regular ALA, not R-ALA, much higher doses will be needed and some of the benefits may not materialize.)

Panax Ginseng

Panax ginseng has been used medicinally for thousands of years in China, Korea, and Japan to alleviate physical and mental fatigue. While there are several types of ginseng on the market, panax ginseng is considered the “true” ginseng.

At a fundamental level, panax ginseng works to protect mitochondria from oxidative damage and improve energy production under conditions of oxidative stress [213,214]. There are numerous ways it does so [215]:

- Reducing mitochondria-specific oxidative stress
- Stimulating mitochondrial biogenesis
- Enhancing mitophagy and targeted cell death protocols
- Increasing mitochondrial respiration
- Modulating mitochondrial dynamics (fusion-fission protocols)



Accordingly, a systematic review and meta-analysis of studies in chronic fatigue patients found that 200–2000 mg of panax ginseng per day was effective for reducing fatigue severity [216].

One study reported that supplementing with panax ginseng for just one month led to a 20% reduction in fatigue severity compared to a placebo [217], while another study reported a 20% fatigue reduction, increased levels of internal antioxidants like glutathione, and reduced biomarkers of oxidative stress [218].

Recommended Dosing: Supplement 200–2000 mg of panax ginseng per day.

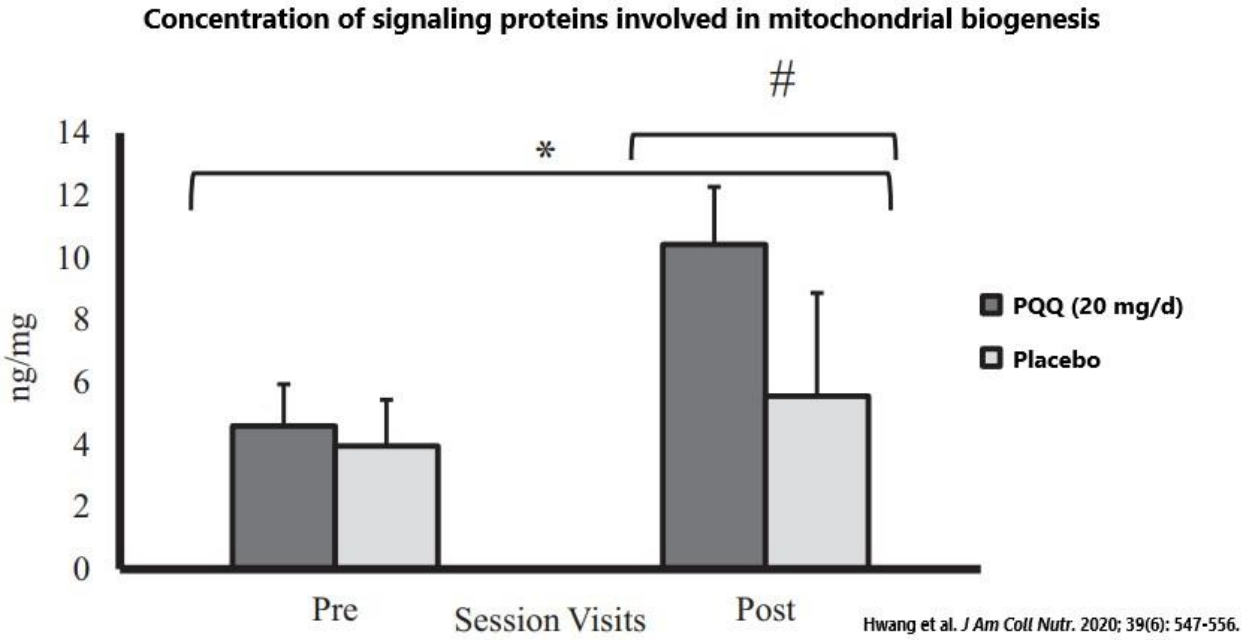
PQQ

Pyrroloquinoline Quinone (PQQ) is an antioxidant pseudovitamin, meaning it isn't essential for our survival but may be essential for optimal long-term health [219,220]. It's an incredibly potent and resilient antioxidant molecule, capable of neutralizing upwards of 20,000 free radicals before self-oxidizing, compared to 4 for vitamin C [221].

It's also a potent stimulator of pathways involved in mitochondrial biogenesis and energy production [222,223]. In particular, it stimulates pathways shared by

exercise training and is believed to potentiate and enhance activity-induced benefits on mitochondria [224].

At least one randomized controlled trial has supported this idea, showing that mitochondrial biogenesis signaling increased by 2.2-fold following 6 weeks of aerobic exercise training plus 20 mg per day of PQQ, compared to a mere 50% increase from training alone [225].



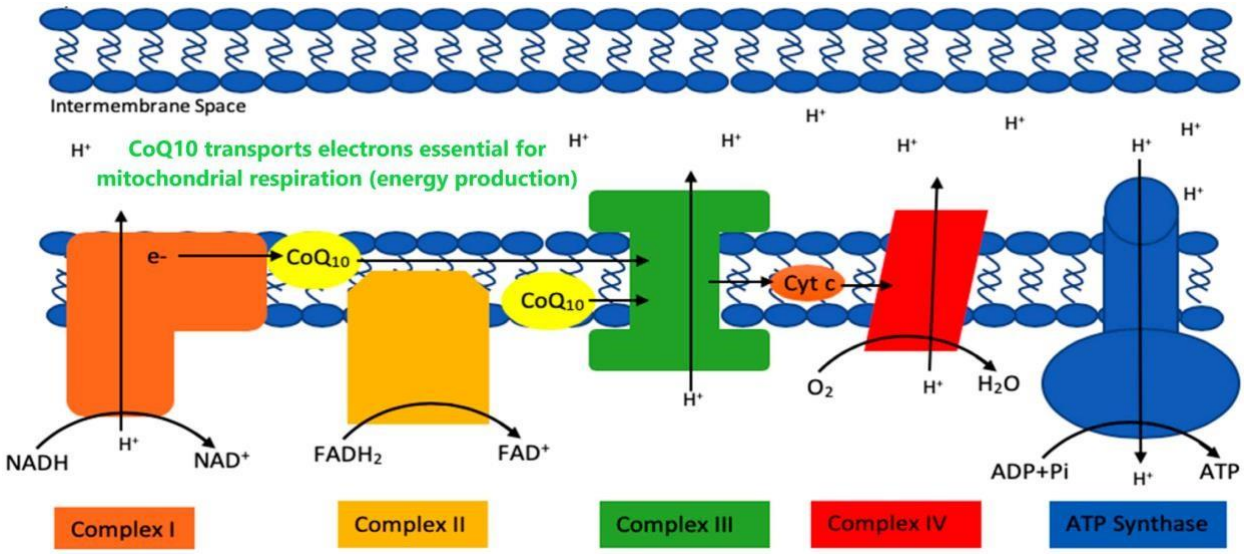
In another study of healthy adults, just three days of supplementing with 20–30 mg of PQQ reduced inflammation and improved markers of mitochondrial respiration [226]. Supplementing with 20 mg of PQQ daily has also been shown to reduce fatigue and increase vigor by 20%, as well as improve mood, sleep quality, and overall quality of life, in adults complaining of poor sleep and energy levels [227].

Lastly, several studies have reported that supplementing with 20 mg per day of PQQ improves cognitive function, particularly attention and working memory, and increases cerebral blood flow after three months [228–230].

Recommended Dosing: Supplement 10–30 mg of PQQ per day.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is an essential component of the electron transport chain through which mitochondria generate energy. It serves a dual purpose as an antioxidant within the chain and an energy-transferring molecule. As such, deficits in CoQ10 will not only lead to a cessation of energy production, but also an increase in oxidative damage.



Individuals with chronic fatigue regularly show deficiencies in CoQ10 concentrations throughout the body [24], as do those with conditions in which fatigue is a common symptom, like fibromyalgia [231–233], those who have survived heart attacks or heart failure [234,235], and multiple sclerosis [236,237].

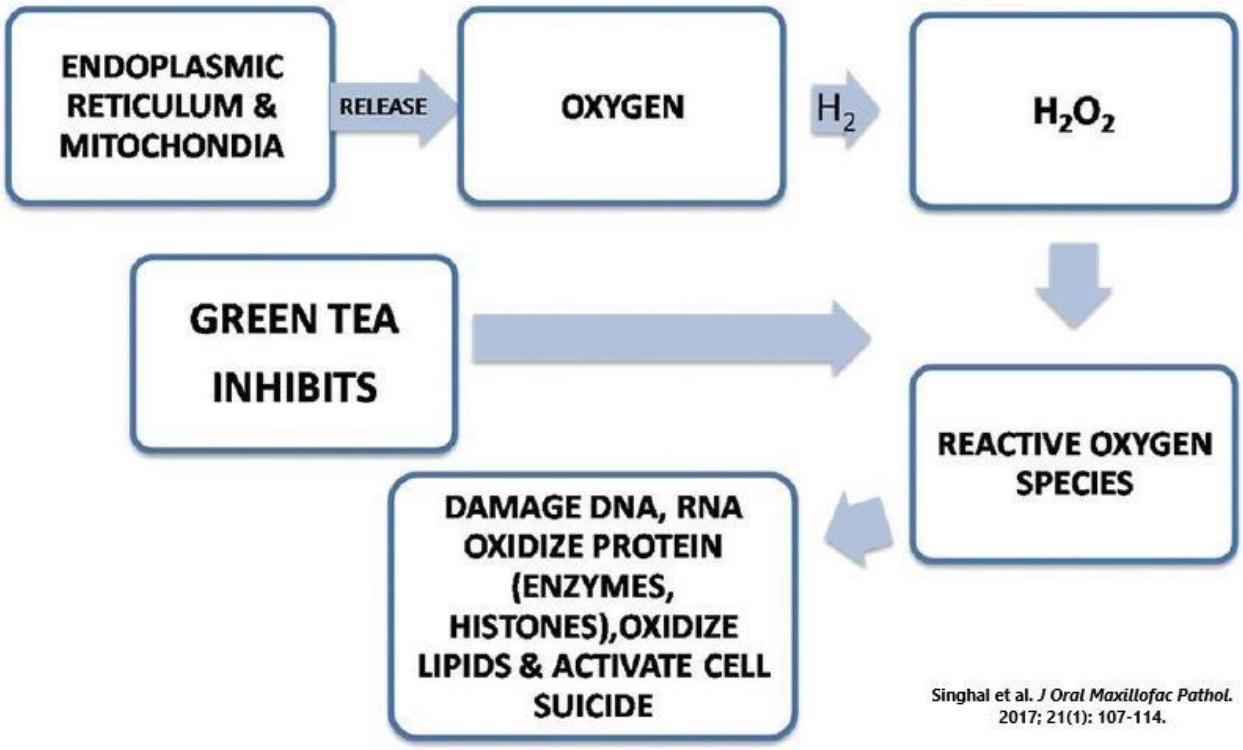
Just several months of supplementing with 150–300 mg of CoQ10 improves fatigue, autonomic nervous system activity (the part of the nervous system involved in rest and recovery), and biochemical parameters of mitochondrial energy production [238–241]. Even in healthy adults, CoQ10 supplementation improves general fatigue and reduces oxidative stress [242,243].

Recommended Dosing: Supplement 50–300 mg of CoQ10 per day.

Green Tea Catechins

Green tea is one of several teas made from the *Camellia Sinensis* plant, with the others being black, oolong, and white teas. The difference between them is simply how long the tea leaves are allowed to oxidize — green tea is the least oxidized.

Green tea catechins include 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 [244–246].



EGCG is neuroprotective [247,248], cardioprotective [249,250], anti-obesity [251–253], anti-carcinogenic [254,255], and anti-diabetic [256], all due primarily to its ability to stimulate mitochondrial biogenesis, enhance energy production, and protect mitochondria from oxidative stress [257,258].

Over the course of 12 weeks, daily supplementation with 280 mg of EGCG with 80 mg of resveratrol (a phytochemical found in grape skin) significantly increased the use of fat as an energy source and mitochondrial function (oxidative metabolism) compared to a placebo [259]. Moreover, several meta-

analyses of clinical trials have concluded that 100–500 mg of EGCG reduces body weight and body fat [260–263], particularly abdominal fat [264].

For reference, a single cup (8 ounces or 250 ml) of brewed green tea typically contains about 50–100 mg of EGCG, with variation from one cup of tea to another depending on many factors (species of tea, length of steeping, time spent oxidizing, etc.).

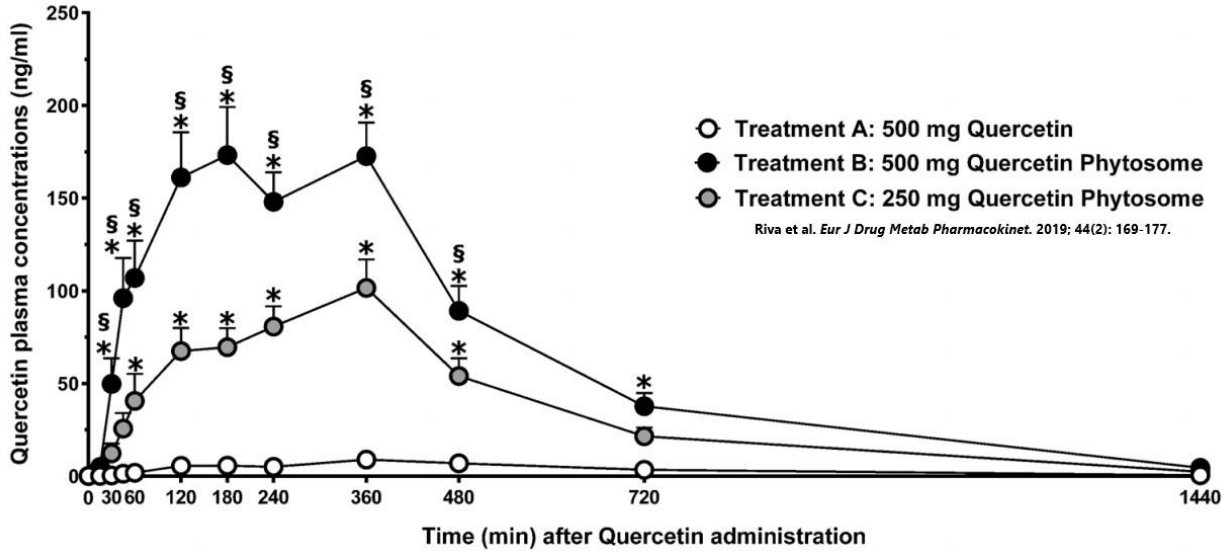
Recommended Dosing: Supplement 100–500 mg of EGCG per day.

Quercetin

Quercetin is a well known bioflavonoid found in many fruits and vegetables, particularly onions and apples. It is a potent antioxidant and antiinflammatory molecule that affects an array of mitochondrial processes, including mitochondrial biogenesis, mitochondrial energy production, and the protection of mitochondria from oxidative stress [265,266].

Several meta-analyses of clinical trials have reported that 500–1000 mg of quercetin taken daily is able to improve endurance exercise performance and maximal oxygen consumption [267,268], and, in those with metabolic dysfunction, reduce markers of inflammation [269,270], improve blood lipids [271–273], and lower blood pressure [274,275].

Importantly, these all use regular unenhanced quercetin. Yet, a quercetin phytosome complex has vastly superior bioavailability, leading to quercetin levels 20-fold greater in the blood following supplementation [276]. In other words, 50 mg of the phytosome is equivalent to 1000 mg of regular quercetin.



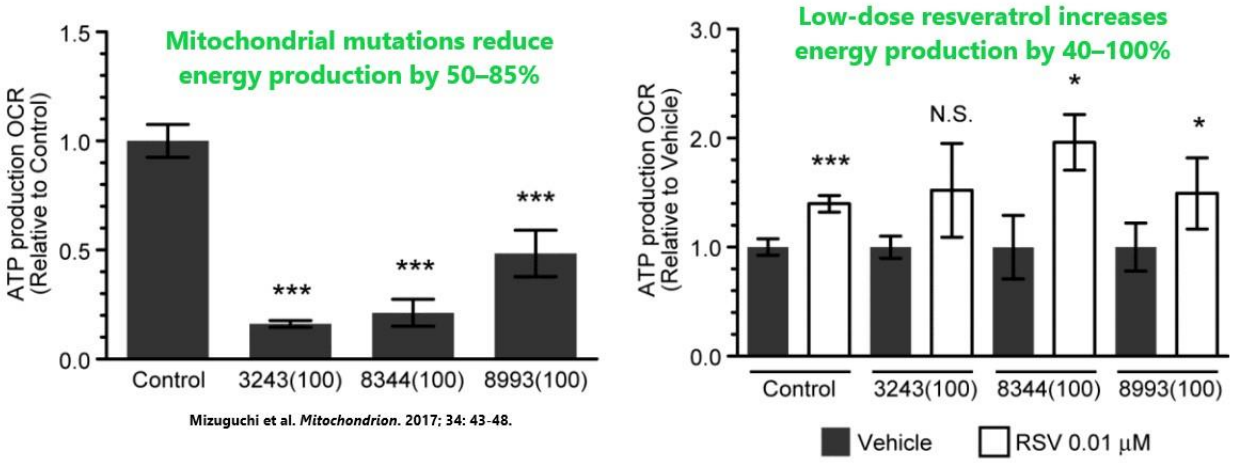
Recommended Dosing: Supplement 300–1000 mg of quercetin per day. Ideally, take the phytosome form, which has greatly improved bioavailability compared to the unenhanced version.

Resveratrol

Resveratrol is a phytochemical found primarily in grape skins and wine. It works primarily through hormesis; it stresses our mitochondria and stimulates adaptations that ultimately make them bigger and stronger. But only if you use enough and not too much.

For almost every outcome that resveratrol has been tested for, there's a hormetic relationship where too little has no effect and too much is either useless or harmful [277]. With mitochondria specifically, benefits are seen with just modest doses of resveratrol from a supplemental standpoint.

For example, energy production in both healthy and genetically mutated mitochondria is increased by 40–100% with a dose of resveratrol that corresponds to supplementing with just several hundred mg [278].



In a trial of adults carrying around excess fat mass, just one month of supplementing with 150 mg per day of resveratrol leads to significant increases in the activation of several mitochondrial regulators, including AMPK, SIRT1, and PGC-1α, while also increasing the ability of mitochondria to oxidize fat as an energy source [279].

Increases in SIRT1 and AMPK were also seen in adults with type 2 diabetes after supplementing with 3000 mg per day of resveratrol for 12 weeks, which coincided with an 8% increase in energy expenditure, likely from the increase in mitochondrial function [280].

Lastly, it's worth mentioning that resveratrol supplementation increases mitochondrial adaptations to exercise [281,282]. For example, in adults undergoing 12 weeks of resistance and endurance training, supplementing with 500 mg per day of resveratrol was superior to a placebo for improving aerobic fitness, muscular strength, size, and fatigue resistance, and mitochondrial density of skeletal muscle [281].

Recommended Dosing: Supplement 150–3000 mg of resveratrol per day.

Pomegranates

Pomegranate is a rich source of ellagitannins, potent antioxidants that can be further broken into other antioxidant compounds like ellagic acid and urolithins [283,284]. These substances have been heavily investigated for their cardiovascular, anti-cancer, and mitochondrial benefits.

Regular intake of pomegranate juice has been shown to reduce blood lipid oxidation and the accumulation of plaque in arteries over the course of 1–3 years [285], particularly in people who have higher levels of oxidative stress [286,287].

The most important benefit of pomegranates is their ability to stimulate mitochondrial function and mitophagy [288]. When ellagitannins are metabolized by the microbes in our gut, they produce a molecule called *urolithin A*, which is arguably the most potent stimulator of mitophagy ever discovered.

Mitophagy (mitochondria + autophagy) is a quality control pathway that preserves mitochondrial health by targeting damaged mitochondria for autophagic degradation, making anything that facilitates mitophagy absolutely vital for optimal health and disease prevention.

Animal studies have shown that urolithin A can induce profound extensions of lifespan of more than 45% in lower animals like worms, and 42% improvements in running endurance in rats (compared to rats not receiving urolithin A) [289]. Another study in rodents showed that urolithin A bolstered skeletal muscle energy content and stimulated mitochondrial biogenesis [290].

Studies in humans are starting to corroborate these initial findings in animals. For instance, supplementing with 500 and 1000 mg of urolithin A daily was able to alter skeletal muscle mitochondrial gene expression in a way indicative of improved mitochondrial function [291].

In recreational endurance athletes, supplementing with 750 mg of pomegranate extract for just two weeks increased the total time the athletes could cycle before complete exhaustion by 14% and increased the amount of time they could rely on their mitochondria to supply most of their energy by 10% [292].

Recommended Dosing: Supplement with at least 750 mg of pomegranate extract per day.

Spirulina

For centuries, natives living around Lake Chad in Africa have consumed spirulina, and it was an important trading commodity between the Aztecs of Central America and Spanish conquistadors [293]. Today it's popular in the New Age movement, and you can find it lining the shelves at many health food stores.

Spirulina's reputation is well-earned; it is one of the most powerful superfoods in existence, possessing amazing, evidence-backed benefits for metabolic health and energy production.

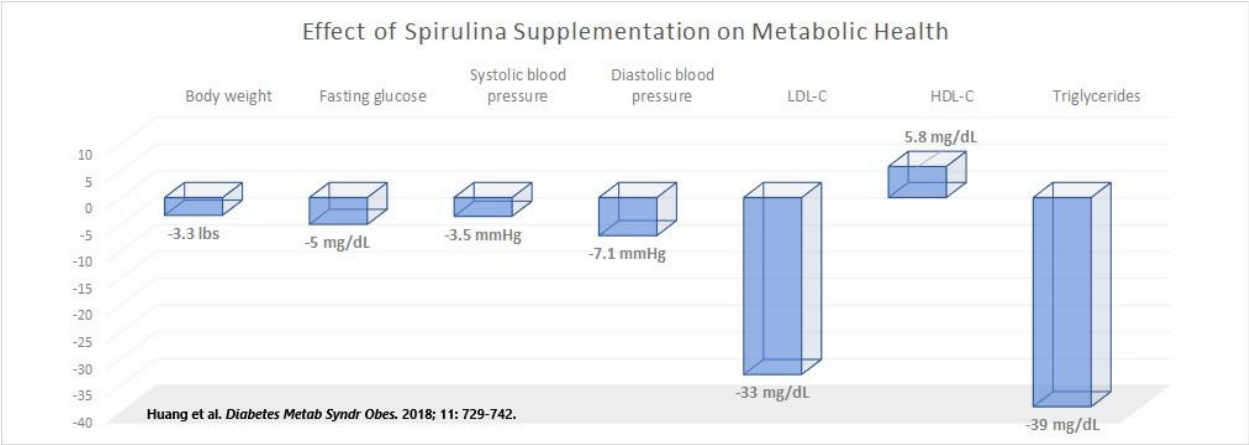
Several studies have shown that spirulina protects the heart, liver, and intestinal cells from oxidative stress and mitochondrial damage, stimulates mitochondrial biogenesis, and attenuates metabolic dysfunction [294–296]. These benefits are largely due to a little molecule it contains called CPhycocyanin, which could possibly be the most potent phytochemical in existence through mimicking the structure of bilirubin and having similar physiological effects [297,298].

