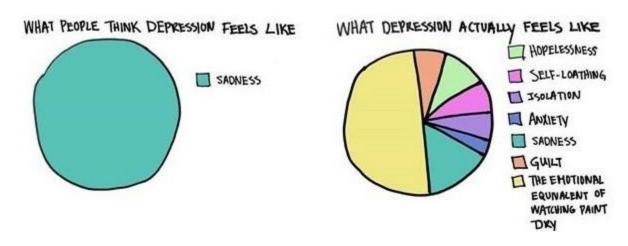


I'm pretty confident that most of us have felt down in the dumps before. Sadness is a normal emotional state of pain, characterized by feelings of loss, despair, grief, and disappointment.

These feelings are distinct from *depression*, which is a mood state characterized primarily by apathy and anhedonia. Sadness is often a component of depression, but you can be sad and still enjoy life. With depression, there's a loss of interest and pleasure from activities that were once enjoyed.

People with depression may have wonderful lives — they would even admit this is true — and yet they still feel horrible. It makes everything less enjoyable, less interesting, and less important; it saps energy, it saps motivation, and it saps the ability to experience joy.



This isn't to say depression is abnormal. Having a depressed mood is a normal reaction to tragic life events like losing a loved one, but only when temporary. If depression persists for weeks, then it's considered a clinical mood disorder, which are psychiatric conditions that cause notable distress in your daily life or impair your ability to function.

And believe it or not, depression is, by far, the most common psychiatric conditions in the world, afflicting roughly 1 in 4 adults [1]. It's also one of the most impactful, coming in as the second leading cause of disability in young and middle-aged adults, second only to low back and neck pain [2].

While there are a variety of antidepressant medications available, these often come with a host of nasty side effects that can actually contribute to worse depression by virtue of how they affect your life. In this article, we're going to discuss some far more safe and effective natural remedies to lift your spirit and restore your hope.

# Lifestyle Interventions

To start off our list, we need to look at our lifestyle. While modernity has blessed us with numerous technological and medical advances, it has also led to a range of lifestyle issues that take a toll on our mental health.

People today are more sedentary, chronically stressed, spend more time indoors, and don't sleep well. All of these factors have been linked to depression and deserve first-line consideration for

improving psychological health and mental wellbeing [3,4]. So, that's what we are going to focus on first, what we consider to be the four pillars of lifestyle for good mental health:

- Regular sun exposure
- Quality sleep
- Exercise
- Stress management

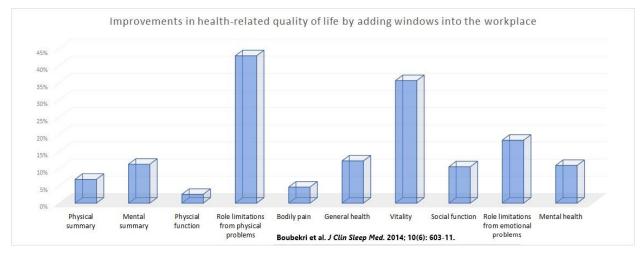
## Sunlight



First and foremost, if you are looking for a supplement to help with depression, then you should start your shopping experience outside under the sun. Through impacting our circadian rhythms and blasting our body with bioactive light, sunlight is truly medicinal when it comes to mental health and especially depression.

Throughout evolutionary history, we awoke to the sun. Depending on the season, we may have gotten up a little before or after sunrise, but the sun was pretty much always there to brighten our days. Yet, modernity has made us transition from a people of the sun to a people of the cubicle.

If we would simply add some natural light back into people's lives, maybe this pandemic of depression wouldn't exist. Consider this: simply working in an office building with windows increases physical and mental health, vitality, and sleep quality compared to working in a windowless prison [5].



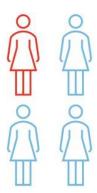
And this isn't the only study showing benefits — several other interventions that increase the amount of natural sunlight into people's lives have shown it improves mood and reduces stress [6–8]. Hell, even using artificial lighting that is designed to mimic an open blue sky on a sunny day leads to improvements [9]:

• A notably higher sense of connectedness to nature

- Higher parasympathetic tone (rest and regenerate)
- Lower sympathetic tone (stress response)
- Similar work performance with a lower perceived effort
- Greater melatonin secretion later on at night

One little known fact about depression is that many depressive bouts are related to changes in seasonality — roughly 1 in 4 people with bipolar disorder have seasonal depression that is worse in the winter [10], and even people with chronic depression experience a bump in symptoms during the winter [11].