People with genetically elevated levels of bilirubin, a condition called Gilbert's Syndrome, seem to have incredible metabolic health compared to those without:

- A 50% lower risk of death from any cause compared to the general population [299].
- A 60–80% lower risk of heart disease [300–302].
- A 20% lower risk of type 2 diabetes [303].
- Higher antioxidant status and less oxidative stress [304–306]. ● Improved blood vessel function [306]; and ● Longer telomeres [307].

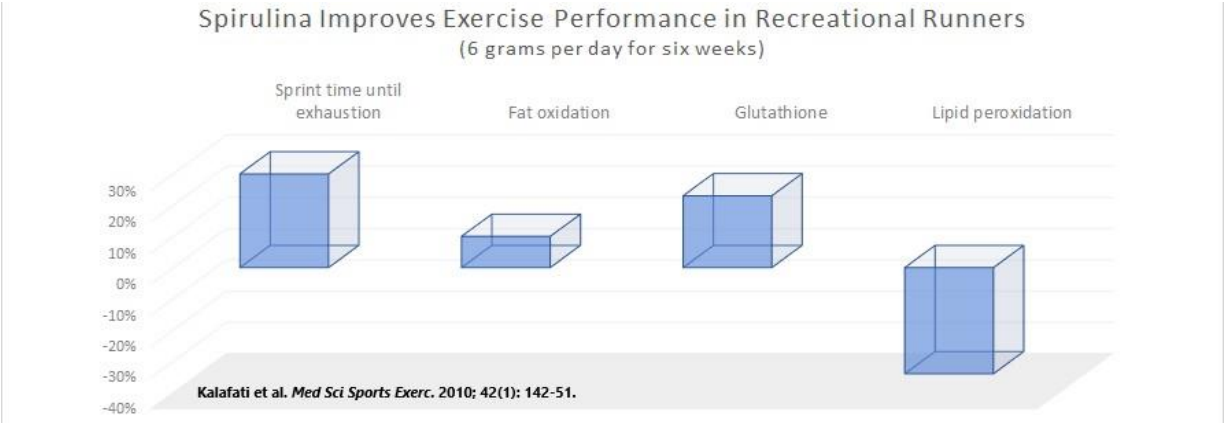
Bilirubin is a potent antioxidant and anti-inflammatory molecule that's been implicated in the prevention of metabolic syndrome and diabetes, cardiovascular diseases, and kidney disease [308–311].

Spirulina may confer many similar benefits due to supplying a bilirubin mimetic. For example, a meta-analysis of 12 studies involving adults with metabolic syndrome found that an average of just 2 grams per day of spirulina significantly lowered fasting glucose, blood pressure, and blood lipids after 2–3 months [312]. Notably, the average reduction in LDLcholesterol (33 mg per dayL) was nearly that achieved in a meta-analysis of statin trials (42 mg per dayL) [313].



On top of improving metabolic health, an abundance of evidence shows spirulina improves endurance exercise performance and reduces fatigue in both recreational athletes and the average joe looking to improve their health through exercise.

In one study, researchers had recreational runners run at a steady state for two hours and then do an all-out sprint for as long as they could handle it [314]. Compared to those taking a placebo, supplementing with 6 grams of spirulina per day for six weeks increased the sprint time until physical exhaustion by 30%, enhanced fat oxidation during the 2-hour run by 10%, increased glutathione concentrations by 23%, and reduced exercise-induced increases in lipid peroxidation by 34%.

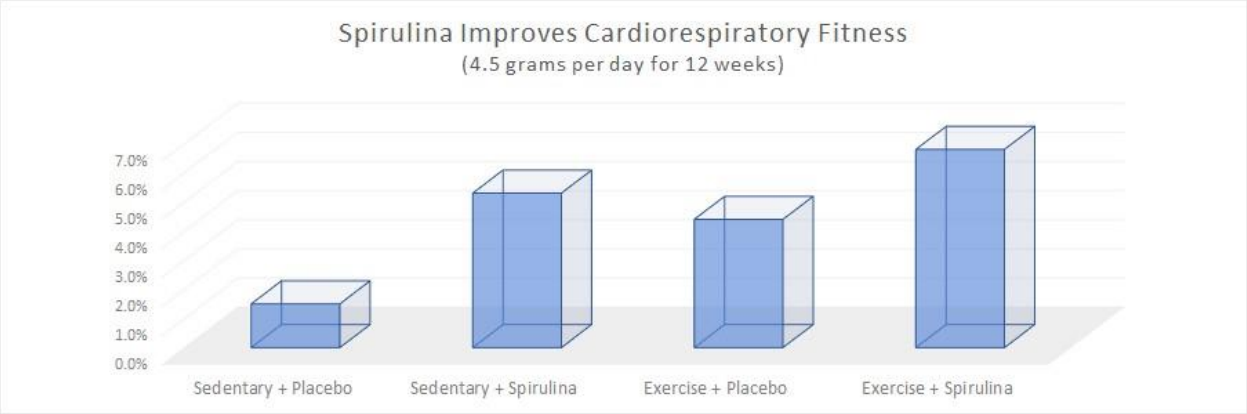


Other studies have reported similar observations. One found that that supplementing with 7.5 grams of spirulina increased the duration that the participants could exercise by 7.3% while reducing markers of oxidative stress

[315], and another reported that 3 grams of spirulina taken for 8 weeks reduced physical fatigue during exercise and mental fatigue afterwards [316].

Lastly, one group of researchers wanted to see how spirulina and exercise interact to affect the health of overweight and obese adults, so they divided participants into four groups for 12 weeks [317,318]. Each group supplemented with either 4.5 grams of spirulina or a placebo daily while undergoing an exercise routine or remaining sedentary.

They found that, regardless of whether the participants exercised or not, spirulina significantly reduced body weight, reduced blood lipids, and improved cardiorespiratory fitness. That being said, the improvements in cardiorespiratory fitness were most pronounced in those who supplemented alongside their exercise program.



Hernandez-Lepe et al. *Antioxidants (Basel)*. 2019; 8(11): 507.

Recommended Dosing: Supplement at least 2 grams of spirulina per day, ideally 6–8 grams.

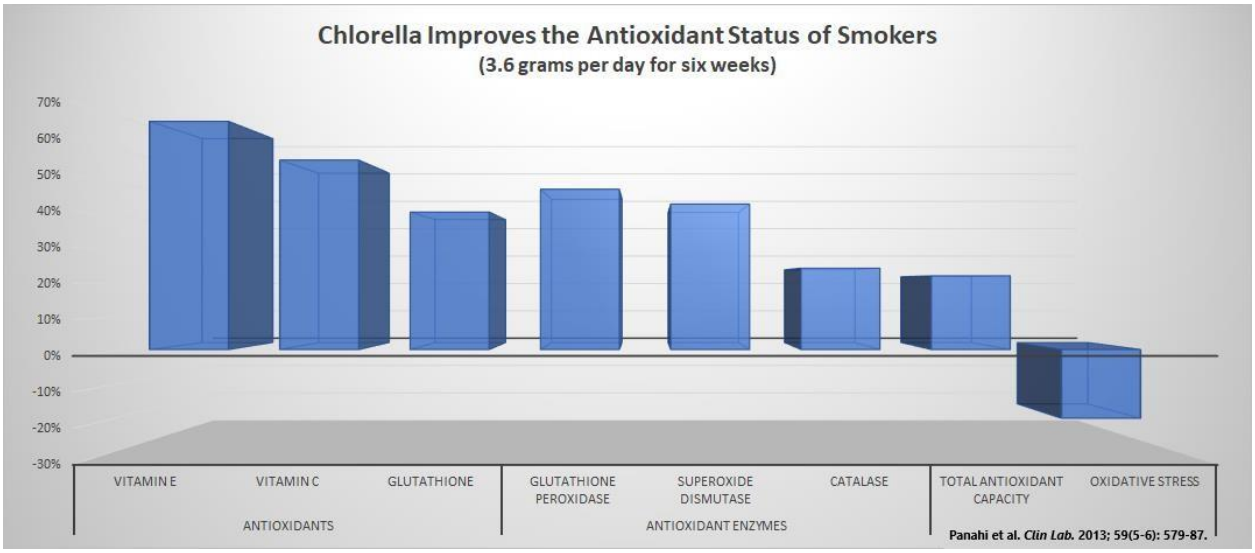
Chlorella

Chlorella is roughly 2.5 billion years old, belonging to some of the first single-celled organisms to inhabit our planet. In order to survive and replicate over that inconceivable span of time, this little algae needed to equip itself with some impressive defenses to protect against famine, drought, radiation, and poisoning.

It developed an impressive array of carotenoids, antioxidants, and enzymes to create energy, minimize oxidative stress, and neutralize toxicants, all housed

within a fibrous armor shell. When we eat chlorella, it passes on many of these defenses to us [319], and it does so with relatively small doses.

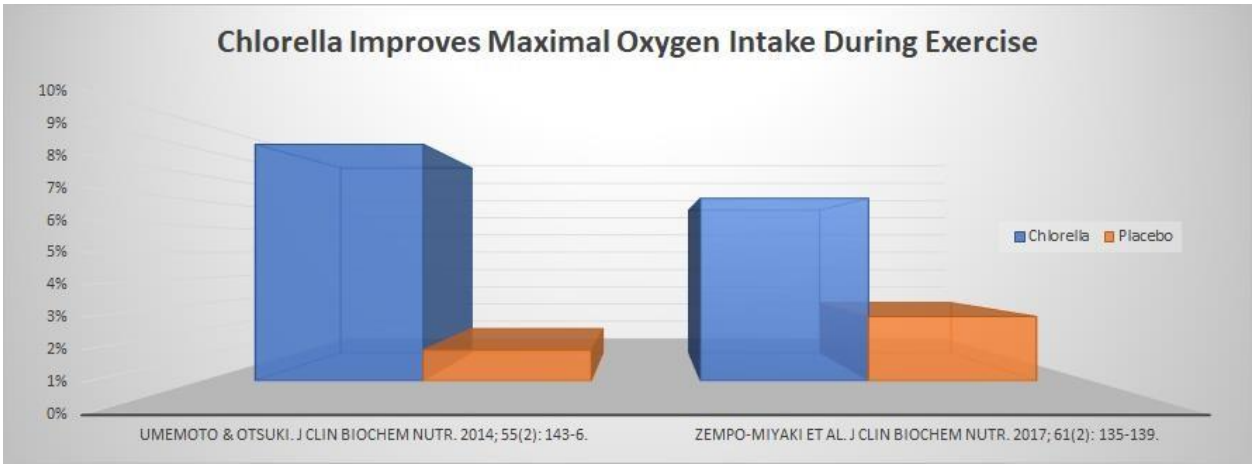
For example, let's say you were a smoker, someone puffing on more than 20 cigarettes per day. Supplementing with just 3.6 grams of chlorella for six weeks has been shown to increase every single tested marker of antioxidant status in these smokers while cutting levels of oxidative stress by 20% [320].



The ability of chlorella to improve one's antioxidant status has been shown in other studies as well, another in smokers using 6.3 grams per day [321], and one in patients with chronic obstructive pulmonary disease (COPD) using just 2.7 grams per day [322].

Now, reductions in systemic oxidative stress can benefit health in a variety of ways, with one of the best-known being improvements in cardiometabolic health. And that's exactly what we see with chlorella supplementation. A meta-analysis of 19 randomized controlled trials reported that supplementing with an average of just 4 grams per day of chlorella significantly reduced LDL-C, blood pressure, and fasting blood glucose after an average of 2 months [323].

Lastly, there's data supporting an energy-boosting effect of chlorella. For example, in young men, supplementing with 6 grams of chlorella daily for one month increased VO_2max by about 7% [324,325]. VO_2max is a measurement of the maximal amount of oxygen that a person can utilize during intense exercise and is an established marker of one's aerobic fitness and mitochondrial function.



And this plays out in people struggling with chronic fatigue too. In adults with fibromyalgia, supplementing with 10 grams of chlorella plus a liquid chlorella extract daily for two months significantly reduced the number of tender muscle points by 8% and pain intensity by 22% [326]. The participants also reported improvements in most of their fibromyalgia symptoms, like general wellbeing and ability to be active.

When the researchers conducted a follow-up study comparing chlorella to a placebo, they saw largely similar results — reductions in the number of tender points and pain severity, along with a 20% reduction in fibromyalgia symptoms [327].

Recommended Dosing: Supplement at least 500 mg of chlorella per day.

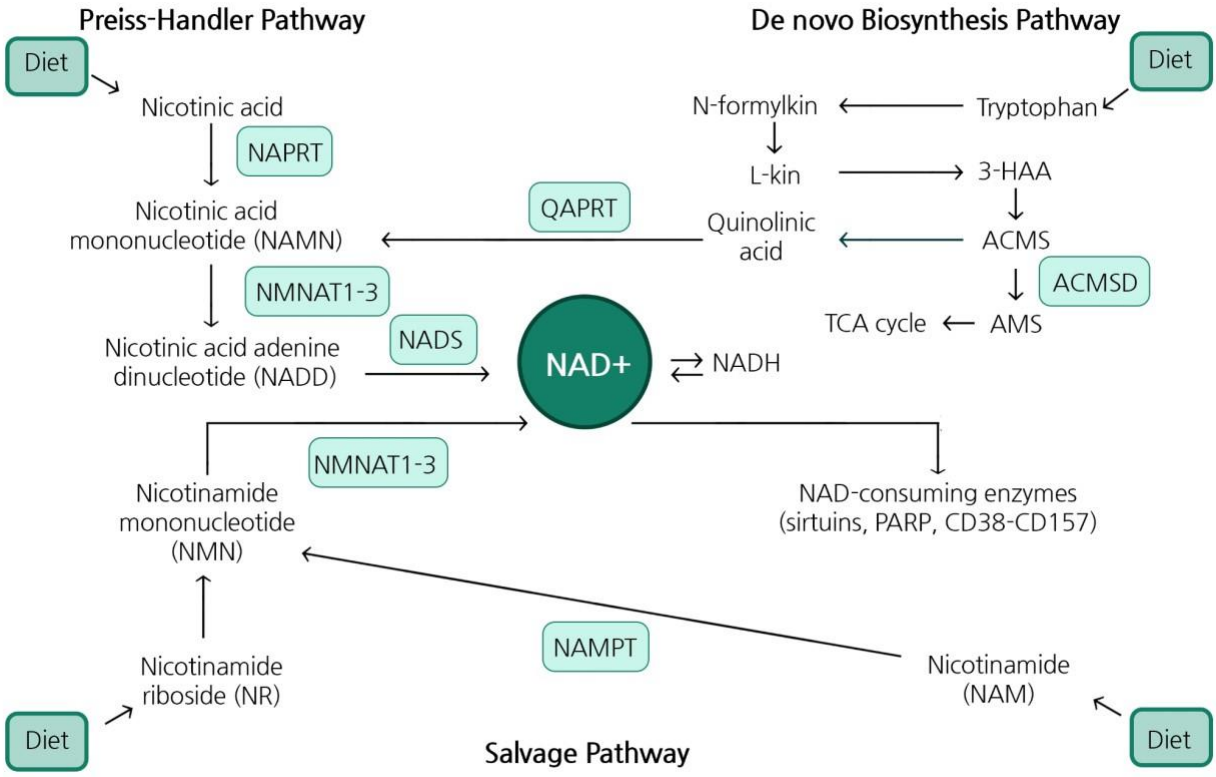
Niacin Derivatives

In mitochondrial respiration, a molecule called *NAD+* is absolutely essential for the generation of energy. You literally can't turn carbohydrates or fats into cellular energy without it. Yet, people with chronic fatigue have lower levels compared to healthy non-fatigued adults [328].

A lot of anti-aging and energy-enhancing research has gone into looking at ways to increase NAD+ concentrations as a means of restoring mitochondrial function. Since NAD+ is made from the essential vitamin *niacin*, there has been a growing

interest in supplementing with niacin and its derivatives for increasing NAD+ levels.

One of the most popular compounds in this regard is *nicotinamide riboside* (NR). There are several pathways that our body uses to synthesize NAD+: *de novo biosynthesis*, *Preiss-Handler* pathway, and *Salvage* pathway. However, each of these pathways has a rate-limiting enzyme that is inhibited when NAD+ concentrations exceed a certain threshold [329].



This is where NR comes into play. Isotopic tracer studies in mice have suggested that the salvage pathway is the primary route of NAD+ synthesis in most tissues, including skeletal muscle, the heart, and the brain [330]. NR directly bypasses the rate-limiting step of NAD+ synthesis through the salvage pathway.

Moreover, both nicotinic acid and niacinamide play many roles in the body and may be sequestered away from NAD+ production depending on the body's needs, whereas NR must be converted into NAD+ before it can be used for other processes that require niacin.

While there has been a lot of hype surrounding these molecules, *the research in humans has not shown benefits.*

Studies using 500–2000 mg of NR per day in healthy adults [331], elderly adults [332,333], and obese adults [334–337] show no appreciable effect on NAD+ concentrations in muscle tissue or several parameters of mitochondrial function, including energy production. A variety of health parameters were also unaffected, including energy expenditure, body composition, glycemic control, insulin sensitivity, exercise performance, or blood lipids.

Recommended Dosing: We do not recommend supplementing with nicotinamide riboside, given the large expense and that the evidence doesn't show significant benefits. We do however advise ensuring adequate intake of niacin.

Glucosamine Sulfate

If there were to ever be a competition of unexpected supplement effects, I think glucosamine would take the top spot. This fascinating little molecule made its way from crustacean exoskeletons and fungi to supplement shelves in the name of joint health, but that's its least interesting benefit.

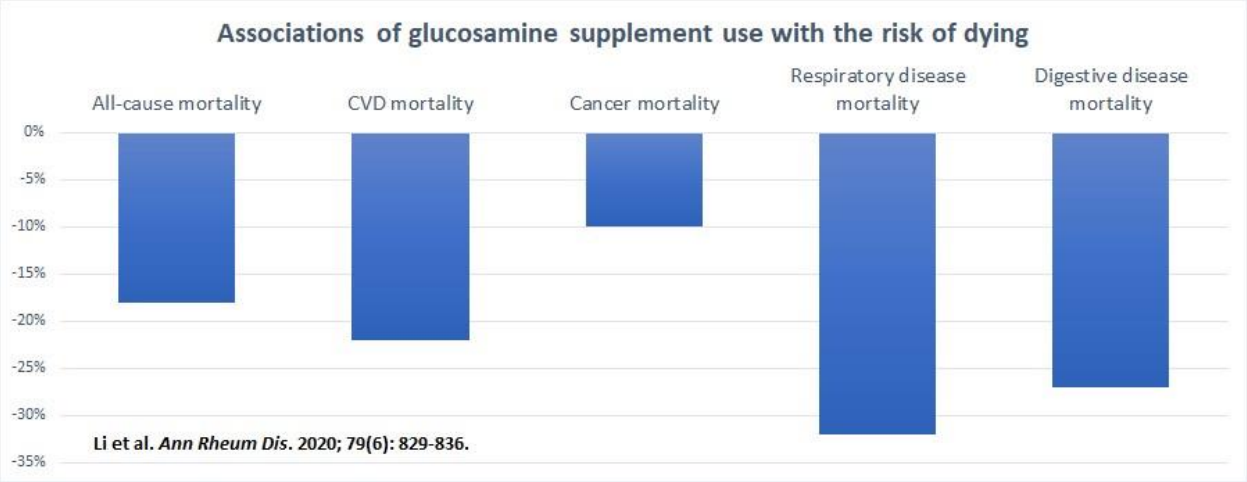
Far less known is that **glucosamine may very well be one of the safest and most powerful longevity supplements available**, and the clues have been there for at least a decade [338].

In 2010, researchers evaluated the relationship between 20 unique supplements and all-cause mortality among nearly 78,000 Washington state residents over 50 years old [339]. While several trends were identified, **only regular use of glucosamine, chondroitin, and fish oil were associated with a lower risk of dying from any cause — each by about 17%**.

Intrigued by these findings, the researchers conducted a follow-up study to identify any nuances of this unexpected relationship with glucosamine [340]. Using the same cohort of Washington state residents, they found that **glucosamine use was associated with not just an 18% lower risk of**

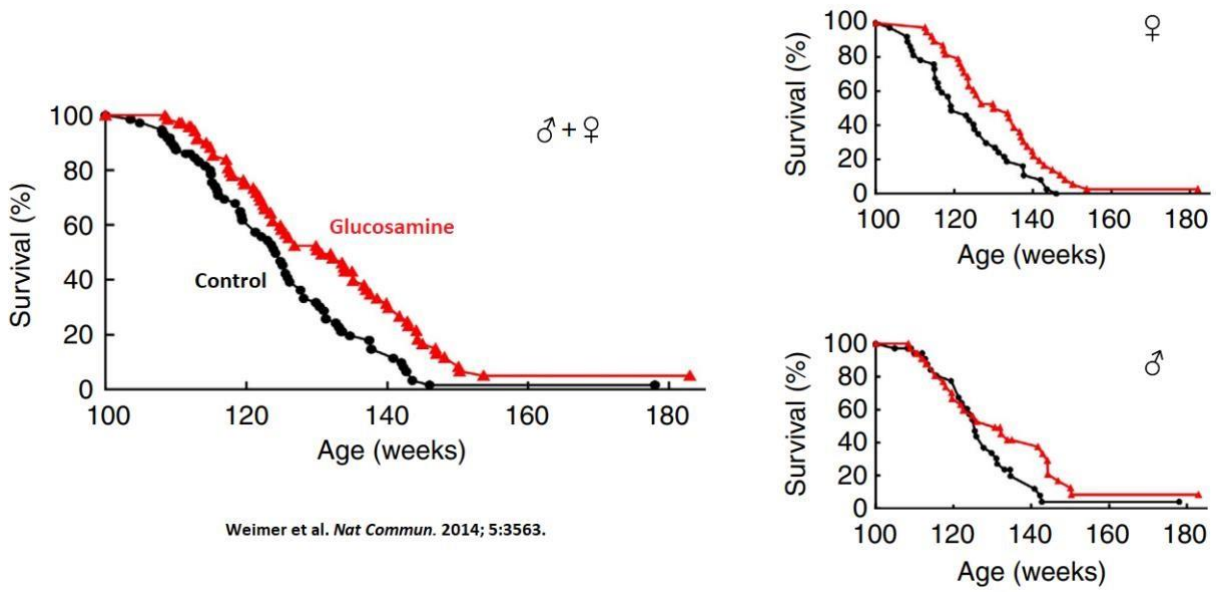
dying from any cause, but a 13% lower risk of dying from cancer and 41% lower risk of dying from a respiratory disease.

The most recent and largest study confirmed all of this with data from a half-million UK residents over 40 years old [341]. **Glucosamine supplementation was associated with a 10–32% reduction in dying from any cause**, cardiovascular diseases, cancer, respiratory diseases, and digestive diseases. These relationships persisted even when stratifying the data by several known risk factors, such as age, sex, smoking, alcohol, physical activity, and metabolic health.



How can a simple joint health supplement be one of the only compounds to consistently associate with a lower risk of dying? That answer comes from a landmark study out of Germany, in which researchers set out to determine if glucosamine supplementation would affect the lifespan of mice and worms and through what mechanisms [342].

They had mice consume glucosamine every day starting in old age (~70 years for a human), and they found that both average and maximal lifespan were increased by 5–10% compared to otherwise identical mice that didn't receive any glucosamine. While the effect tended to be more pronounced in females than males, both sexes unambiguously benefited.



Further extensive analysis of mice, worms, and cell cultures revealed that glucosamine likely had these longevity effects by **inhibiting the use of glucose as an energy source, leading to increased AMPK signaling, mitochondrial respiration, and mitochondrial biogenesis**.

In other words, regular glucosamine supplementation cuts off mitochondria from one of their primary fuels to make energy, **forcing them to adapt by increasing the number of mitochondria and their ability to make energy from fatty acids and amino acids**.

When the researchers blocked any of these effects from occurring through either genetic manipulation or the use of specific drugs, the longevity effects of glucosamine disappeared.

This isn't something new. It's been known for a long time that aging is associated with reductions in mitochondrial respiration and an accumulation of dysfunctional mitochondria, and that a common theme of lifespan extending interventions is their ability to increase the number of healthy mitochondria via promoting biogenesis [343].

Other avenues of research support these observations. For example, glucosamine is a potent inhibitor of the NLRP3 inflammasome, which activates in response to cellular damage and infection [344]. One of the ways it has this

inhibitory effect is by preserving mitochondrial function in the face of these stressors.

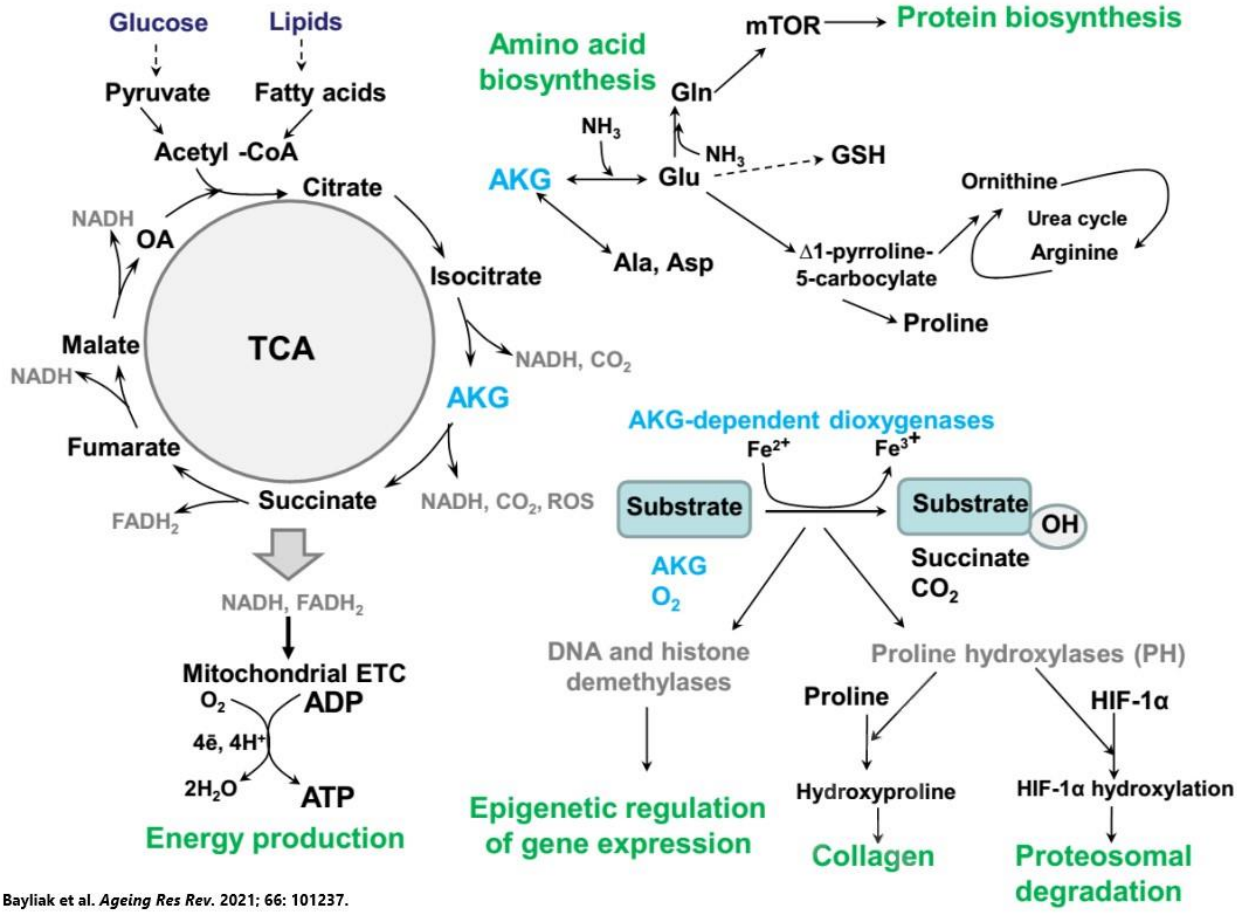
Recommended Dosing: Supplement 500–1500 mg of glucosamine sulfate per day.

Calcium AKG

One of the most important molecules for your health and longevity is something you've probably never heard of: Alpha-ketoglutarate (AKG). It's involved in numerous metabolic and regulatory pathways essential for cellular function [345]:

- Energy production
- Amino acid biosynthesis
- Collagen biosynthesis
- Gene expression
- Redox balance ● Detoxification

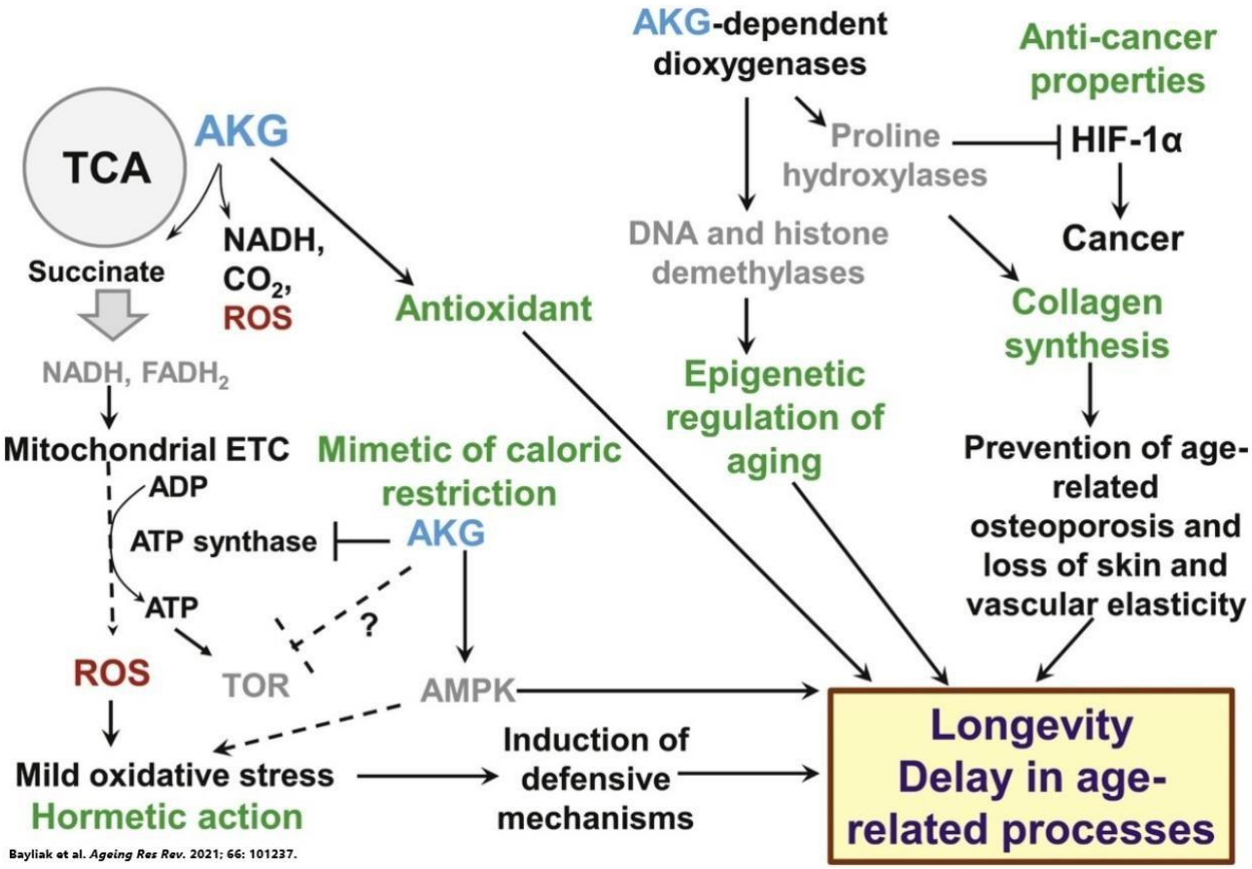
All of these functions start within the tricarboxylic acid (TCA) cycle of our mitochondria, which produces the electron carrying molecules necessary for the electron transport chain to produce cellular energy.



Bayliak et al. *Ageing Res Rev.* 2021; 66: 101237.

AKG is first and foremost a TCA cycle intermediate, produced from glucose, fatty acids, and amino acids as the cycle turns to facilitate mitochondrial energy production. However, it can also be taken away from the TCA cycle and used to synthesize amino acids necessary for protein synthesis or used as a cofactor by enzymes necessary for gene expression, collagen synthesis, and cell death processes.

It's through each of these processes that AKG is believed to be a true antiaging molecule. It has a hormetic effect on mitochondria that promotes cell survival adaptations, much like what occurs with calorie restriction, it has direct antioxidant effects, it makes DNA more youthful, it helps stave off cancer, and it supports the maintenance of our collagen scaffolding.



AKG is a critical regulator of energy production within mitochondria. The enzyme responsible for using AKG to perpetuate the TCA cycle is the slowest of all the TCA cycle enzymes, meaning that the cycle can spin only as fast as this enzyme works [346].

The two primary determinants of how quickly this enzyme works are AKG concentrations and oxidative stress [347]. Increasing AKG concentrations enhance the enzyme's activity while higher levels of oxidative stress inhibit it. Supplementing AKG has been shown to reduce oxidative stress and increase overall antioxidant capacity of cells [348], thereby hitting two birds with one stone and enhancing the rate of TCA cycle operation.

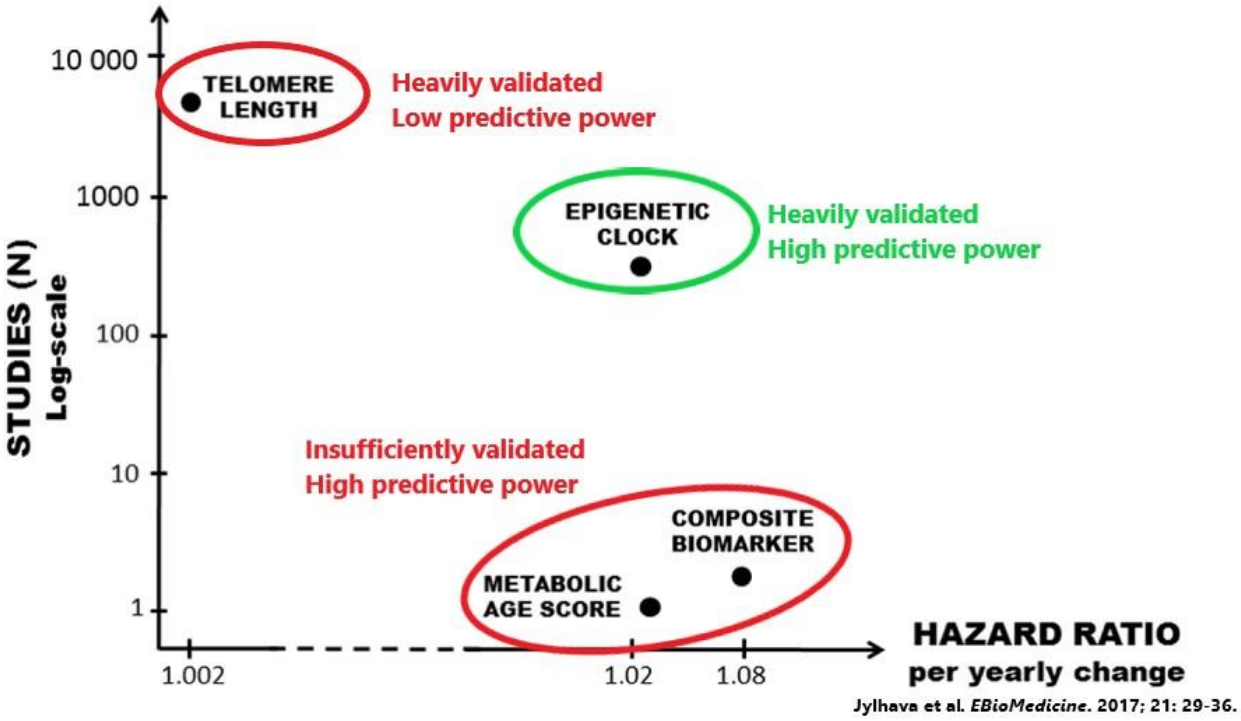
Yet, somewhat ironically, enhanced energy production itself creates more oxidative stress that mitochondria must deal with. AKG itself also binds to and inhibits the primary energy production enzyme ATPsynthase [349]. Both effects force mitochondria to adapt and increase their resilience, making them become stronger and more energy efficient.

The end result, as has been observed in fruit flies and worms, is an upregulation of pathways involved in mitochondrial mitophagy and biogenesis, and a longer lifespan [350,351]. These effects are the exact same as chronic dietary restriction, and AKG may actually be the key molecule that dietary restriction affects in order to extend lifespan.

Virtually all research relies on chronological age for determining what participants to include, how age groups differ in their risk of various diseases, and so forth. Yet, two persons could be the exact same age and have vastly different health states or be born decades apart and have the same health risks.

Chronological age is better than nothing, but it's flawed. The past several decades have been filled with research looking at how we can better determine someone's true biological age, and the best predictor we currently have is one's rate of DNA methylation — what researchers have deemed the epigenetic clock [352].

DNA methylation has hundreds of studies validating its use as a biomarker for biological aging and has great predictive power for mortality. Comparatively, telomere length has thousands of validating studies but is virtually useless for predicting one's risk of death, and other biomarkers simply haven't been independently validated sufficiently. This could change with time.

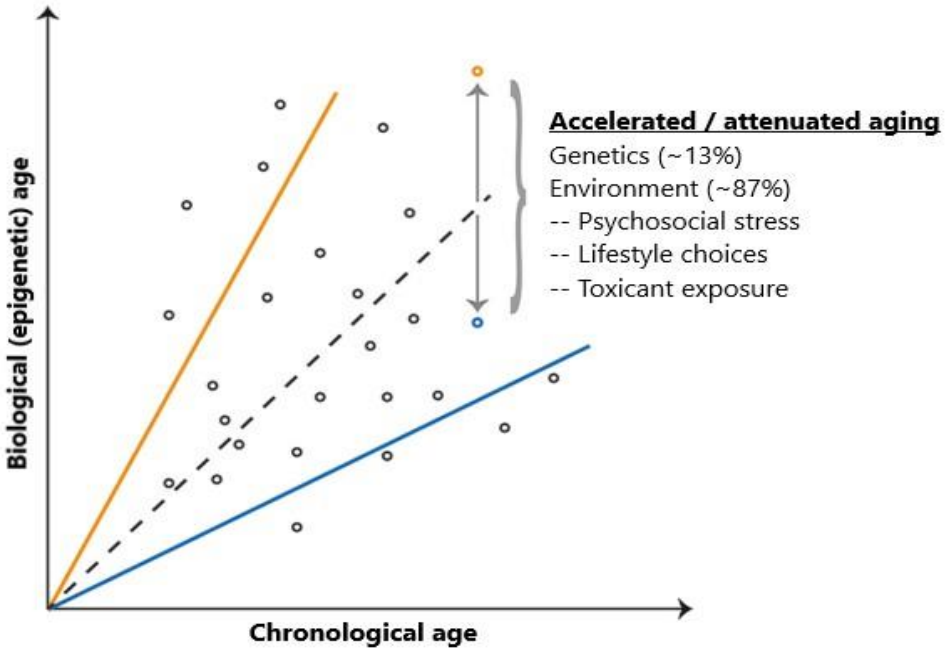


Several meta-analyses have found that epigenetic age is an independent predictor of one's risk of death above-and-beyond other established risk factors like chronological age, BMI, alcohol intake, smoking status, physical activity, and several chronic diseases [353–355]. According to these analyses, every 5-year increase in epigenetic age is associated with an 8– 16% greater risk of dying from any cause.

Numerous studies have also linked an older epigenetic age to the development of many common chronic diseases that affect older populations:

- Frailty [356,357]
- Physical decline [358]
- Osteoarthritis [359]
- Cognitive decline [360]
- Alzheimer's disease [361,362]
- Cancer [363,364]
- Cardiovascular disease [365]
- Type 2 diabetes [366]

The best part of all of this is that you have a tremendous amount of control over your epigenetic age. An analysis of twins, parents, and spouses found that genetic factors explained just 13% of the variation in epigenetic age, meaning that the strongest influence comes from environmental factors [367].



All of this is to say that your life lived, rather than your genetics, is the primary determinant of your biological age. What you experience, and how you respond to those experiences, can be the reason you have a heart attack at 40 or live to see 100.

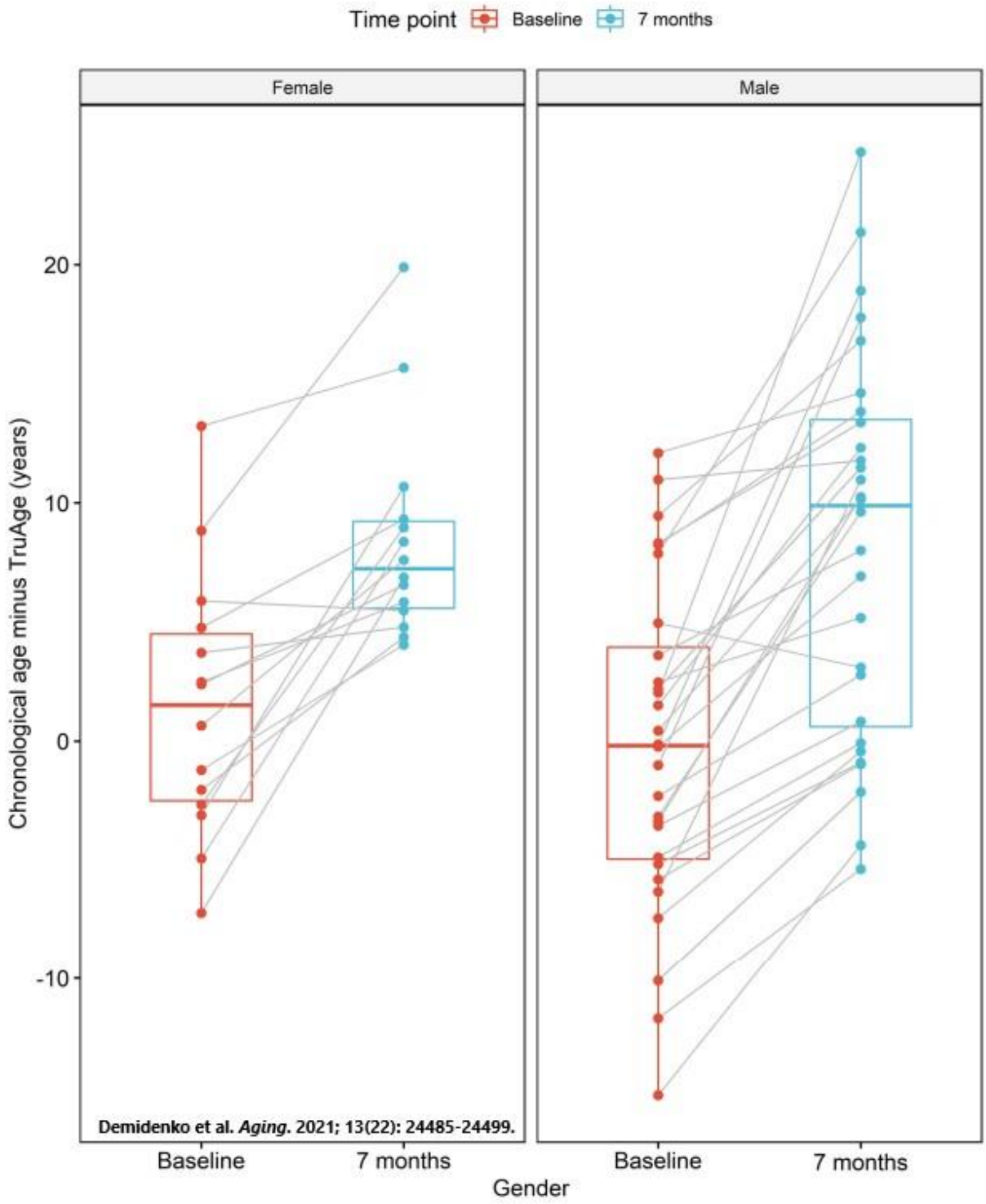
Supplementing with AKG is one of those life decisions that you can make.

In humans, plasma AKG levels decline 10-fold between the ages of 40 and 80 years [368], and this decline with aging is accompanied by consistent increases in DNA methylation at sites necessary for stem cell activation and differentiation [369,370].