# Roughly 1 in 4 people with bipolar disorder have seasonal depression that is worse in the winter



Seasonal affective disorder and non-seasonal affective disorders: Results from the NESDA study





The seasonal distribution of major depressive episodes was not different for participants with or without SAD. Conclusions SAD may be a measure of severity of depression with a subjectively perceived worsening of symptoms in the winter months. Declaration of interest Y.M. has received research funding and served as a consultant for Royal Philips Electronics

This type of seasonal depression is called seasonal affective disorder (SAD) and it's believed to come about from changes in brain chemistry that result from a lack of sunlight. At a population level, clinical and subclinical SAD affects roughly 1 in 5 people living at

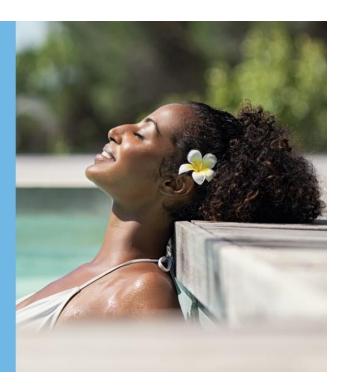
latitudes around New York but only 4 in 100 people living in sunny Florida [12].

And that's a huge problem because depression, whether intermittent or chronic, can be a tremendous risk to the individual due to its perpetuation of suicidal thoughts [13]. In non-equitorial countries, Google searches for depression peak in the winter [14], and suicide rates are highest around the end of winter and beginning of Spring [15]. In both cases, these patterns aren't observed in areas around the equator where the sun always shines.

Unsurprisingly, SAD is treated by mimicking the sun. It's literally the condition that launched the entire bright light-box industry, since hitting yourself with at least 10,000 lux of white light in the morning is an established way to prevent the development of SAD [16]. But even in chronic, non-seasonal depression, meta-analyses have shown that bright light therapy reliably improves depressive symptoms [17–19].

And that's just bright light. The sun also puts out UV radiation that itself has shown to have antidepressant effects [20,21], likely through stimulating vitamin D synthesis.

Combining bright light therapy with UV radiation therapy provides a greater antidepressant benefit than bright light therapy alone.



Several studies have reported that vitamin D deficiency is related to more severe depression in those with clinical depression [22–24], particularly an inability to feel pleasure [23], and a meta-analysis of interventions reported that vitamin D supplementation significantly improved depressive symptoms [25]. Sunlight is likely to accomplish the same thing.

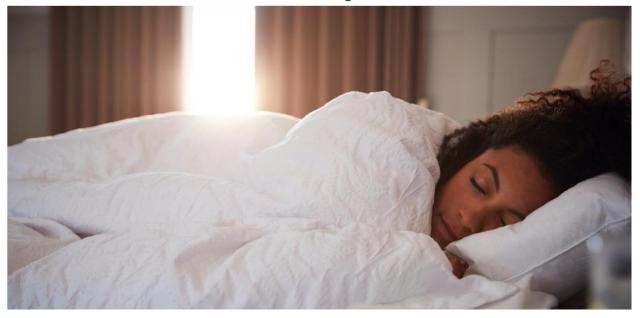
Plus, in both humans and animal models, depression is linked to mitochondrial deficits and inflammation within the brain that can be resolved with the use of infrared light therapy [26]. At least one pilot study has shown that hitting the forehead with infrared light puts some individual's depression into remission, with an overall reduction in depressive symptoms of 54% [27].

Guess what the largest natural source of infrared radiation is? Yep, sunlight. About 30% of the light put out by the sun is infrared radiation.

Through facilitating changes in brain chemistry and function, sunlight directly battles depression.

Regular sun exposure can be considered central to the treatment of depression through synthesizing vitamin D, providing an ambient source of bright light, and correcting brain deficits in mitochondrial function with infrared light.

Sleep



Coming off the heels of getting ample sun exposure during the day, we need to talk about getting ample quality sleep during the night — our second lifestyle pillar for good mental health.

The American Academy of Sleep Medicine and the Sleep Research Society agree that getting too little sleep is really bad for health [28]. They agree that getting less than 7–8 hours of sleep per night is linked to worse:

- Cardiovascular health
- Metabolic health
- Mental health
- Immune function
- Physical performance
- Pain
- Risk of dying

Roughly 3 out of 4 adults with depression have symptoms of insomnia and sleep disturbances are a predictor for one's treatment success, including their risk of relapse and depressive recurrence [29]. In a meta-analysis of 21 studies, individuals with insomnia had a 2- to 3.5-fold greater risk of developing depression [30].

The sleep-depression cycle is rather straight-forward and selfperpetuation. Poor quality sleep causes fatigue and difficulty coping with daily life, which can reduce self-esteem and increase feelings of worry and stress in susceptible individuals, which can feed back into reducing sleep quality. Then the cycle repeats.



While there are many aspects of getting a good night's rest, the most important is minimizing artificial light at night. Blue and green light tell the body that it's daytime, so exposure to artificial lighting at night absolutely wrecks our circadian system. Thankfully, the solution is relatively simple: block it!

Wearing amber glasses has been shown to help maintain sleep quality in people exposed to light at night [31]. It's even been shown to help insomniacs sleep [32]! Can you imagine having insomnia and experiencing a 16–20% improvement in sleep quality, distress caused from poor sleep, and quality of life from just wearing some goggles for 2 hours before bed?

One particularly relevant study had college students play on their smartphone for an hour while lying in bed before going to sleep [33]. They fell asleep roughly 25% faster when they wore amber glasses that filtered out most of the blue light compared to when they didn't wear any light-filtering glasses.

The mental health and sleep benefits of minimizing artificial light at night have such a strong foundation of evidence that there is currently an intervention being conducted in hospitalized psychiatric patients looking at the health effects of eliminating blue light from the psych ward lighting system between 6:30 p.m. and 7:00 a.m [34].

Getting a good night's rest is a critical component of mental health. There's a clear link between poor quality sleep and the risk of depression, so focusing on optimizing sleep hygiene should be prioritized.

One of the easiest ways to do this is to simply block out artificial light at night, which inappropriately signals daytime to the brain.

#### **Exercise**



Our third lifestyle pillar for good mental health is exercise. Generally speaking, the health consequences of sedentariness and health benefits of exercise need no introduction. Suffice to say, they play out when it comes to mental health too.

Dedicated exercise and being more leisurely active interacts with our brains in numerous ways to help balance mood and make us feel good [35]:

- Reduce neuroinflammation and oxidative stress [36].
- Increase brain-derived neurotrophic factor (BDNF) [37].
- Enhance neurogenesis [38].
- Increase serotonin signaling [39].
- Increase beta-endorphins [40].

• Balance the neuroendocrine axis and normalize cortisol [41].

Aside from exercise providing marked beneficial effects on neuroendocrine systems, it also increases self-efficacy and self-esteem (via activity scheduling and attainment of goals) which are important psychological issues among people who are depressed [42].

From a practical standpoint, at least 8 separate meta-analyses of randomized controlled trials have reported that both aerobic and resistance exercise effectively reduce depression in children, adults, and older adults [43].

For example, the most recent meta-analysis looking at aerobic exercise exclusively, which involved 11 randomized controlled trials, found that just 45 minutes of exercise 3 days per week substantially reduces depression after 2–3 months [44]. In fact, the effect of exercise was superior to that of antidepressant drugs and psychological counseling.

As another example, the most recent meta-analysis looking at resistance training exclusively, which involved 33 randomized controlled trials, found that regular training reduced depressive symptoms regardless of the total training volume, that 1 person would benefit for every 4 that participated, and that you were more likely to benefit the more depressed you were to begin with [45].

Now, if you had to choose between aerobic exercise and resistance training, then your best bet is to go with what you enjoy. While resistance training does have a small benefit over aerobics, it's not enough to really push in that direction if you would much rather go for a run or do the stair-stepper.

And if you simply don't want to do any type of formal exercise, then don't worry, we have plenty of evidence indicating that even low levels of regular and consistent activity — like walking or gardening — can help raise your spirits and prevent depression [46].

Exercise, whether it be aerobic exercise or resistance training, is one of the best things you can do for your brain and mood state, being even more effective than antidepressant drugs and psychological therapies.