Stem cells, which are like blank slates ready to become whatever the body needs, contain a very limited amount of AKG despite an incredibly high demand for its actions on gene expression, making AKG the rate-limiting factor for stem cell differentiation [371].

Aging simply exacerbates this AKG insufficiency.

In the first of its kind clinical trial, researchers had 42 middle-aged and elderly adults (40–80 years old) supplement with 1000 mg of calcium AKG daily for six months [372]. That was it, and this small intervention **reduced their biological age by nearly 8 years!**


Time point
Baseline
7 months
Female
Male
Chronological age minus TruAge (years)
20
10
0
-10
Demidenko et al. Aging. 2021; 13(22): 24485-24499.
Baseline
7 months
Baseline
7 months
Gender

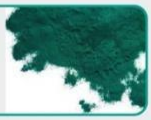
These findings are supported by a study done with mice, where administering calcium AKG reduced several biomarkers of chronic inflammation, reduced frailty ratings by 40%, and extended lifespan by 10– 20% [373,374].

In other research, supplementing obese mice with AKG increases circulating AKG concentrations and enhances the differentiation of new fat cells into a more metabolically active phenotype [375]. These mice were also protected from some of the fat gain and insulin resistance experienced by nonsupplemented mice.

Recommended Dosing: Supplement 1000 mg of calcium AKG per day.

25 TOP SUPPLEMENTS FOR ENERGY AND MITOCHONDRIAL OPTIMIZATION

ENERGY BLUEPRINT LABS

- NTFactor® Phospholipid Complex 
- Creatine Monohydrate 
- Acetyl-L-Carnitine 
- Methylation Support
  - Folate 
  - Vitamin B6 
  - Riboflavin 
  - Betaine 
  - Vitamin B12 
- Taurine 
- Astaxanthin 
- N-Acetyl-Cysteine 
- D-Ribose 
- Alpha-Lipoic Acid (Ideally R-ALA) 
- Panax Ginseng 
- Calcium AKG 
- PQQ 
- Coenzyme Q10 
- Green Tea Catechins 
- Quercetin 
- Resveratrol 
- Pomegranates 
- Spirulina 
- Chlorella 
- Niacin Derivatives 
- Glucosamine Sulfate 

18 Best Nootropics For Optimizing Mood, Brain Performance, and LongTerm Brain Health

What would you think if someone told you that taking a pill could make you feel smarter, sharper, and more creative? What if they told you a pill could maintain those feelings throughout your life? Would you call BS?

Those pills exist!

They're called nootropics and include an array of compounds that either improve cognitive function, particularly executive function, memory, focus, and the ability to work under stressful conditions, or prevent cognitive decline.

While the best-known examples include synthetic drugs like adderall, modafinil, and piracetam, there are numerous herbs and naturally occurring molecules that possess similar properties while being far safer, especially with long-term use.

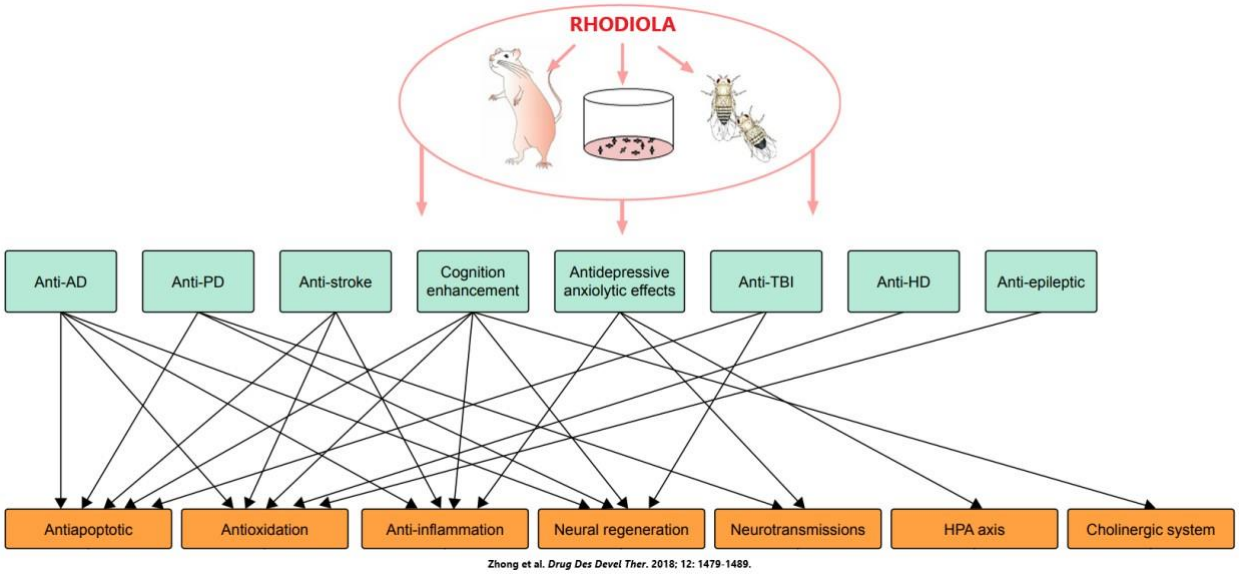
These brain-boosting supplements work through a variety of mechanisms to improve brain health and functionality [376–378] including:

- Increase blood flow and nutrient delivery to brain cells.
- Reduce neuroinflammation and oxidative stress.
- Bolster mitochondrial function and energy production.
- Facilitate the removal of neurotoxins.
- Promote the growth of neurons.
- Improve neuronal communication and synaptic plasticity; and ● Optimize neurotransmitter levels.

The following supplements are some of the most powerful brain-boosting compounds in existence. They can help you fight brain fog, become more vigilant, maintain cognitive performance, and ensure your mind is fully functional, which will contribute to improved energy levels too.

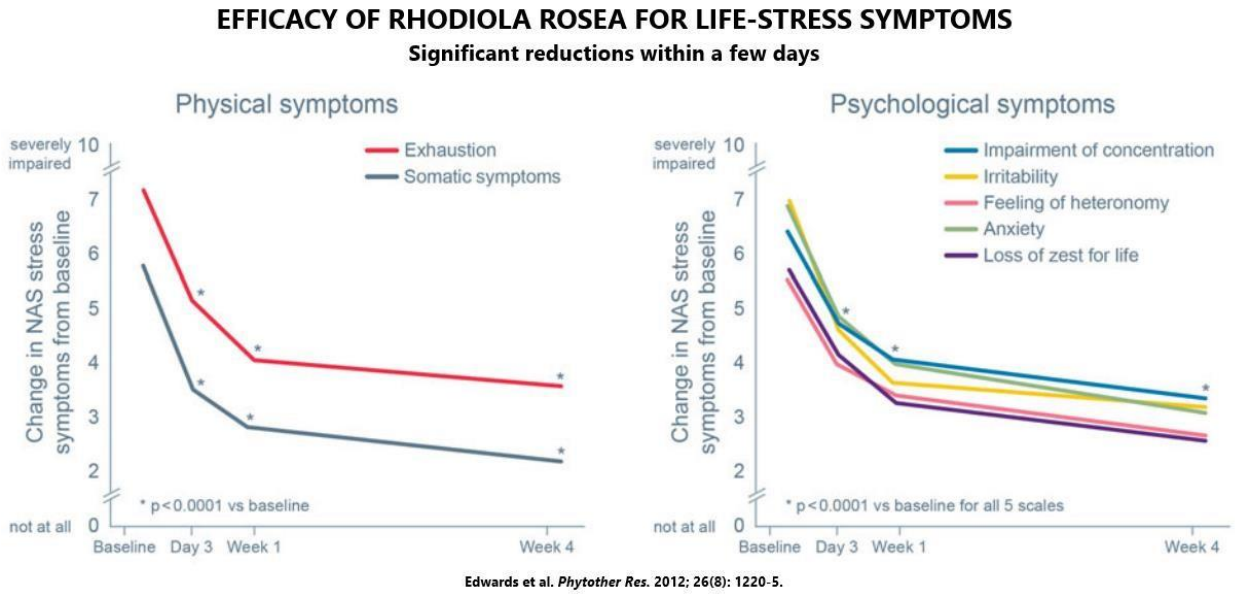
Rhodiola Rosea

Rhodiola rosea is a medicinal herb traditionally used for enhancing mental performance and resilience to stress [379], effects that are due to the numerous ways rhodiola interacts with genes, signaling pathways, and molecular networks within the brain to alter emotional behavior [380].



Specifically, rhodiola acts within the brain as a neuroprotective, cognitive enhancing, and mood stabilizing agent through reducing neuronal cell death and promoting regeneration, functioning as an antioxidant and antiinflammatory, facilitating neurotransmission, and regulating several key mediators of the stress response within the hypothalamic-pituitary axis [381–383].

It’s an incredibly powerful adaptogen, with effects noticed soon after supplementation. In one study of over 100 adults dealing with chronic stress, supplementing with 400 mg per day of rhodiola reduced feelings of physical exhaustion, difficulty concentrating, and anxiety after as few as three days, nearly *cutting them in half* after just one week [384].



Similarly, in adults with chronic fatigue, 400 mg of rhodiola per day improved every aspect of fatigue after just 1 week, with further improvements seen after 8 weeks [385]. Ultimately, 83% of the participants reported "very much" or "much" improved conditions, with fatigue, stress, anxiety, and brain fog being *cut in half!*

Several other studies have also shown that supplementing with 100–400 mg of rhodiola improves physical and mental energy, reduces stress, and ultimately improves quality of life in adults struggling with job burnout [386], first-year medical students [387], military cadets [388], and adults with stress-related fatigue [389].

Recommended Dosing: Supplement 100–400 mg of rhodiola per day.

Lion's Mane Powder

Lion's mane mushroom (also called *Yamabushitake* or *Hericium erinaceus*) is a medicinal mushroom that has been extensively studied for its neurohealth properties [390,391]. Research has shown that lion's mane:

- Stimulates the production of Nerve Growth Factor (NGF) [392–394], which promotes neuronal growth, development, and regeneration [395].

- Restores levels of key neurotransmitters serotonin, noradrenaline, and dopamine in the brain (that are often suppressed due to chronic stress) [396].

- Reduces neuroinflammation [396,397]; and

- Stimulates the expression of brain derived neurotrophic factor (BDNF) [396], which has neuroprotective effects, plays a role in neuronal development, and helps in the formation of neuronal connections important for memory and cognition [398].

Studies in mice have demonstrated that these effects ultimately lend lion's mane cognitive-enhancing [399], neuroprotective [400], and moodstabilizing properties [396].

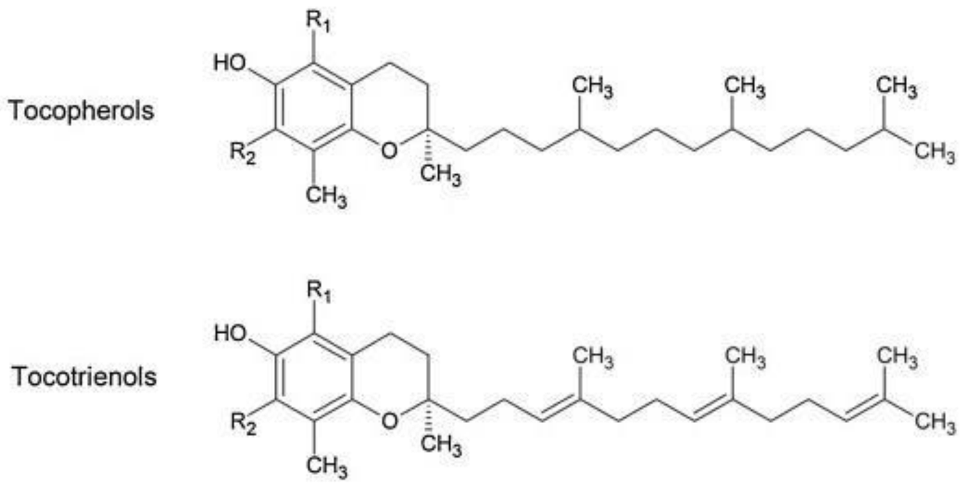
In men with mild cognitive impairment, 3000 mg per day improved cognitive function by 12% over 16 weeks compared to placebo [401]. In overweight and obese adults, 1500 mg per day for 8 weeks reduced feelings of anxiety by 27% and feelings of depression by 39% [402].

Recommended Dosing: Supplement 500–3000 mg of lion's mane powder per day.

Tocotrienols

You're probably familiar with vitamin E. At the very least, you've heard the term thrown around every now and again in discussions related to health or nutrition. Which would make sense given that it's an essential nutrient, making up one of the four fat-soluble vitamins we need for optimal health.

What you may not know is that vitamin E isn't a single molecule, it's a group of eight related molecules: four tocopherols and four tocotrienols. All of them share a similar chemical structure characterized by a long hydrocarbon chain attached to a chromanol ring, with a couple nuances that ultimately determine their exact classification as alpha, beta, gamma, or delta.



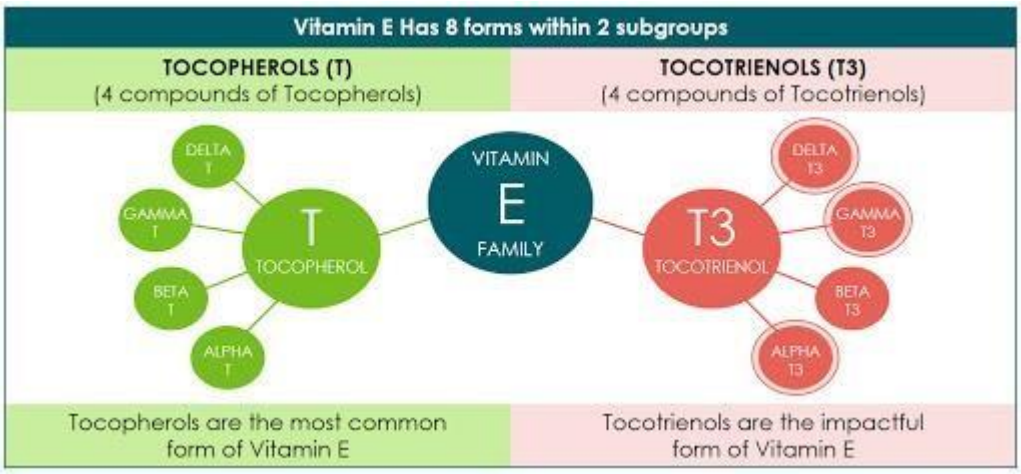
	R_1	R_2
α	CH_3	CH_3
β	CH_3	H
γ	H	CH_3
δ	H	H

While these structural differences seem minor, they have broad implications for the biological activity of each molecule and, consequently, how they impact our health [403]. The best example of this is the alpha-tocopherol transfer protein (ɑTTP) within the liver.

You see, whenever vitamin E reaches the liver, its either metabolized and excreted or bound to ɑTTP and exported throughout the body. As the name implies, this protein preferentially binds to alpha-tocopherol due to its structural configuration, resulting in the metabolism and excretion of other vitamin E analogues [404].

Unfortunately, such an observation has led to the belief that alphatocopherol is the only form of vitamin E that matters for our health. (And it’s almost never included in vitamin E supplements!) In fact, the Dietary Reference Intake for vitamin E is based entirely on alpha-tocopherol, with the report clearly stating that other forms don’t contribute to requirements because they aren’t well recognized by ɑTTP [405].

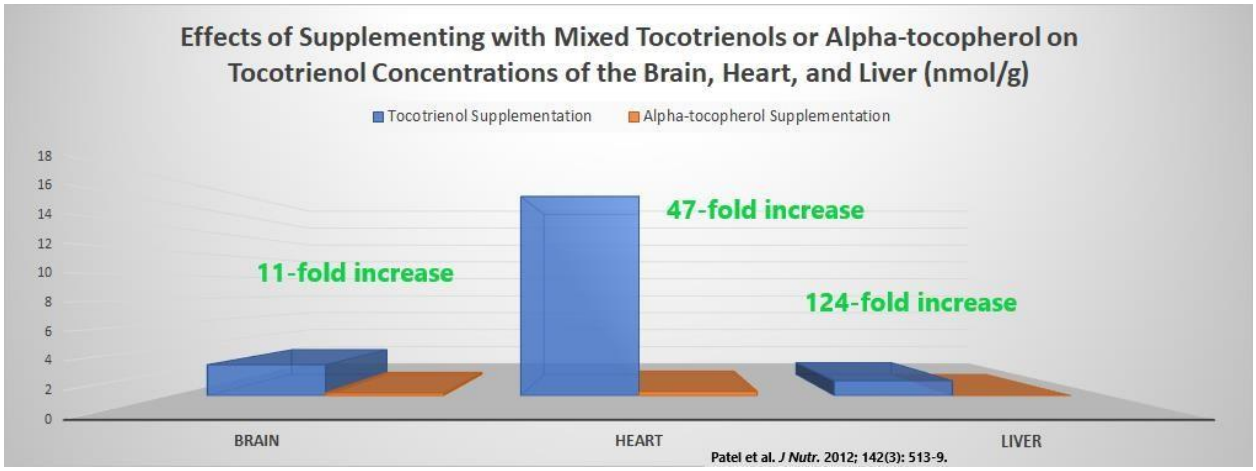
While undoubtedly an important molecule, alpha-tocopherol’s spotlight has cast a shadow on the other forms of vitamin E like the tocotrienols — a conventional wisdom that needs reconsideration.



Vitamin E tocotrienols are potent antioxidant molecules that incorporate into cell membranes and neutralize free radicals that would otherwise cause peroxidation of the phospholipids [406–408].

It's an incredibly important job, one that works synergistically with other antioxidants like vitamin C and glutathione to ensure the integrity of our cell membranes [409]. Most of the vitamin E deficiency symptoms can be linked to unrestrained lipid peroxidation, such as the deterioration and our nerves that ultimately causes neuropathy and ataxia.

Supplementation with tocotrienols significantly increases their concentration in critically important organs like the brain, heart, and liver [410]. Moreover, the concentrations achieved within the brain are precisely around the concentrations needed to prevent brain damage and neurotoxicity from excessive glutamate and other toxicants [411].



Because of their neuroprotective and antioxidant effects, an ever-growing body of research is looking into using tocotrienols for the prevention and treatment of Alzheimer's disease [412]. For example, a randomized controlled trial of individuals with active white matter lesions of their brains, a sign of neurodegeneration, found that 400 mg per day of mixed tocotrienols completely halted the loss of white matter and further brain deterioration after two years [413].

Comparatively, the white matter loss of the placebo group had increased by 23%!

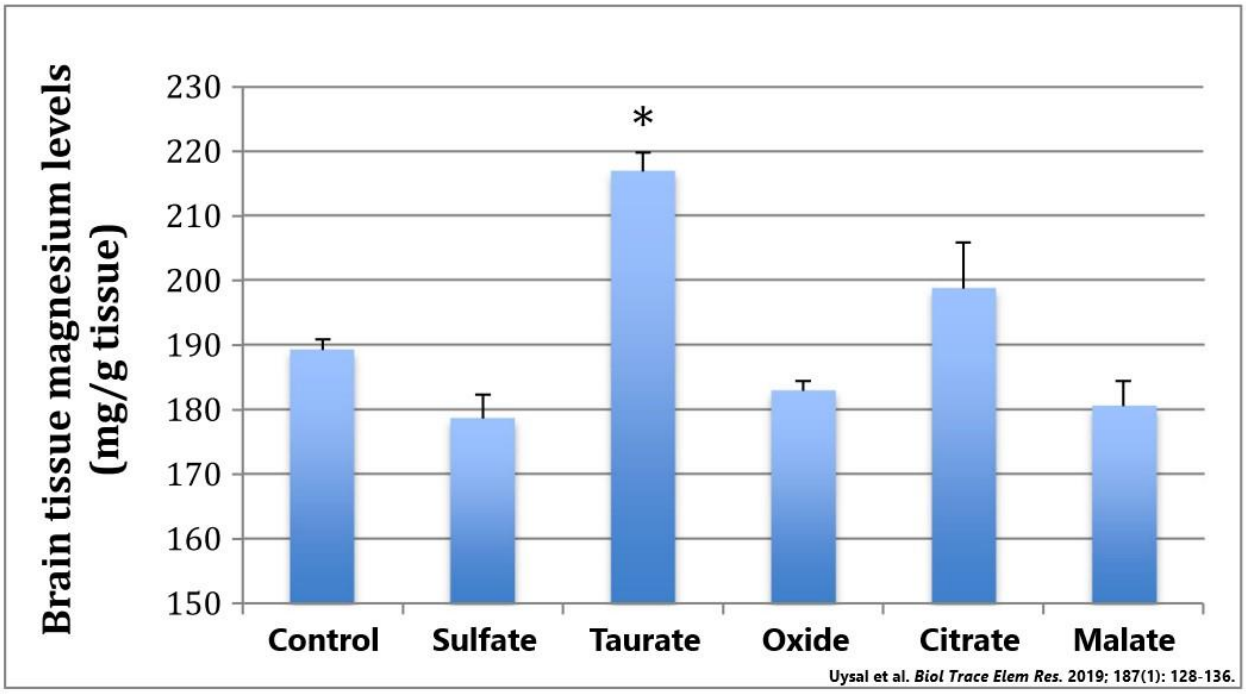
Recommended Dosing: Supplement 100–400 mg of vitamin E tocotrienols per day.

Magnesium Taurate

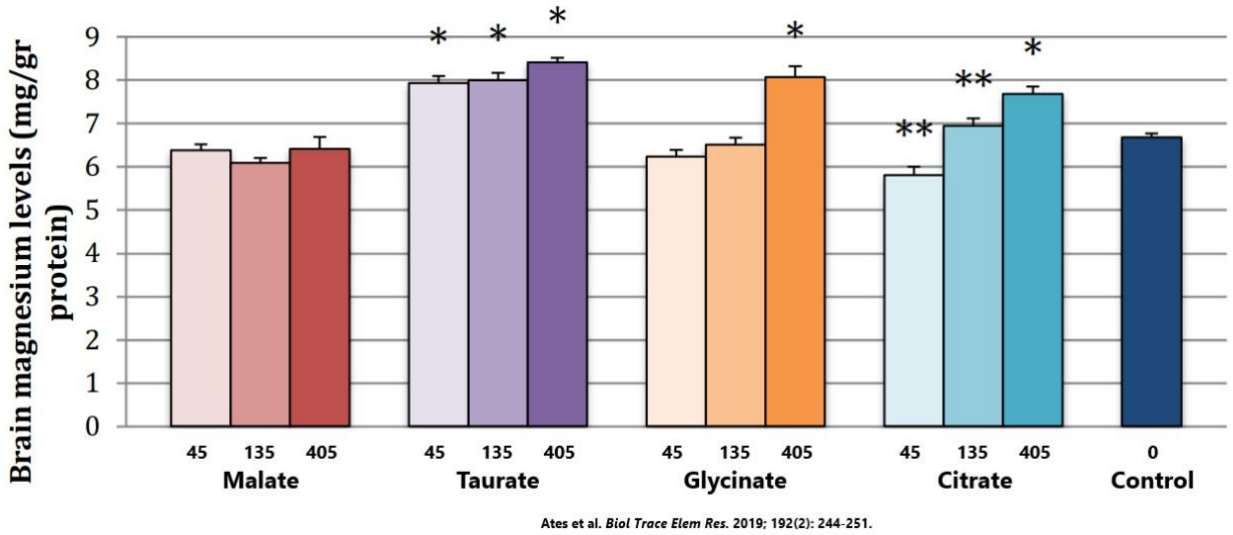
Magnesium is an essential mineral required for over 300 enzymes to function properly [414], including those necessary for mitochondrial function and energy production [415,416]. Within the brain, magnesium is required for optimal nerve transmission and protection against neurotoxicity [417,418].