# **Stress Management**

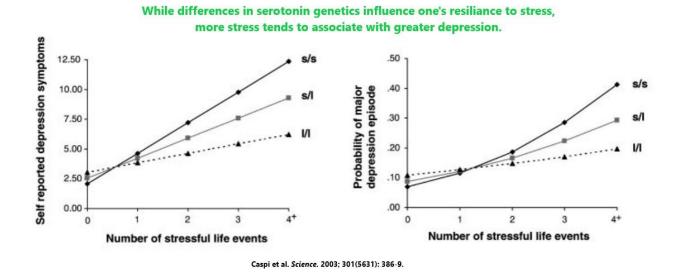


Our fourth and final lifestyle pillar of mental health is stress management. We all get stressed out in life — it's a normal part of existing! But chronic stress is an artifact of modernity.

From an evolutionary perspective, chronic stress didn't exist. If you were being chased by a lion, you either died or survived, and the stress response came and went. Today, we get stressed by countless artifacts of the modern world, like work overload, financial troubles, and social embarrassment.

And this chronic stress seriously messes with our mental wellbeing, to the extent that some researchers have proposed certain subtypes of depression be called *stress-induced depression* [47]. This was evident when researchers from King College London followed over 1,000 individuals from the time they were 3 years old up until they were 26

— greater stress through childhood and young adult life was significantly associated with a greater likelihood of experiencing depression [48].



One reason for the stress-depression link is due to how stress affects neurotransmitter signaling in the brain, particularly that of serotonin. Serotonin is a tiny molecule with a big job: regulating brain development and function, sleep, appetite, mood, memory, aggression, and digestion. It's been implicated in practically every type of behavior.

Normal, temporary stress causes increases in serotonin levels that help us cope with the event — it's a form of adaptation. Chronic stress completely screws up this system.

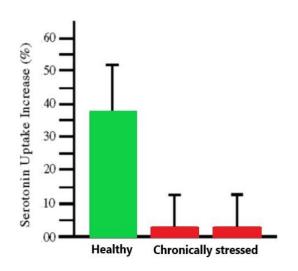
With serotonin, the receptors that it needs to bind with in order to have an effect start to take a break from work, with less and less

showing up when serotonin calls [49]. The result is that less serotonin is able to transmit its signal, regardless of how much you have.

Another way to look at this is that serotonin is the worker and its receptor is the machine needed to work. You can have hundreds of workers show up at the factory, but that doesn't matter if only 10 machines are available to work with — 90 of the workers may as well not be there.

These concepts are easily illustrated in a study by researchers from the Weizmann Institute of Science in Israel, who looked at how much serotonin was taken up by cells in response to an infusion of cortisol in both healthy folk and people under chronic stress [50]. The normal increase in serotonin

#### Effect of chronic stress on serotonin uptake

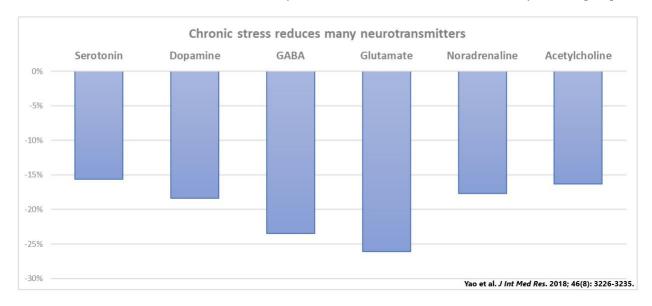


Tafet et al. Cogn Affect Behav Neurosci. 2001; 1(4): 388-93.

uptake caused by cortisol was completely abolished in people under chronic stress.

What all this means is that being chronically stressed will leave your body and brain deprived of serotonin due to its natural response of down-regulating serotonin receptors to prevent overstimulation.

And it's not just serotonin that's affected. People who report higher levels of burnout at work have 15–25% lower concentrations of several neurotransmitters compared to their less stressed peers [51].

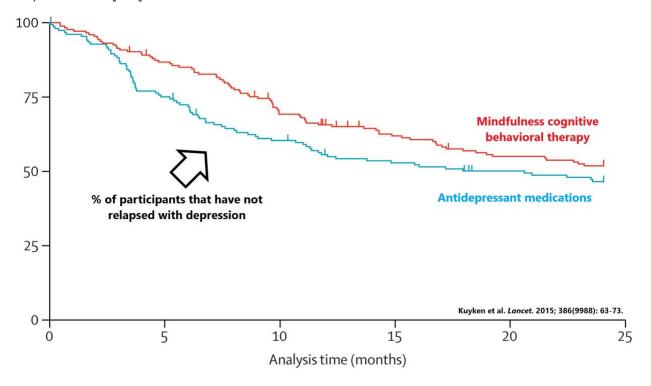


Thankfully, stress reduction techniques like mindfulness meditation are incredibly effective at treating depression. Meditation isn't mainstream and probably conjures up images of Buddhist monks for most people. But it serves as a good opportunity to mindfully introspect about what troubles us and help us work through our stress.