Individuals with neurodegenerative disorders like Parkinson's disease [419,420] and Alzheimer's disease [421–423] have lower brain concentrations of magnesium than healthy adults, and studies in mice suggest that elevating brain magnesium concentrations can provide neuroprotective effects and enhance cognitive function [424,425].

But not all forms of magnesium have the same ability to enter the brain. One study compared the tissue distribution of magnesium 8 hours after taking equal amounts of magnesium citrate, malate, oxide, sulfate, and taurate [426]. It was shown that magnesium taurate increased brain magnesium concentrations 10–20% more than the other forms.



In another study, the tissue distribution of magnesium 24 hours after supplementation was compared between different doses (45, 135, and 405 mg) of magnesium citrate, glycinate, malate, and taurate [427]. Just 45 mg of magnesium taurate was enough to increase brain concentrations to the same extent as 405 mg of glycinate or citrate and was 23% more effective than 405 mg of magnesium malate.



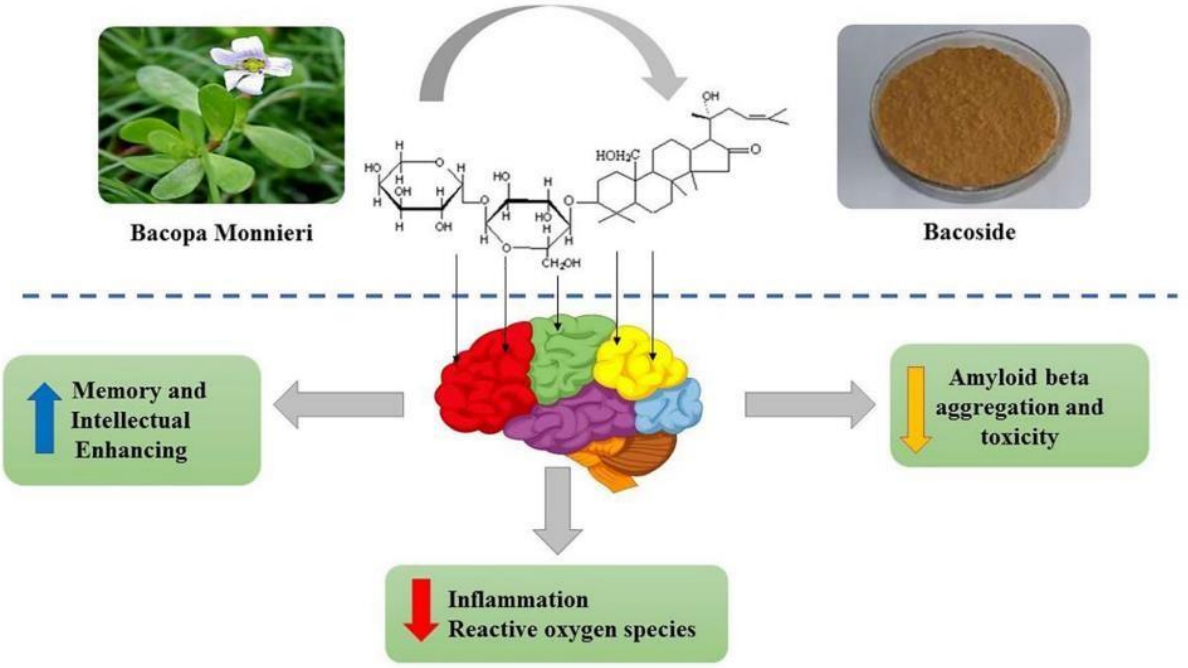
Importantly, another form of magnesium not tested in these studies but touted for its neurological benefits is magnesium L-threonate. This form of magnesium was developed by Guosong Liu at Tsinghua University as a means of increasing brain magnesium concentrations in rats, but has only been compared to magnesium citrate and gluconate, showing just marginal superiority [425]. As it stands, magnesium taurate is the best option.

Recommended Dosing: Supplement 45–400 mg of magnesium taurate per day.

Bacopa Monnieri

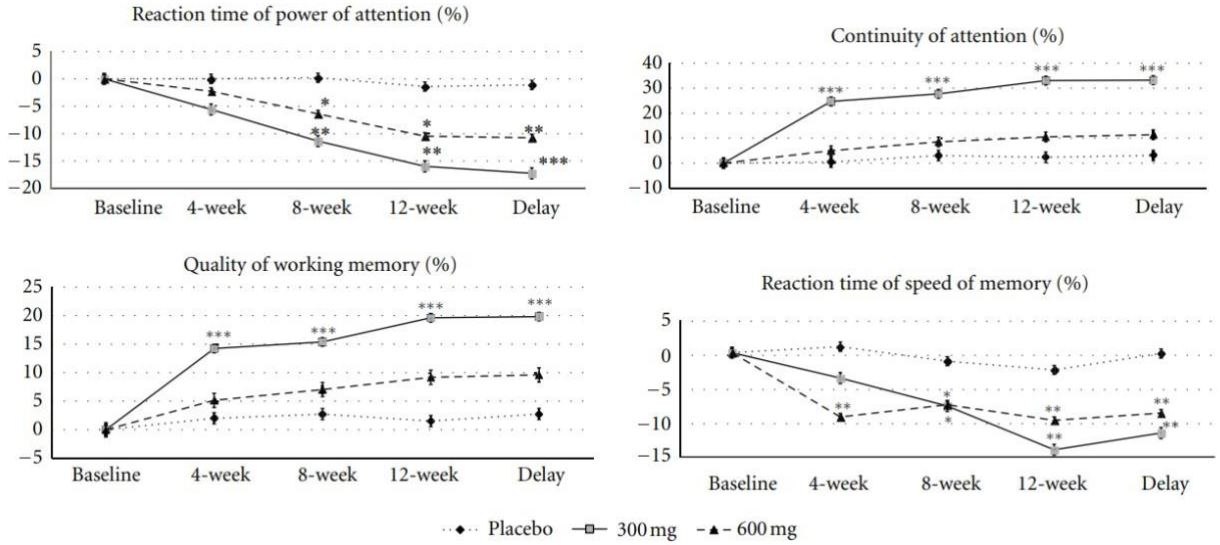
Bacopa monnieri is an Ayurvedic swamp plant (*Brahmi*) traditionally used for the enhancement of memory and cognition, as well as a general brain tonic. It's bioactive constituents, the bacosides, have numerous biological effects within the brain that facilitate this use [428–432]:

- Reduce oxidative stress and increases antioxidant enzyme activity
- Reduce inflammation
- Neuroprotective
- Reduce β-amyloid deposition
- Increase the growth of nerve endings to enhance neuronal communication
- Increase blood flow and the delivery of oxygen and nutrients



Abdul Manap et al. *Drug Target Insights.* 2019; 13: 1177392819866412

In healthy eldery adults (average 62 years), supplementing with 300 mg per day of bacopa for 12 weeks significantly improved reaction times, the continuity of attention, the quality of memory, and the speed of memory by 15–30% compared to placebo [433]. Similar but less pronounced benefits were observed with 600 mg per day of bacopa, suggesting that more is not always better.



Peth-Nui et al. *Evid Based Complement Alternat Med.* 2012; 2012: 606424.

In young medical students, 300 mg per day of bacopa (50% bacosides) for 6 weeks significantly improved efficiency of attention, freedom from distractibility, and working memory [434].

In healthy adults, 300 mg per day of bacopa (50% bacosides) for 12 weeks significantly improved speed of visual information processing, learning rate, memory consolidation, and decreased anxiety compared to placebo [435].

In healthy adults, 300 mg per day of bacopa (50% bacosides) for 12 weeks significantly improved working memory and visual processing ability [436].

In healthy elderly adults (average 73 years), 300 mg per day of bacopa (50% bacosides) for 12 weeks significantly improved multiple measures of cognitive performance and mood state compared to placebo, including memory, reaction time, depression, and anxiety compared to placebo [437].

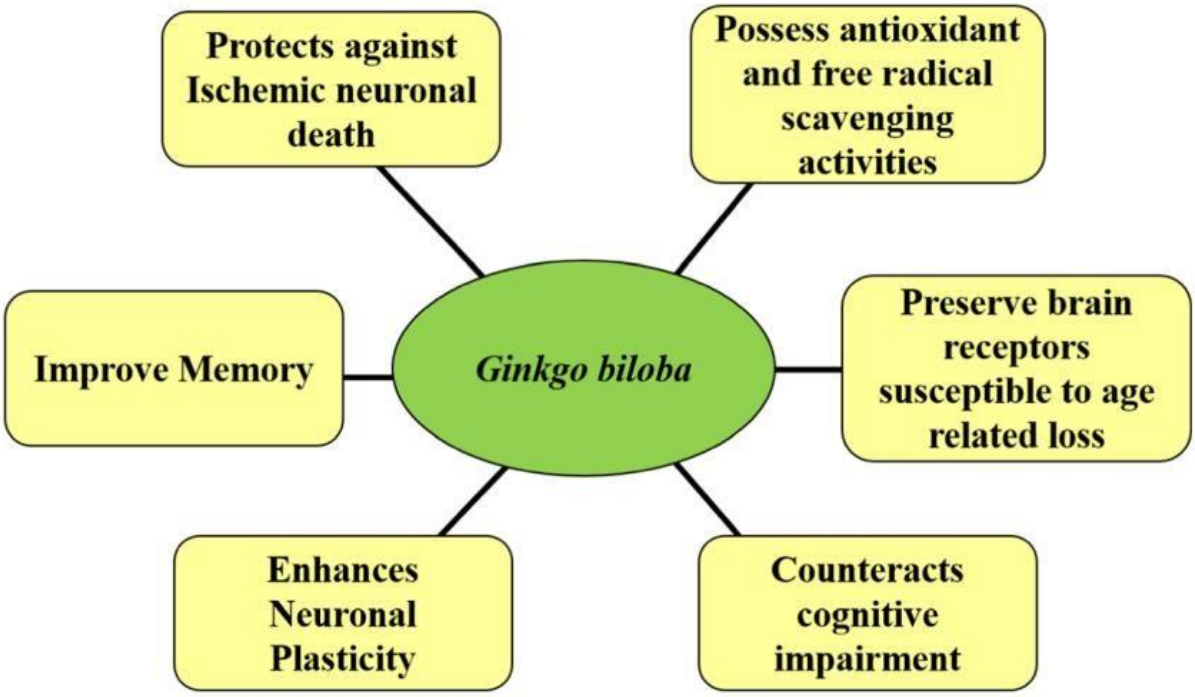
In healthy older adults (>50 years), 300 mg per day of bacopa (50% bacosides) for 12 weeks significantly improved verbal learning, memory acquisition, and memory retention compared to placebo [438].

Even in those with Alzheimer's disease, 600 mg per day of bacopa (50% bacosides) for six months significantly improved various components of MiniMental State Examination Scale (MMSES), including orientation of time, place and person, attention, and their language ability in terms of reading, writing, and comprehension [439].

Recommended Dosing: Supplement 300–600 mg of bacopa monnieri per day.

Ginkgo Biloba

Ginkgo biloba possesses an array of activities relevant to brain health and neurological function, with numerous studies showing that it is neuroprotective, an antioxidant, preserves brain receptors susceptible to age-related loss, counteracts cognitive impairment, enhances neuronal plasticity, and improves memory [440].



Singh et al. *Neurotherapeutics.* 2019; 16(3): 666-674.

Numerous interventions have been conducted with ginkgo biloba supplementation, usually in the form of a 50:1 concentrated extract called *EGb-761*, and systematic reviews of this evidence have found that it improves cognitive performance and quality of life in older adults experiencing cognitive decline, but doesn't have much of a benefit in young and cognitively healthy adults [441,442].

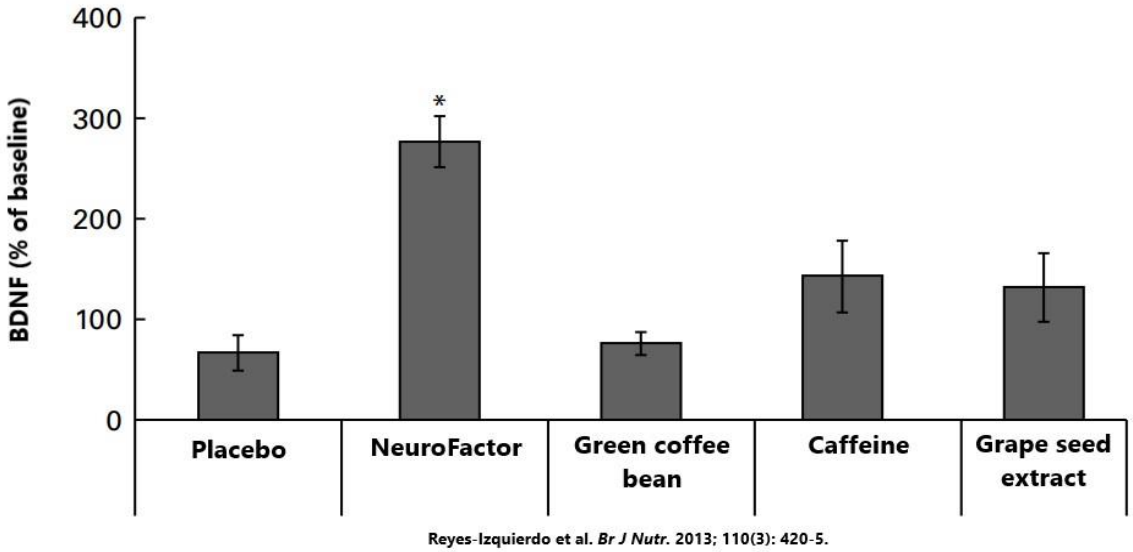
The evidence is strong enough to convince the Asian Clinical Expert Group on Neurocognitive Disorders that ginkgo biloba should be part of the treatment, either alone or in combination with other drug therapies, for the management of Alzheimer's disease, vascular dementia, and behavioral and psychological symptoms of dementia [443].

Recommended Dosing: Supplement 240 mg of the EGb-761 ginkgo biloba extract per day.

Coffee Fruit (CognatiQ™)

CognatiQ™ is a patented extract of the whole coffee fruit, including both the fruiting body and the coffee bean it contains. While many are familiar with the coffee bean and the joy it brings through brewing into a morning cup of Joe, the fruit contains powerful antioxidant compounds that benefit our brain [444,445].

Clinical studies in healthy adults have shown that 100 mg of NeuroFactor nearly doubles concentrations of brain-derived neurotrophic factor (BDNF) after 1–2 hours [446,447], beating out other forms of coffee bioactives, caffeine, and the phytochemical-rich grape seed extract.



Reyes-Izquierdo et al. *Br J Nutr.* 2013; 110(3): 420-5.

BDNF is a key protein involved in brain health, well established to be critical for:

- Neuroplasticity (helps the brain adapt to new situations) [448].
- Neurogenesis (the growth, regeneration and creation of new neurons and synapses) [449,450].
- Long-term memory [451].
- Prevention of neurodegeneration [452].

Recommended Dosing: Supplement 100 mg of CognatiQ™ per day.

Agmatine sulfate

Agmatine is a neurotransmitter and neuromodulator (affects neurotransmission of entire neurons) that has anti-seizure, anti-pain, antianxiety, and antidepressant effects; modulates some of the processes involved in learning and memory; and interacts with the mechanisms of drug withdrawal [453].

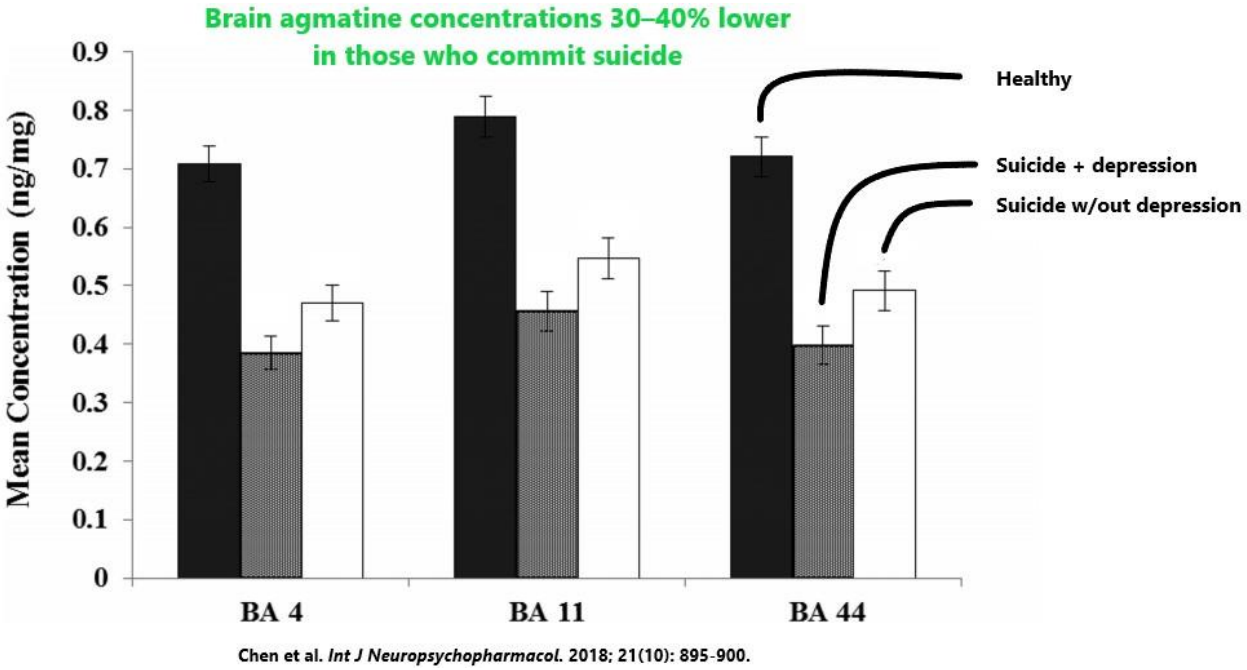
- Blocks the NMDA (N-methyl-D-aspartate) receptor and prevents excitotoxicity [454].
- Activates imidazoline receptors that increase beta-endorphin secretion [455].
- Activates mTOR (mammalian target of rapamycin) involved in cell growth [456].
- Activates the Nrf2 (nuclear factor E2-related factor 2) pathway that increases the production of antioxidant enzymes [457,458].
- Protects mitochondria from oxidative stress and cell death [459,460].

Collectively, the effects of agmatine have given it a high therapeutic value for treating neurological disorders and preventing neurodegeneration [461,462]. Unfortunately, human clinical trials haven't caught up to its vast potential.

In a pilot study of two men and one woman with clinical depression and currently in the grip of a major depressive disorder episode, supplementing 2–3 g/d of agmatine for 3–4 weeks *"showed total/incontrovertible remission of depression" [463]*. Their depressive rating dropped from 32, with >17 indicating severe depression, to a depression-free score of 3. All without apparent adverse effects.

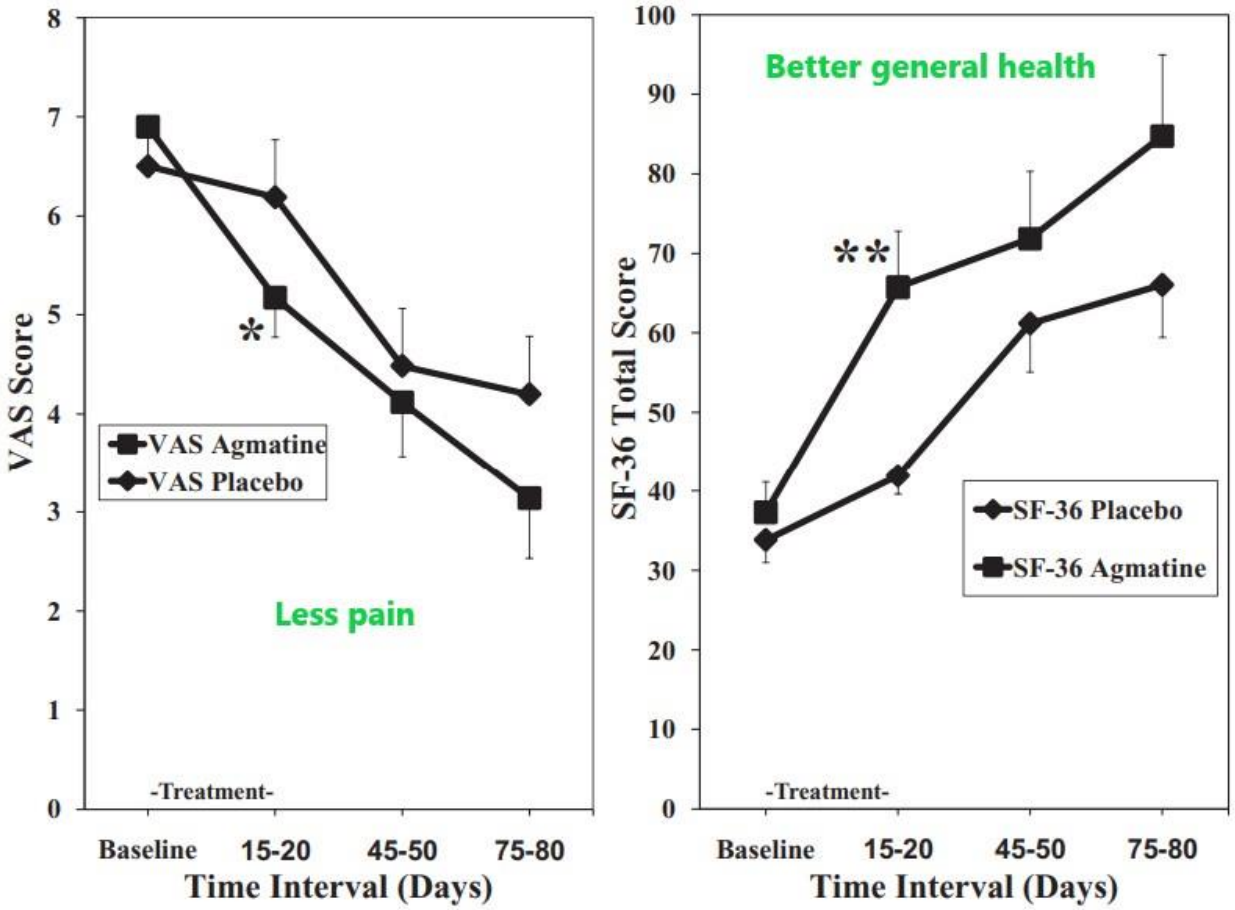
These effects persisted even when given a drug that completely blocked serotonin signaling, which should have caused depressive relapse. The patients were so amazed that they refused to stop taking agmatine when the intervention ended, especially in light of the fact that their depressive episodes would historically last for months with antidepressant drugs and for up to a year without.