A huge analysis of 47 studies with over 3,500 people clearly showed that mindfulness meditation programs reduce levels of anxiety,

depression, pain, and stress while increasing mental health-related quality of life [52]. These benefits were seen in as little as three to four 1-hour sessions over 8 weeks.

Mindfulness may even be able to replace pharmaceutical antidepressants. The PREVENT trial showed that, over a 2-year period, mindfulness cognitive behavioral therapy led to similar rates of relapse and remission as standard drug therapies in those with depression [53].



It makes sense, really: If you have unproductive worries, you can train yourself to experience those thoughts differently. Mindfulness meditation teaches you to recognize your stressful thoughts and reframe them in a positive manner.

Chronic stress drains the brain of neurotransmitters, particularly serotonin, and predisposes us to depression. Engaging in healthy stress management techniques, like mindfulness meditation, can go a long way towards improving mental health, possibly rivaling the effects of antidepressants.

# Supplements

With our lifestyle pillars in place, let's turn our attention to supplements. There are several natural compounds that have been shown to have amazing benefits for those dealing with depression - several of these compounds have even been shown to have as strong of an impact as antidepressant drugs (and without the side effects)!

### Saffron



Saffron is a medicinal and culinary spice that has been traded and used throughout Eurasia for thousands of years.

It's a mainstay of Middle

Eastern cuisine and currently

the most expensive spice in

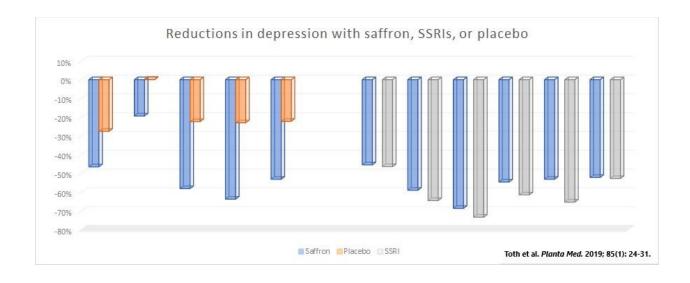
the world.

Ancient Persians used saffron to treat a variety of ailments, including depression. Modern research has since supported this use, with studies indicating that saffron has a variety of antidepressant actions in the brain [54,55]:

- Increases serotonin signaling Antioxidant
- Reduces neuroinflammation
- Neuroprotective

Numerous meta-analyses of clinical trials have reported that 30 mg/d of saffron has a potency comparable to routinely prescribed antidepressant drugs but with less side effects in individuals with mild-to-moderate depression [56–59].

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 [56]. Saffron reduced levels of depression by an average of 52%, which was comparable to standard drug therapies.



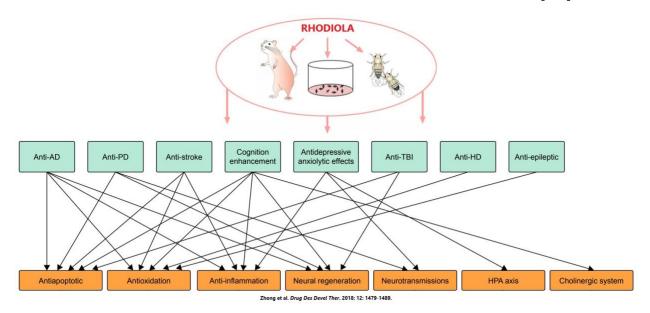
Saffron is a potent antidepressant herb, able to cut depression in half and rival pharmaceutical drugs through increasing serotonin signaling and protecting the brain from inflammation and oxidative stress.



# Rhodiola Rosea

Rhodiola is a medicinal herb traditionally used for enhancing mental performance and resilience to stress [60], effects that are due to the numerous ways

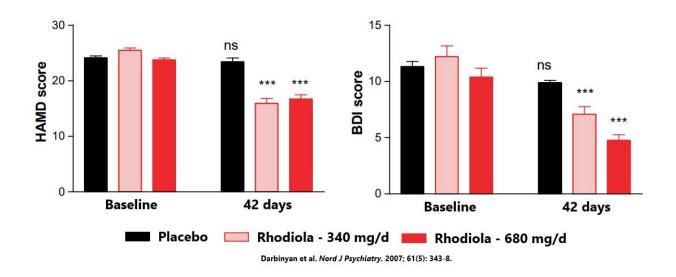
rhodiola interacts with genes, signaling pathways, and molecular networks within neuronal cells to alter emotional behavior [61].



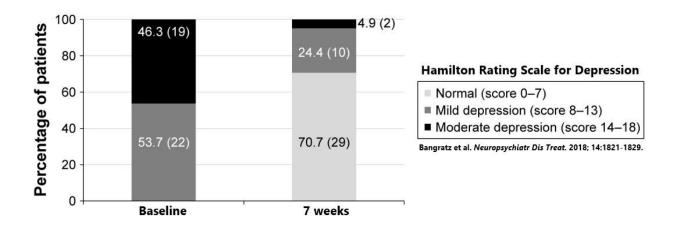
Specifically, rhodiola acts within the brain as a neuroprotective, cognitive enhancing, and mood stabilizing agent through reducing neuronal cell death and promoting regeneration, functioning as an antioxidant and anti-inflammatory, facilitating neurotransmission,

and regulating several key mediators of the stress response within the hypothalamic-pituitary axis [62–64].

One of the ways these effects manifest is by reducing depression. For example, in adults with mild to moderate depression, 340 mg/d of rhodiola cut depression by a third after just 7 weeks [65].



In another study, combining 310 mg/d of rhodiola with 30 mg/d of saffron reduced depressive symptoms by 60% after 6 weeks, causing 70% of the participants to no longer suffer from clinical depression [66].



Rhodiola rosea is an adaptogen best-known for its ability to increase stress resilience by interacting with genes, signaling pathways, and molecular networks within neuronal cells to alter emotional behavior.

These effects have also lent it potent antidepressant effects, particularly when combined with saffron.

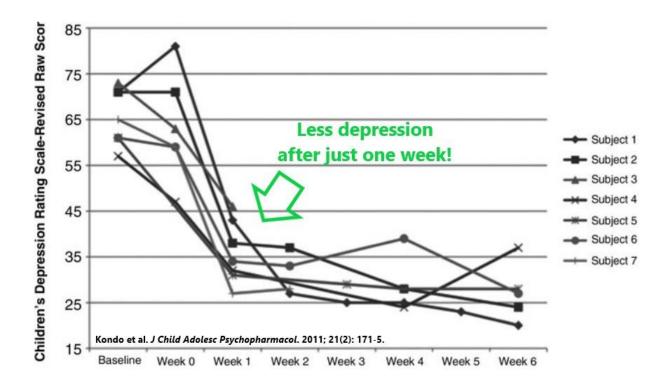
## **Uridine Monophosphate**



Uridine is one of the five standard nucleosides that make up the nucleic acids of genetic material (DNA and RNA). It is known to pass the blood-brain barrier [67], and is involved in several neurologically critical functions [68]:

- Required for the synthesis of brain phospholipids [69], and supplementation increases concentrations of phospholipid precursors in the brains of healthy adults [70].
- Plays a role in the formation of brain synapses that are required for learning and communications [71,72].
- Induces nerve growth and differentiation [73,74].

While research on uridine's antidepressant effects is preliminary, it is promising. In a study of bipolar adolescents suffering from depression, supplementation with 1000 mg/d of uridine was associated with a 58% reduction in depression after just 6 weeks [75].



Uridine is a necessary component of brain phospholipid synthesis, synapse formation, and nerve growth, with preliminary research suggesting it is able to drastically reduce depression in as little as one week.

## **Agmatine sulfate**

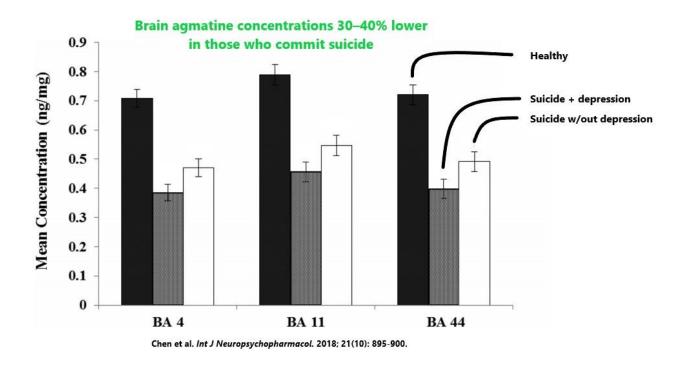
Agmatine is a neurotransmitter and neuromodulator (affects neurotransmission of entire neurons) that has anti-seizure, anti-pain, anti-anxiety, and antidepressant effects; modulates some of the processes involved in learning and memory; and interacts with the mechanisms of drug withdrawal [76].