Additionally, an analysis of the postmortem brains of individuals who committed suicide found that agmatine concentrations were 30–40% lower than in non-suicidal individuals in all three tested brain regions [464].



Chen et al. *Int J Neuropsychopharmacol.* 2018; 21(10): 895-900.

Other clinical research has demonstrated agmatine's pain-relieving properties. In a randomized, double-blind, placebo-controlled study of individuals with back pain from herniated lumbar discs, 2.7 g/d of agmatine sulfate for two weeks reduced pain by 25–28% and improved parameters of general health by 65–76% [465]. Moreover, these benefits persisted for 2 months after supplementation ended.



Keynan et al. *Pain Med.* 2010; 11(3): 356-68.

For a comparison point, short-term use of a common oral steroid (prednisone) for herniated lumbar disc patients was just as effective as agmatine at reducing disability but had almost no effect on general health [466], increasing the SF-36 score by a mere 6 points after 3 weeks, compared to the 30-point increase with agmatine.

Another study of individuals with neuropathy resistant to conventional pain medications found that 2.7 g/d of agmatine sulfate reduced pain by 46% [467].

Finally, agmatine may be an effective adjunct to alcohol withdrawal. The anxiety-lowering effects experienced from drinking alcohol are prevented by inhibiting the enzyme that creates agmatine, and the increase in anxiety from alcohol withdrawal can be prevented with agmatine supplementation [468]. Agmatine also prevents other symptoms of alcohol withdrawal, such as tremors [469], and protects against withdrawal-induced neurotoxicity [470].

Recommended Dosing: Supplement 500–3000 mg of agmatine sulfate per day.

Polygala Tenuifolia

Polygala tenuifolia is one of the fundamental herbs used in traditional Chinese medicine, used to improve memory and combat forgetfulness with aging [471]. There are several mechanisms through with Polygala tenuifolia may accomplish these goals:

- Inhibiting the breakdown of acetylcholine, dopamine, serotonin, and noradrenaline, neurotransmitters required for learning new information, memory storage, and overall mental health [472,473].

- Increasing the expression of brain derived neurotrophic factor (BDNF), which is fundamental for neuroplasticity and neurogenesis [474].

- Promoting the growth of new neurons in the brain [475].

In **healthy adults**, 300 mg/d of Polygala tenuifolia for 4 weeks improved spatial and verbal memory [476]. The participants also made fewer errors and scored better on a test measuring working memory.

In **elderly adults**, 300 mg/d of Polygala tenuifolia for 8 weeks improved cognitive function by 5–10% compared to placebo [477].

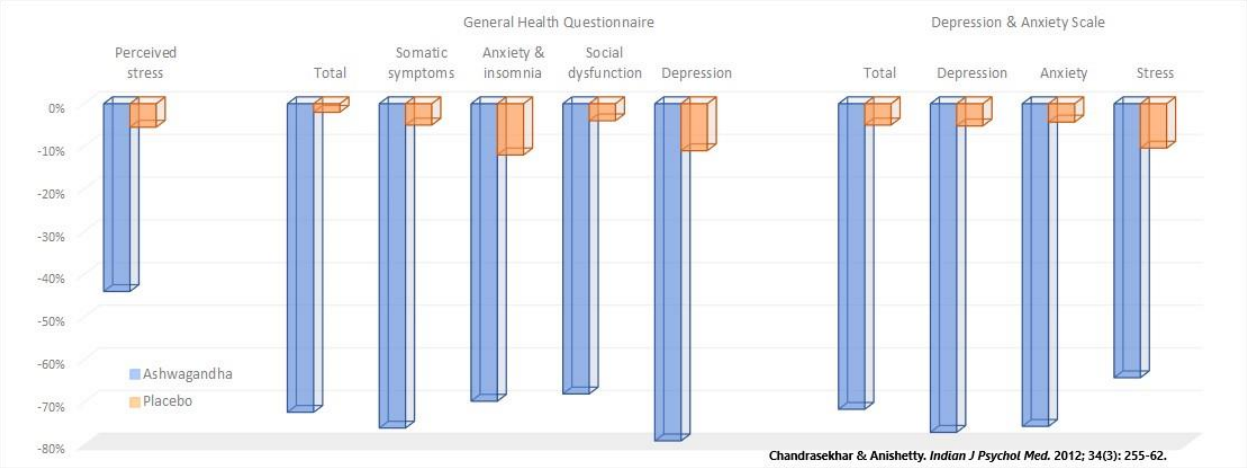
Recommended Dosing: Supplement 100–300 mg of polygala tenuifolia per day.

Ashwagandha

Ashwagandha (*Withania somnifera*) is a nightshade revered in Ayurvedic medicine for its physical- and mental-enhancing effects [478]. Today, it's considered an adaptogen for similar reasons, able to increase a person's resilience to stress and help reduce anxiety [479,480].

These effects are largely due to its constituent withanolide structures, which have several important neuroprotective effects within the brain, such as scavenging free radicals, reducing neuroinflammation, and promoting neurotransmitter signaling [481]. They also bind to and activate GABA receptors [482].

Several studies have reported reductions in stress and anxiety following supplementation with 600–1000 mg per day of an ashwagandha extract called KSM-66. The reductions ranged from 15–20% in otherwise healthy adults dealing with mild stress [483,484], to 40–70% in adults battling chronic mental stress [485], to 50% in adults with an anxiety disorder [486].



These stress- and anxiety-reducing benefits also translate to improved sleep. For instance, in mildly stressed adults, the 15% reduction in perceived stress was accompanied by a 30% improvement in sleep quality [483]. Other studies have documented improvements in sleep quality of 30% in elderly adults [487], and by 18% in those with insomnia [484].

Although the KSM-66 extract is the best-researched, it is not the most potent. The concentration of withanolides in regular dried ashwagandha root is less than 1%, at least 5% in the KSM-66 extract, but a whopping 35% in what's called the Shoden extract (which is why we chose it for our mitochondrial formula, *Energenesis*).

To illustrate this difference, in mildly stressed healthy adults, compared to the 15–20% reduction in anxiety with 600 mg of the KSM-66 extract [483,484], just 240 mg of the Shoden extract reduces anxiety by 60% [488].

Recommended Dosing: Take 600 mg per day of a KSM-66 extract or 150 mg per day of a Shoden extract.

Dopamine Boosters

Dopamine is a tiny molecule with a big job: motivation and reward. Whenever you do something pleasurable, like eat cake, orgasm, or accomplish a goal, dopamine is released to help reinforce that behavior. It makes us feel good and motivates us to continue engaging in behaviors that bring us pleasure.

Addiction is probably the best-known example of dopamine involvement [489]. Whether it's a drug, a food, or a behavior, the dopamine burst we experience leads us to crave more of that experience. With regular exposure, we form habit routines whereby the experience is expected to give us that pleasurable dopamine reward.

Yet, there’s a downside as well: regular exposure leads to tolerance. Tolerance means that we need more of the experience to get the same effect we once enjoyed in the beginning. This is why drug use tends to escalate with time. Tolerance also means that ceasing to use a drug or engage in a behavior causes a dopamine withdrawal, leading to agitation, irritability, difficulty concentrating, and excessive preoccupation of your thoughts with the pleasurable experience.

The reason we want to ensure that our dopamine system is functioning optimally is because low levels of dopamine can lead to apathy, a lack of motivation, an inability to complete or follow-through with tasks, mood swings, and addictive tendencies.

In particular, if you’re struggling with a maladaptive habit that you can’t seem to kick, optimizing your dopamine system can help counteract withdrawal and make establishing healthier habits easier.

Mucuna Pruriens

Arguably the best supplement to increase dopamine signaling within the brain is mucuna pruriens, more commonly known as velvet bean. Mature seeds are about 4% L-DOPA, meaning that every gram of velvet beans provide about 40 mg of L-DOPA [490].

L-DOPA is the only reliable way of increasing dopamine synthesis for two reasons:

1) Dopamine itself can't cross the blood-brain barrier, so supplementing with it would be futile [491]. L-DOPA can cross the blood-brain barrier with ease.

2) The rate-limiting step in dopamine synthesis is the conversion of tyrosine to L-DOPA because high levels of dopamine inhibit the enzyme responsible for this conversion [492]. Taking L-DOPA directly bypasses this negative feedback loop.

These reasons are why L-DOPA is the go-to molecule for increasing dopamine synthesis in conditions that need it, like Parkinson's disease. And velvet beans might be the ideal way to get L-DOPA because it is not only more potent than isolated L-DOPA, but also safer [493].

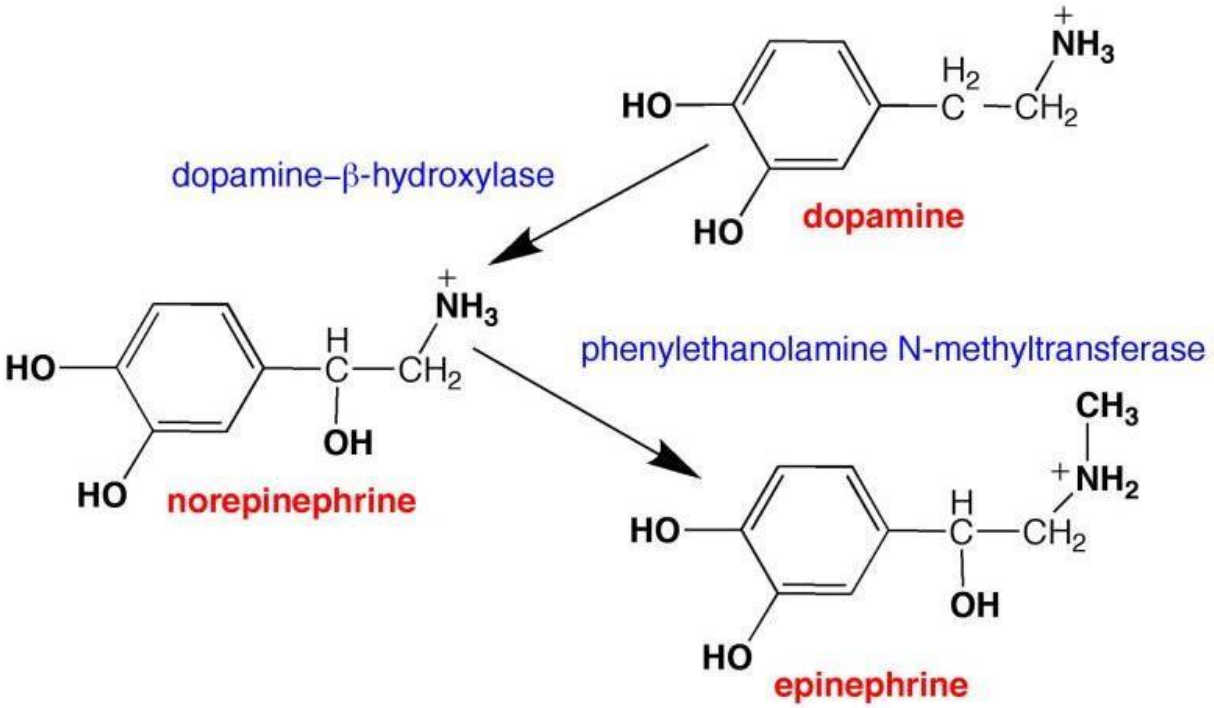
In studies of Parkinson's disease patients, for example, velvet beans were just as efficacious as standard drug treatment with L-DOPA, but with a lower risk for adverse effects like dyskinesias [494–496]. Accordingly, if you feel that you may have low dopamine levels, supplementing with some velvet beans may be able to help.

Recommended Dosing: The dose of velvet bean will be variable depending on one's needs. Start with a low dose of 1–2 grams and work your way up until your symptoms of dopamine insufficiency are minimized.

Tyrosine

If you are under a lot of stress, taking tyrosine may also be helpful because dopamine is the precursor to the stress hormones adrenaline and noradrenaline.

If you are chronically stressed, then you can expect your dopamine levels to dwindle as it is further metabolized into these molecules [497,498].



As dopamine levels fall, the conversion of tyrosine to L-DOPA picks up, but you need to ensure that you have sufficient tyrosine available to let that happen. Accordingly, supplementing with extra tyrosine can help offset this reduction in dopamine by allowing for its continued synthesis [499].

Several clinical trials have shown that supplementing with 500 mg–12 g/d of tyrosine improves cognition, alertness, memory, and energy levels in stressful and demanding situations that would otherwise drain dopamine and impair our ability to think [500,501].

Recommended Dosing: Supplement 0.5–12 grams per day to increase dopamine signaling and improve mood and cognitive function when under stress.

Acetylcholine Boosters

Acetylcholine is one of the most prevalent neurotransmitters in the body, involved in regulating muscle contractions of the heart, blood vessels, and

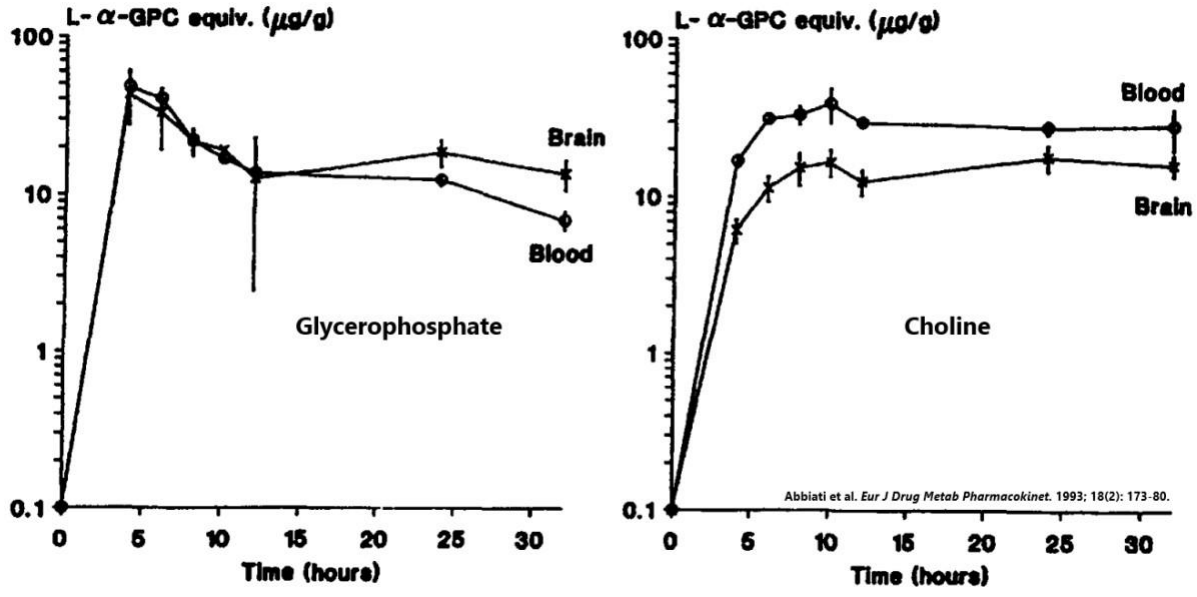
skeletal muscle, as well as the ability to learn and remember. Accordingly, disturbances in acetylcholine signaling can have widespread consequences for cognitive function, cardiovascular health, and physical function [502].

For example, if you take young adults and inhibit acetylcholine signaling with drugs, they demonstrate similar impairments to long-term and working memory as elderly adults suffering from cognitive decline [503]. Moreover, reductions in acetylcholine signaling set the brain up to be less plastic and more vulnerable from other insults like oxidative stress, inflammation, and injury [504].

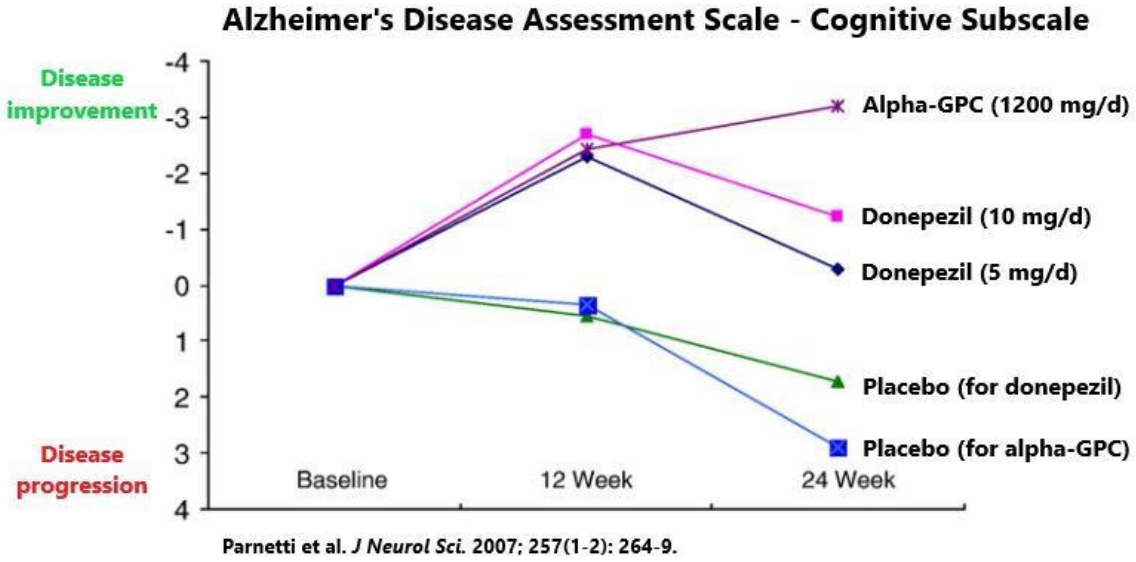
For these reasons, it's currently believed that Alzheimer's disease and dementia have a strong acetylcholine component, with medical treatments revolving around the use of drugs that inhibit acetylcholinesterase, the enzyme that degrades acetylcholine.

Alpha-GPC

Alpha-glycerophosphocholine (Alpha-GPC) is a highly bioavailable source of choline for the brain [505]. After ingestion, blood and brain levels of choline and glycerophosphate (the molecule bound to choline in alpha-GPC) increase over 5–10 hours and remain elevated for more than a day [505].



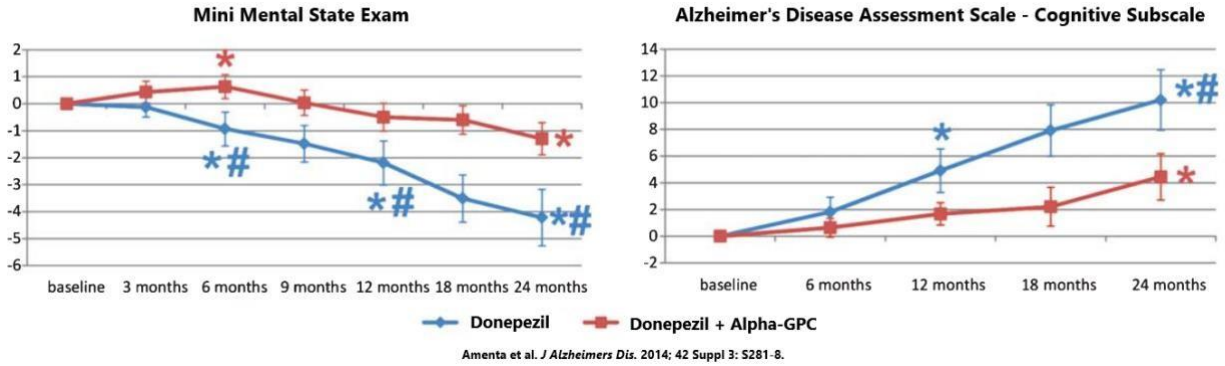
The most recent meta-analysis of alpha-GPC, published in 2007, aggregated the data from 14 clinical trials enrolling individuals with neurodegenerative disorders, vascular dementia, or stroke, and the results have been very positive [506]. For example, compared to standard drug therapy for Alzheimer's disease (the cholinesterase inhibitor called donepezil), 1200 mg/d of alpha-GPC was more effective at improving cognition over 6 months [506].



Parnetti et al. *J Neurol Sci.* 2007; 257(1-2): 264-9.

More recently, a series of publications from the ASCOMALVA study have been reported. This clinical trial recruited older adults with Alzheimer's disease to take either donepezil alone or alongside 1200 mg/d of alpha-GPC.

The group that took alpha-GPC showed a 2.5- to 4-fold slower rate of cognitive decline over 2 years of follow-up compared to the group taking the drug alone [507], with benefits being evident as early as 1 year after starting the supplement [508]. Alpha-GPC also reduced the extent of behavioral abnormalities [509].

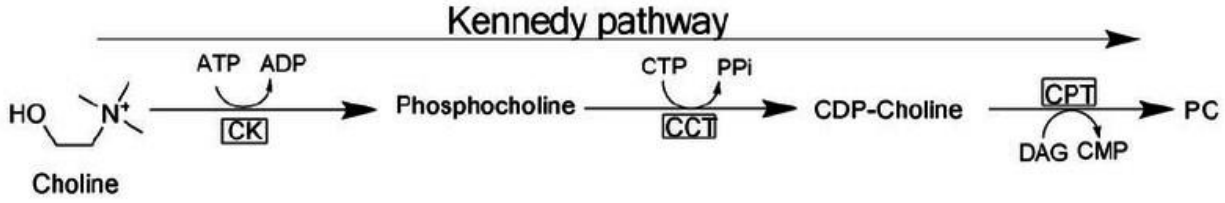


The enhanced brain activity has been shown to translate into improvements in exercise performance, with 250–600 mg taken before exercise shown to improve strength and power output [510–513]. At least one comparative study has found that 400 mg of alpha-GPC may be more effective than caffeine [514].

Recommended Dosing: Supplement 150–1200 mg of alpha-GPC per day.

CDP-choline

Like with alpha-GPC, CDP-choline is a bioavailable source of choline for the brain [515]. Unlike alpha-GPC, however, CDP-choline is the direct precursor for the synthesis of phosphatidylcholine [516], one of the most abundant and important structural components of cell membranes.



Research in humans has shown that taking CDP-choline increases phosphatidylcholine synthesis within the brain [517], with maximal concentrations occurring after 6 weeks of supplementation with 500 mg of CDP-choline per day [518].

In-line with the effects of CDP-choline on phosphatidylcholine concentrations and acetylcholine signaling, supplementation has been shown to improve cognitive function in both healthy adults and those suffering from cognitive decline.

For example, a Cochrane Systematic Review of 14 double-blind, placebocontrolled trials of older adults with cognitive deficits like dementia reported that 600–1000 mg per day of CDP-choline was able to improve memory, correct abnormal behaviors, and increase the global impression that physicians have towards the participants [519].

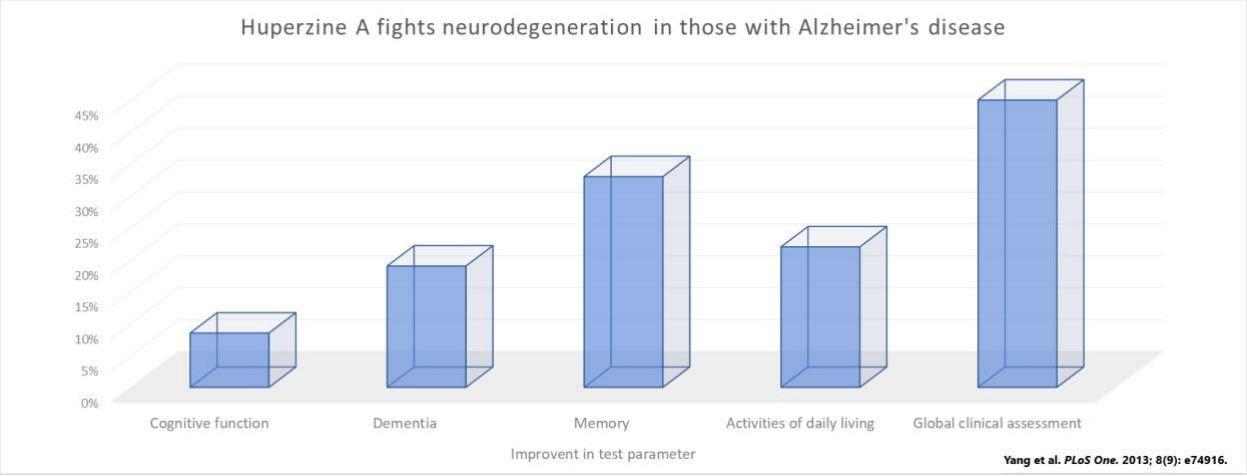
Several studies published after this review have also shown benefits in older adults with dementia or Alzheimer's disease [520,521], older adults with mild vascular dementia [522], adolescents [523], and healthy women [524].

Recommended Dosing: Supplement 150–1000 mg of CDP-choline per day.

Huperzine A

Huperzine-A is an alkaloid derived from the moss *Huperzia serrata*, which itself has been used in traditional Chinese Medicine for centuries to treat neuronal- and cognitive-based illnesses [525]. It's a naturally occurring acetylcholinesterase inhibitor, meaning it prevents the breakdown of acetylcholine just like many Alzheimer's drugs do [526].

At least 20 randomized controlled trials have evaluated the efficacy of huperzine A in patients with Alzheimer's disease, with a meta-analysis showing improvements for cognitive function, daily living activity, and global clinical assessments with doses of 200–800 mcg (average: 370 mcg) over 8–36 weeks [527].



Other meta-analyses have reported that huperzine A improves cognition in those with vascular dementia [528], as well as in those with major depression [529].

Recommended Dosing: Supplement 200–800 mcg of huperzine A per day.

GABA Boosters

GABA is the most potent depressive neurotransmitter in the brain and regulates many of the sedative actions required for relaxation [530,531]. It is also critical for the regulation of neuronal communication, cognition, emotion, and memory [532–534].

For example, it's been suggested that higher GABA levels help reduce distraction in the brain [535], which makes it possible to react and make decisions more quickly, and supplementing with GABA has been shown to improve attention and task switching in healthy young adults [536,537].

Other research has documented a relationship between lower levels of GABA in the brain and a variety of cognitive deficits in humans:

- Worse memory [538].
- Self-reported cognitive failures (e.g., inability to attend to relevant details while being distracted by irrelevant details) [539].
- Lower visuospatial IQ [540].
- Less empathy [541].
- Reduced resilience to stress and greater susceptibility to depression and anxiety [542].
- Susceptibility to addiction [543].

If you aren't supporting your GABA system, then you can definitely expect to have difficulty concentrating, feelings of anxiety, a lower resilience to stress, and trouble sleeping.

Nearly all of the GABA boosting supplements will be discussed in the following section on maximizing deep and rejuvenating sleep. Passionflower, chamomile, lemon balm, and theanine all induce a state of relaxation that helps us calm down and get to bed in part by increasing GABA signaling.

However, we can also supplement GABA directly. It's actually a rarity that we can just supplement a neurotransmitter and have it not only survive digestion and absorption, but also cross the blood-brain barrier and be integrated into our GABA system. But that's the case with dietary GABA.

A systematic review of 14 studies concluded that 20–100 mg of GABA could reduce stress and increase feelings of calmness, while 100–300 mg could improve sleep quality [544]. However, it's important to note that some people can't tolerate GABA supplements and don't feel well using them, so don't stress if GABA isn't working for you personally and try some of the other options.

Recommended Dosing: Supplement 100–300 mg of GABA per day.

Serotonin Boosters

Serotonin is possibly the most diverse neurotransmitter in our body, regulating both how we think and behave, as well as numerous physiological processes involved in digestion and bowel motility, our breathing, cardiovascular function, and sexual function [545].

However, serotonin's effects in the brain are the best-known. Believe it or not, serotonin modulates virtually all behavioral and psychological processes, including mood, perception, reward, anger, aggression, appetite, memory, and attention, to name just a few [545].

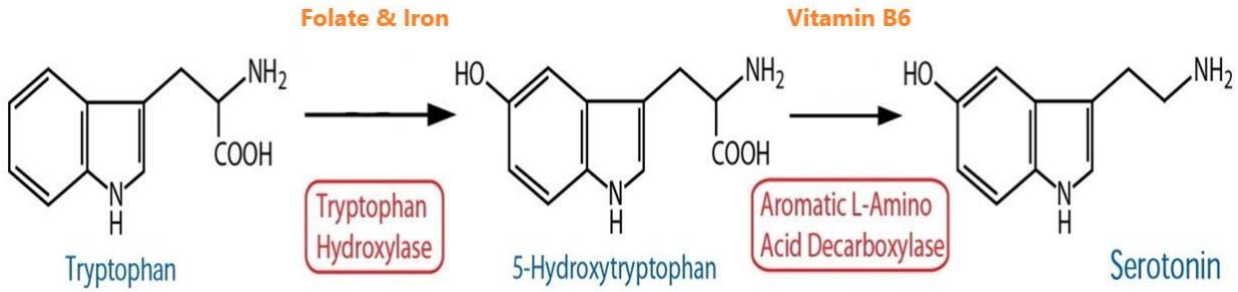
As an illustration of this point, consider psychedelics. No matter what psychedelic you talk about — magic mushrooms, ayahuasca, LSD — all of them cause altered states of consciousness and hallucinations through potently binding to and activating serotonin receptors within the brain [546].

On the flipside, many mood disorders are related to too little serotonin activity, the best example being depression [547,548]. While low levels of serotonin don't outright cause depression, they do alter the way in which we perceive and process information, predisposing us to negative thought patterns, apathy, and an inability to enjoy pleasurable things [549].

If you aren't optimizing your serotonin levels, then you can expect to be moody, lose interest in things that once brought you pleasure, and worry needlessly.

5-HTP

One of the best supplements you can take to bolster serotonin production is 5-HTP, the intermediate molecule between tryptophan and serotonin. The conversion of tryptophan to 5-HTP is the bottleneck step for serotonin production, so supplementing 5-HTP directly is able to bypass this step and reliably increase serotonin levels in the brain [550].



While research looking into how 5-HTP supplementation affects mood is limited, what data is available shows that it does effectively alleviate depression in those with clinical depression [551,552]. In particular, slowrelease 5-HTP that results in a more modest and prolonged increase in brain serotonin levels could be an effective adjunct in depression that's been resistant to standard drug therapies [553].

Recommended Dosing: Supplement 250–500 mg of 5-HTP per day.

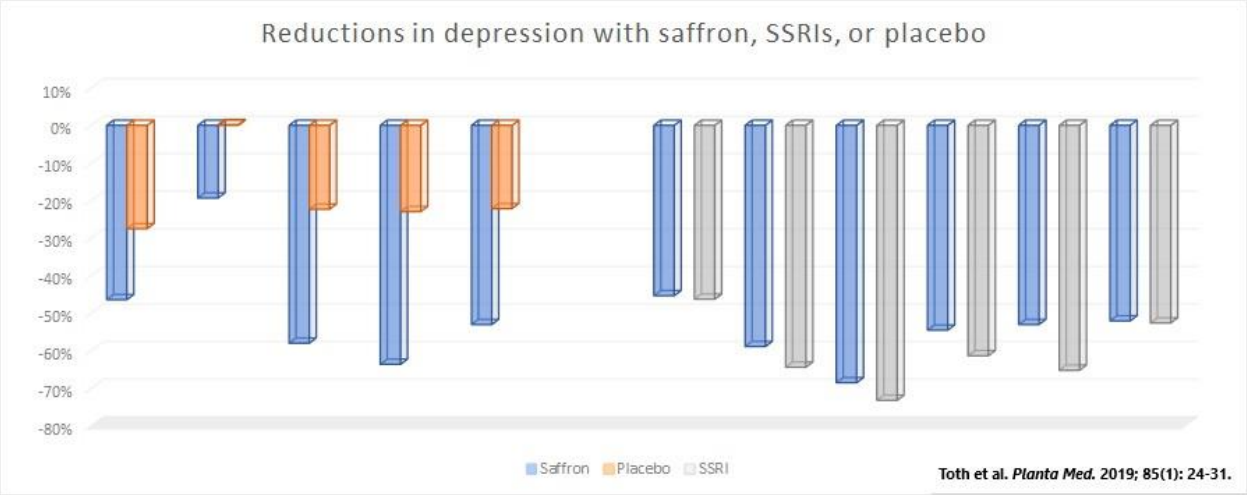
Saffron

Saffron is a medicinal and culinary spice that has been traded and used throughout Eurasia for thousands of years. Ancient Persians used saffron to treat a variety of ailments, including depression, and modern research has since supported this use, with studies indicating that saffron has a variety of antidepressant actions in the brain [554,555]:

- Increases serotonin signaling
- Antioxidant
- Reduces neuroinflammation
- Neuroprotective

Numerous meta-analyses of clinical trials have reported that 30 mg per day of saffron has a potency comparable to routinely prescribed antidepressant drugs but with less side effects in individuals with mild-to-moderate depression [556–559].

To illustrate this point, let's look at the largest of these meta-analyses, which included 11 randomized controlled trials comparing saffron to either placebo or antidepressant medication in individuals with mild-to-moderate depression [556]. Saffron reduced levels of depression by an average of 52%, which was comparable to standard drug therapies.

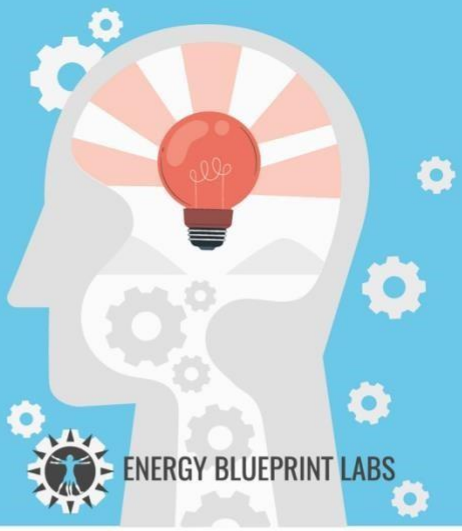


Recommended Dosing: Supplement 30 mg of saffron per day.

Start boosting your brain power, mood and focus today! Click the button below, to buy our premium supplement UltraBrain

Buy Now !

THE 18 BEST NOOTROPICS FOR OPTIMIZING MOOD, BRAIN PERFORMANCE, AND LONG-TERM BRAIN HEALTH



Rhodiola Rosea

Lion's Mane Powder

Tocotrienols

Magnesium Taurate

Bacopa Monnieri

Ginkgo Biloba

Coffee Fruit (CognatiQ™)

Agmatine sulfate

Ashwagandha

Dopamine Boosters

Mucuna Pruriens 

Tyrosine 

Acetylcholine Boosters

Alpha-GPC 

CDP-choline 

Huperzine A 

GABA

Serotonin Boosters

5-HTP 

Saffron 

Polygala Tenuifolia

Deep and Rejuvenating Sleep

The health benefits of a good nights' rest can't be understated. Much like an old-school analog clock, our biology requires synchronized gears and a timesetter to work properly. If just one gear isn't working, or if no one sets the time, the entire clock is useless — and you can't tell time with a broken clock.

If your master clock isn't matching up to your environment, either because of too little sunlight during the day or too much artificial light and not enough sleep at night, then your body won't be receiving the signals it needs to function properly. There is an ever-growing body of evidence linking circadian dysregulation to many of the most common chronic diseases of civilization:

- Mitochondrial dysfunction [560]
- Oxidative stress [561]
- Chronic, low-grade inflammation [562]
- Obesity [563]
- Type 2 diabetes [564]
- Cardiovascular diseases [565,566]
- Neurodegenerative diseases [567,568]
- Psychiatric disorders [569,570]
- Cancer [571]

These chronic diseases have also been linked to sleeping less than 7–8 hours per night and having poor quality sleep [572]. All it takes is just several days of poor circadian hygiene and sleep quality to reduce vigilance and cognitive performance [573,574], as well as cause signs of metabolic dysfunction like increased blood glucose levels, worsened insulin sensitivity, heightened inflammation, blunted leptin and cortisol rhythms, and elevated blood pressure [575–577].

Some researchers have even proposed changing the term *metabolic syndrome* — a cluster of physiological abnormalities that are associated with heart disease and type 2 diabetes — to the term *circadian syndrome*, due to the unfailing ability of circadian dysregulation to cause metabolic dysfunction [578].

The following supplements can help you fall asleep more quickly, stay asleep, and wake up refreshed and rejuvenated. Most increase GABA signaling and have

a sedative effect, thereby helping calm anxiety, promote relaxation, and smooth the transition from wake to sleep.

The benefits of these compounds will be greatest in those who are struggling with circadian dysregulation, insomnia, chronic fatigue, chronic stress, or an anxiety disorder. They should all be taken 30–60 minutes before bed.

Melatonin

Melatonin is naturally secreted by our brain at night to help transition us from wakefulness to sleep. As such, it should be no surprise that supplementation has been heavily investigated for its benefits towards sleep.

Numerous meta-analyses have reported that supplementing with 1–12 mg of melatonin improves sleep quality in adults and children with a variety of health conditions including:

- Primary sleep disorders like insomnia [579,580].
- Secondary sleep disorders resulting from other medical conditions [581].
- Neurodegenerative disorders like Alzheimer's disease [582,583]; and
- Neurodevelopmental conditions like autism and attention-deficit hyperactive disorder [584,585].

Moreover, these doses of melatonin have also been shown to lower fasting glucose [586], blood pressure [587], systemic inflammation [588], and oxidative stress [589,590], suggesting that there are multiple health benefits including energy above-and-beyond improved sleep quality with supplementation.

Particularly notable is a study of adults with chronic fatigue syndrome, where nightly supplementation with 5 mg of melatonin significantly reduced fatigue and improved concentration, motivation, and activity levels by 12–16% after just three months [591].

All that said, there are anecdotal reports of melatonin interfering with sleep when taken in too high of a dose, which is obviously opposite of its intended purpose. This appears to be highly individual and not well-researched in the scientific literature, but it's possible that individual differences in melatonin receptor distribution and density play a role [592,593].

Thankfully, the solution is rather simple: Start with a low dose of melatonin and slowly work your way up to higher doses until your personal upper-limit for tolerability is found. You'll know that you hit that threshold if you wake up feeling groggy or experience any sleep difficulties for two to three nights (not just a one-off occurrence). Just 300 mcg of melatonin mimics what we could obtain with good sleep hygiene [594], so this is a good dose to start with. In *The Energy Blueprint* program, we've found that a subset of individuals (possibly as high as 20% of people) are *extremely* sensitive to even small doses of melatonin, where any more than 1 mg disturbs sleep.

As a final point, it also needs to be mentioned that supplementing with melatonin does not interfere with your own natural production at doses of 500 mcg [595], 2 mg [596], 5 mg [597], or 50 mg [595]. However, keep in mind that regularly using melatonin to improve your sleep will cause a sensation of reduced sleep quality if you stop using it.

Recommended Dosing: Take 300 mcg to 10 mg of melatonin per day.

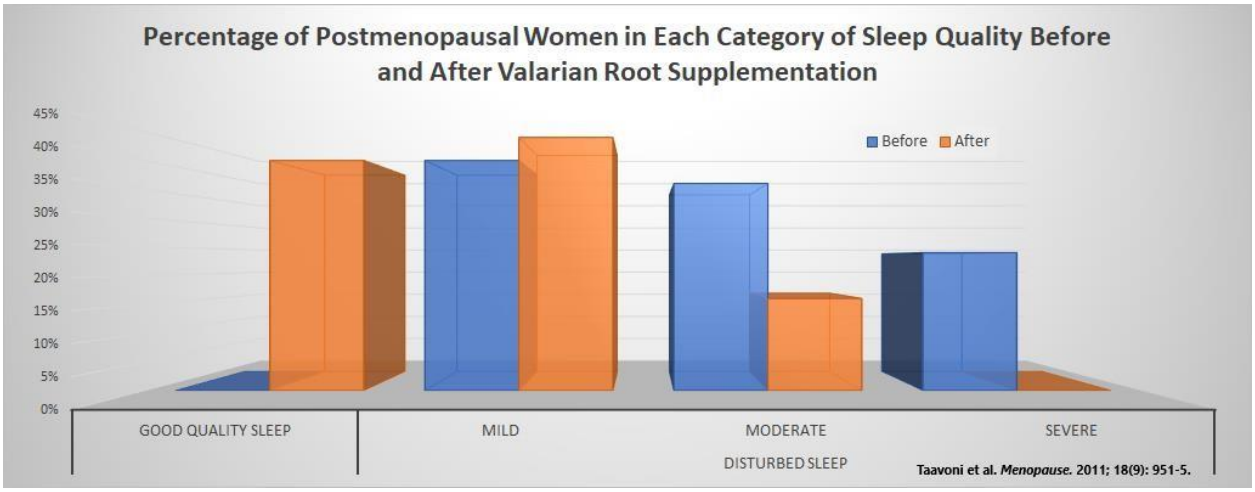
Valerian Root

Valerian root (*Valeriana officinalis*) is one of the best-researched and most common sleep aid supplements on the market, second only to melatonin. It's use as a sedative dates back to the first century, with particular use for treating nervous disorders and insomnia in the Middle Ages.

Based on a systematic review of 23 studies looking at how valerian impacts sleep quality, consistent benefits were observed with supplementation of 450–1400 mg per day, provided that the whole root was used [598]. While benefits were observed with valerian root extracts, they were inconsistent, likely due to the diversity of bioactive compounds that may be lost or reduced in the extract preparation.

In other words, for valerian root to consistently benefit your sleep, you want to go with the whole nature-made root, not some modern extract. Benefits were observed in healthy adults, those suffering from insomnia, and those with conditions in which sleep is often impaired.

In particular, given that women are far more likely to suffer from chronic fatigue and poor quality sleep than men, it's notable that valerian has shown substantial benefits for postmenopausal women. Nursing and midwifery researchers from Tehran University of Medical Sciences provided postmenopausal women with a gram of valerian root to be taken nightly for a month, and found that average sleep quality improved by a staggering 40% [599]!



Here's another way to view their incredible findings: before supplementation, zero of the women had good quality sleep, and a quarter had severe sleep disturbances. After supplementation, 40% had good quality sleep, zero had severe sleep disturbances, and the number with moderate sleep disturbances was cut by more than half.

While the precise mechanism of action hasn't yet been pinned down, current evidence points towards an increase in GABA signaling and direct sedative effect of its phytochemicals on the brain [600,601].

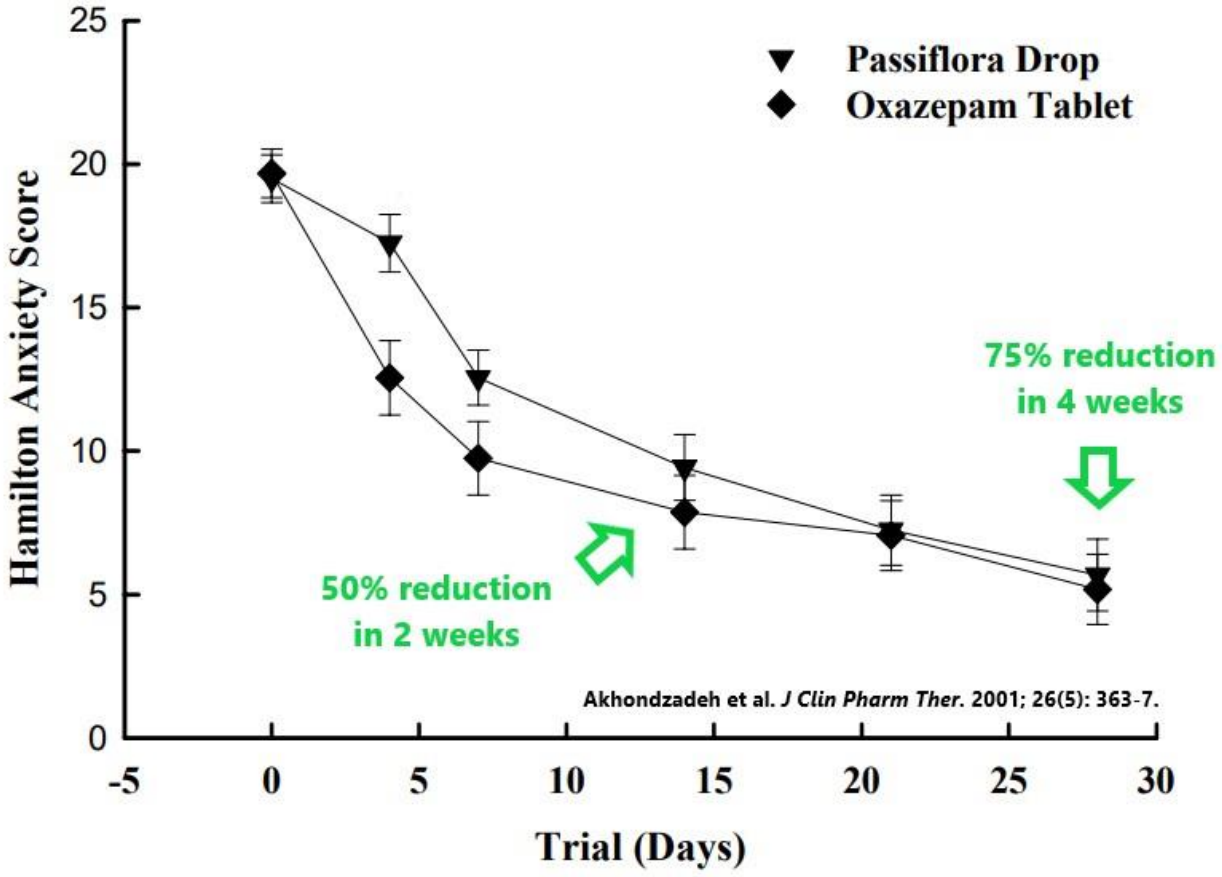
Recommended Dosing: Take 450–1400 mg of valerian root per day.

Passionflower

Passionflower (*Passiflora incarnata Linneaus*) has been used for thousands of years by Native Americans as a sedative and treatment for anxiety [602]. It works primarily through activating GABA receptors in the brain that are responsible for relaxation [603].

There is a subset of people who struggle with sleep primarily because of stress and anxiety, and perhaps difficulty turning off racing thoughts at night. Passionflower is a very useful supplement for this group of people, as it is a supplement that can help those with stress and anxiety unwind for the day and have an easier time getting a good night's rest. Several studies have shown that supplementing with 360–700 mg of passionflower reduces anxiety in the 30–90 minutes after taking it [604–606].

In fact, in adults with generalized anxiety disorder, 45 drops of a passionflower tincture was just as effective as a common anti-anxiety medication (benzodiazepine) for reducing anxiety, with both cutting anxiety scores by half after just 2 weeks and by nearly 75% after 4 weeks [607].



Expectedly, the data strongly supports the use of passionflower for inducing sleep and improving sleep quality [608,609]. In particular, passionflower increases the amount of time that is spent in deep, rejuvenating, slow-wave

sleep [610], and without any side effects common with sleep and antianxiety medications [611].

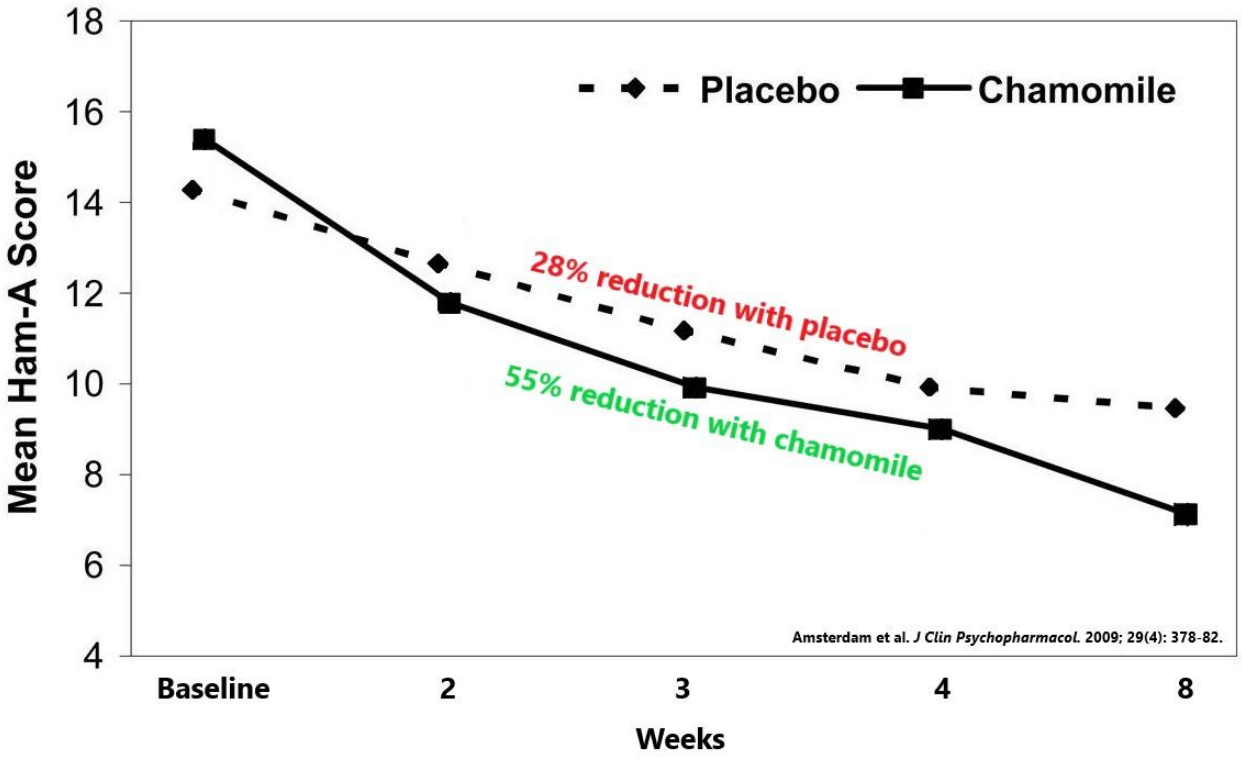
Recommended Dosing: Take 360–700 mg of passionflower per day.

Chamomile

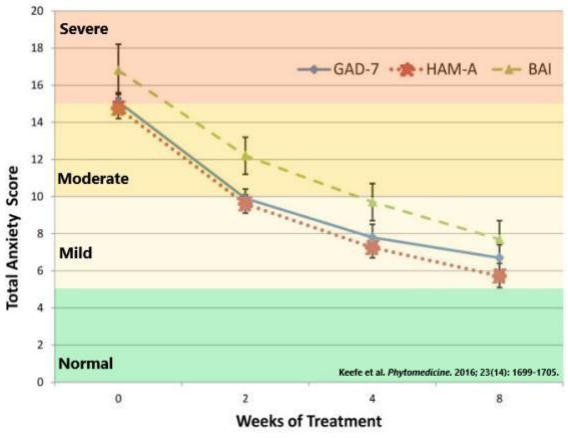
Chamomile is a daisy-like flower traditionally brewed into tea and used to treat a variety of ailments, particularly those characterized by inflammation and oxidative stress [612]. It's also been used as a mild sedative to calm nerves and reduce anxiety.

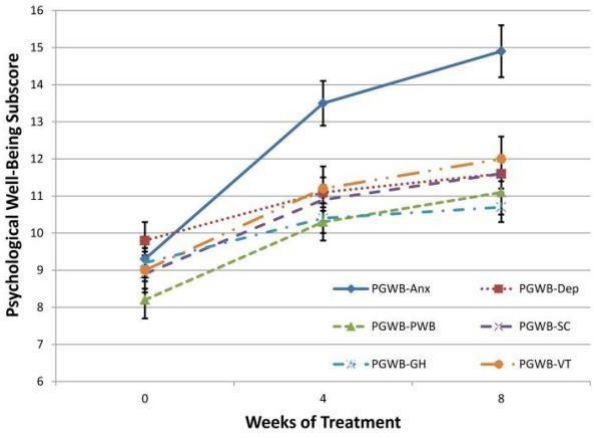
You've likely seen it in teas and supplements that are advertised to help with sleep, and with good reason. A meta-analysis of six studies administering 400–2000 mg of chamomile before bed found it to significantly improve sleep quality [613].

For those of you battling anxiety, there may be additional benefits. A group of researchers from the University of Pennsylvania School of Medicine have published several studies in adults with generalized anxiety disorder demonstrating the clinical efficacy of chamomile. It started with a small placebo-controlled pilot study, in which 1100 mg/d of chamomile was shown to cut anxiety in half after 8 weeks [614].



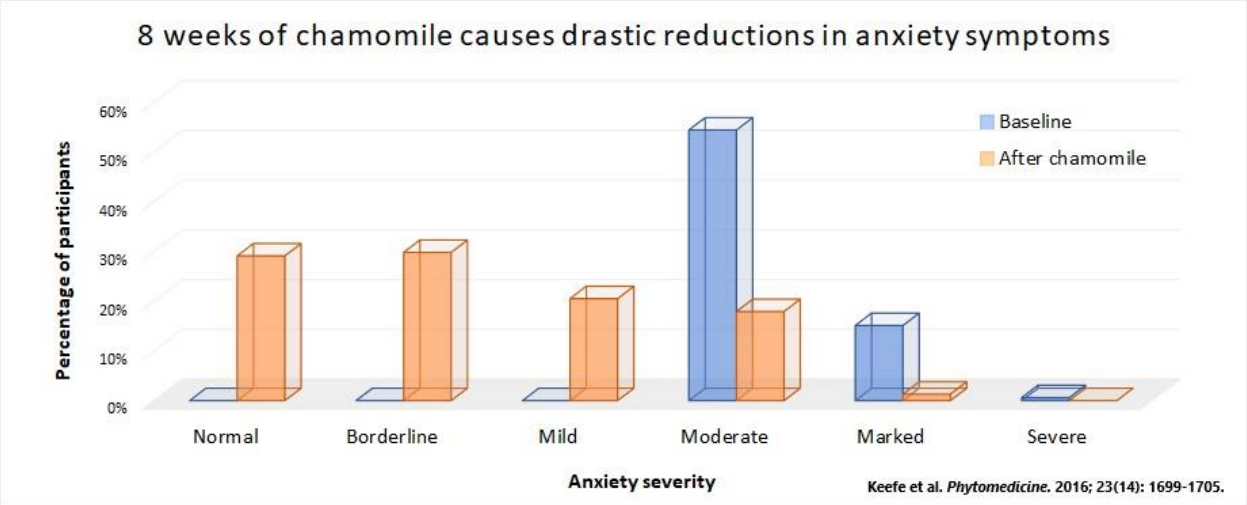
In a larger follow-up study, the researchers confirmed their previous findings — after 8 weeks of supplementing with 1500 mg/d of chamomile, the participants had their anxiety cut in half and improved several other aspects of mental well-being [615]. Basically, the average participant went from having moderate-to-severe anxiety down to barely mild anxiety.





To really hammer this point home, here's another way to look at these findings. When the study started, about 84% of participants had moderate anxiety and 15% had marked anxiety. After just 2 months of using chamomile, almost none

had marked anxiety, only 18% had moderate anxiety, 21% had mild anxiety, and 60% either had no anxiety or borderline anxiety.



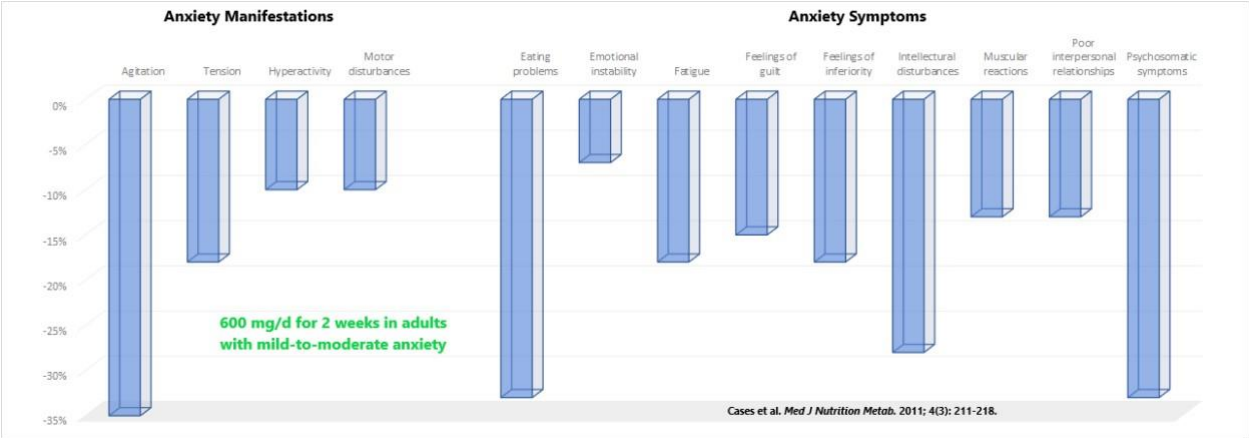
So, in their third and final study, the researchers took a group of these participants who had their anxiety reduced by at least 50% and had them continue taking the chamomile or start on a placebo for another 6 months [616]. Those who continued with chamomile were 48% less likely to relapse with anxiety symptoms compared to those using the placebo. Moreover, the average time to relapse was 3 months in those using chamomile, compared to just 6 weeks in the placebo group.

Recommended Dosing: Take 1100–1500 mg of chamomile per day.

Lemon Balm

Lemon balm (*Melissa officinalis*) is a plant native to the Mediterranean basin and central Asia, where it was traditionally used for the treatment of mental disorders and complaints relating to the central nervous system [617]. Today, it is commonly used to promote sedation and relaxation.

Several studies have found that taking 300–1600 mg of lemon balm promotes calmness in the hours following supplementation [618,619], particularly when dealing with stressful situations [620,621]. These benefits extend to individuals battling anxiety as well, where supplementing with 600 mg per day has been shown to reduce a variety of anxiety manifestations and symptoms [622].



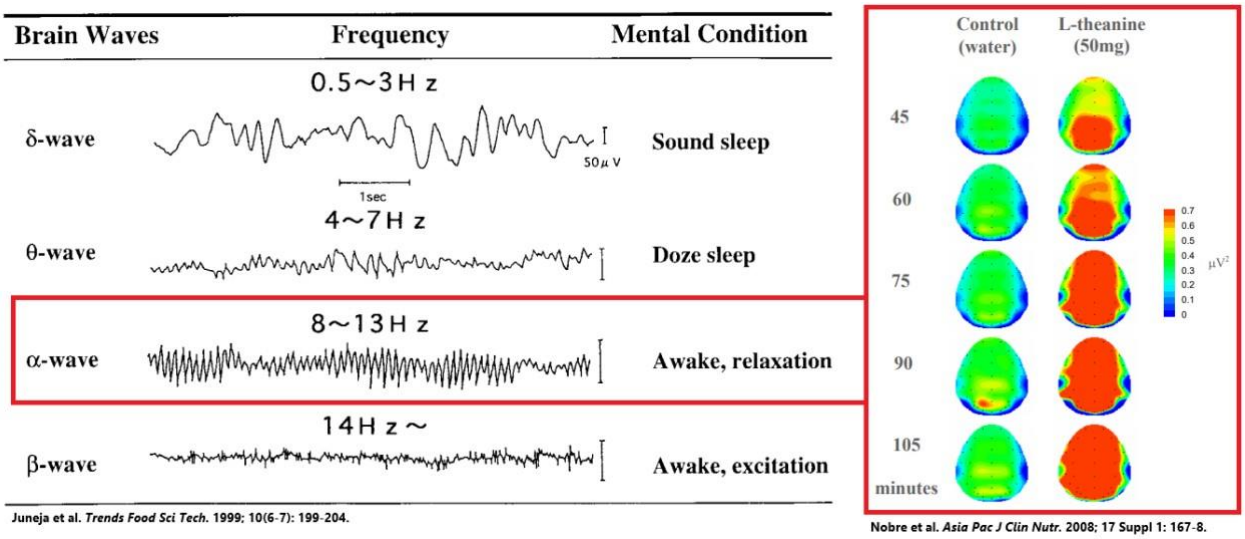
Notably, insomnia was one of the most debilitating symptoms for anxious adults, and lemon balm supplementation reduced it by an average of 42%, with 85% of people dealing with insomnia experiencing a benefit. Other studies have found similar benefits for sleep when lemon balm is combined with valerian root [623,624].

Recommended Dosing: Take 300–1600 mg of lemon balm per day.

Theanine

Theanine is a naturally occurring amino acid found in tea that alters neurotransmitter signaling within the brain. After consumption, it crosses the blood-brain barrier, interferes with excitatory glutamate signaling, stimulates dopamine release, and promotes inhibitory neurotransmission, thereby helping promote a state of relaxation [625,626].

In fact, electroencephalography (EEG) studies have shown that theanine shifts brain waves towards alpha oscillatory patterns indicative of a relaxed state, particularly in those with high levels of baseline anxiety [627–631].



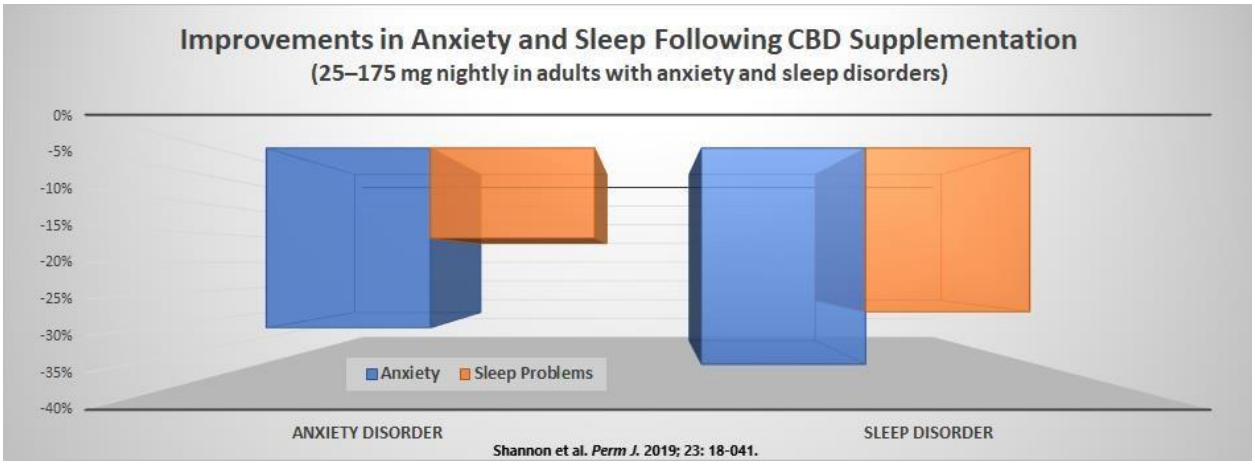
Accordingly, several studies have found that theanine supplementation improves feelings of relaxation, tension, calmness, and anxiety in the hours following doses of 200–600 mg [632,633]. There is also evidence that theanine improves sleep quality, likely through its anti-anxiety and calming effects [634,635], and can help offset the stimulatory effects of caffeine [636,637].

Recommended Dosing: Take 200–600 mg of theanine per day.

CBD Oil

Cannabidiol (CBD) oil is the non-psychoactive component of cannabis plants (marijuana and hemp). It's currently being heavily investigated as a therapeutic for anxiety, depression, addiction, epilepsy, neurodegeneration, chronic pain, and inflammatory diseases [638,639]. While research on CBD and sleep is still in its infancy, it is promising [640].

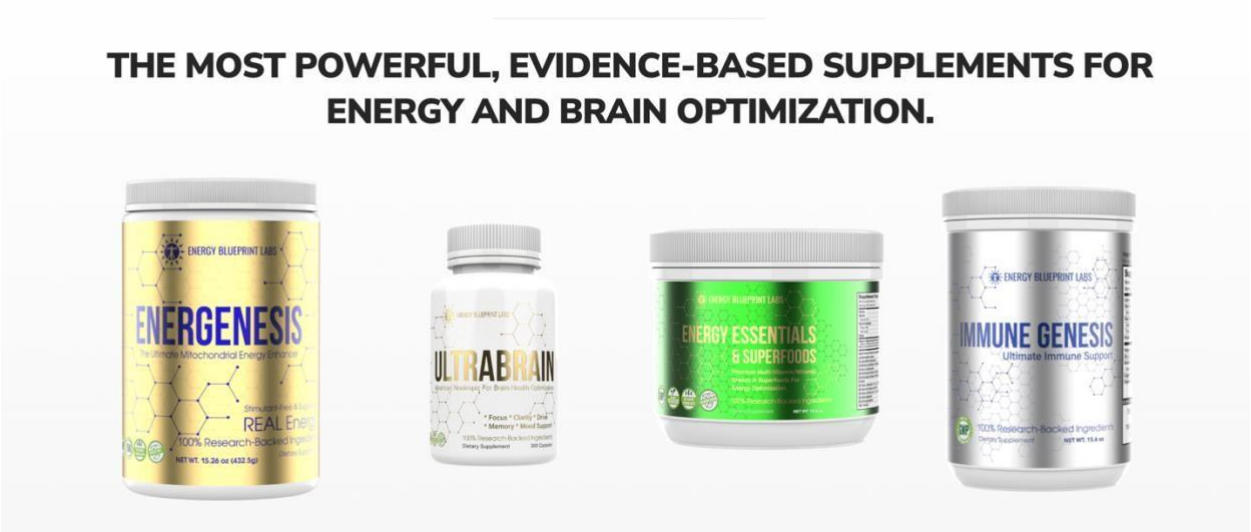
The cannabinoid system is intimately tied to the sleep-wake cycle by inhibiting the arousal system in the brain and promoting a hypnotic-like state [641,642]. The sleep benefits of CBD have been shown in adults with sleep disorders at doses of 75 mg per night [643], and at 25 mg in children [644]. Another study involving 72 adults complaining of anxiety and poor sleep found that 25–175 mg of CBD nightly reduced anxiety by 31–38% and improved sleep quality by 15–28% after three months [645].



Anecdotally, in *The Energy Blueprint* program, we've observed that individuals who seem to be resistant to other sleep aids, like melatonin and the variety of herbs already discussed, often have excellent results using CBD oil before bed. The only issue with CBD is that the research that used CBD for sleep enhancement used high doses, which can be quite expensive and often unaffordable for many people. Still, if you're interested in trying it and it's within reach financially, then we recommend experimenting with doses of 25–100 mg taken 30–60 minutes before bed.

Recommended Dosing: Take 25–100 mg of CBD oil per day.

Check out our science backed supplements for energy, brain performance and mood resilience.



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THE TOP 7 COMPOUNDS

FOR DEEP AND REJUVENATING SLEEP

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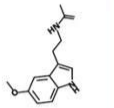
- Melatonin 
-  Lemon Balm
- Valerian Root 
-  Theanine
- Passionflower 
-  CBD Oil
- Chamomile 

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