In particular, agmatine has several unique biological effects within the brain that can help it fend off depression:

- Blocks the NMDA (N-methyl-D-aspartate) receptor and prevents excitotoxicity [77].
- Activates imidazoline receptors that increase beta-endorphin secretion [78].
- Activates the Nrf2 (nuclear factor E2-related factor 2) pathway that increases the production of antioxidant enzymes [79,80].
- Protects mitochondria from oxidative stress and cell death [81,82].

Collectively, the effects of agmatine have given it a high therapeutic value for treating neurological disorders and preventing neurodegeneration [83,84]. Unfortunately, human clinical trials haven't caught up to its vast potential.

For example, 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 [85].



Yet, to date, only one study exists looking at how agmatine supplementation impacts depression. In this 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" [86].

To put this in perspective, a score of 18 or higher on the Hamilton scale indicates severe depression, and these participants went from a score of 32 at the beginning of the study to a score of 3 within a month!

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.

While preliminary, these findings are almost unbelievable and definitely make agmatine something to consider for fighting depression.

Agmatine is a neurotransmitter and neuromodulator that affects numerous processes in the brain to produce nearly unbelievable antidepressant effects.

Research on this compound is incredibly preliminary but highly promising.

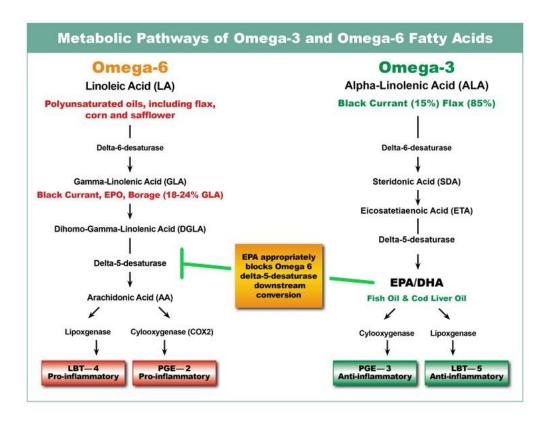
#### **EPA & DHA**



Most of you are probably familiar with the two classes of polyunsaturated fatty acids (PUFAs), omega-3 and omega-6, which each encompass several fatty acids that play a unique role in our immune system.

 Omega-3 fatty acids include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).  Omega-6 fatty acids include linoleic acid and arachidonic acid.

While a bit over simplistic, the omega-3 fatty acids support antiinflammatory processes in the body by creating resolvins and protectins, while the omega-6 fatty acids support inflammatory processes within the body by creating prostaglandins and leukotrienes.



Nutritionally, the long-chain omega-3 and omega-6 fatty acids are what matter, as these are the precursors to important signaling molecules in the immune system. When it comes to the omega-3

fatty acids, it's all the more important to obtain preformed EPA and DHA in the diet because ALA is not efficiently converted into them.

Studies of ALA metabolism in healthy young men indicate that approximately 8% of dietary ALA is converted to EPA and less than 4% is converted to DHA, with the values increasing to 21% and 9% in women thanks to the effects of estrogen [92]. So, plant-based omega-3 fatty acid sources, which contain only ALA, aren't a reliable source of EPA and DHA.

The entire reason EPA and DHA have been investigated for their role in depression is because depression has a strong inflammatory component. Quite a few randomized controlled trials have been conducted looking at fish oil supplementation as a treatment for major depressive disorder, and meta-analyses of these studies reported that supplementing with 1–6 grams of EPA and DHA does appear to have a significant benefit, especially with higher EPA doses and when used alongside antidepressants [93,94].

However, meta-analyses can't account for every little detail and it has been argued that fish oil really only benefits depressed people who have an insufficient EPA and DHA intake in their diet [95]. Granted, most people in the Western world don't consume a lot of seafood that would supply the EPA or DHA, and all it really takes is a little salmon or sardines on a regular basis.

EPA and DHA are long-chained omega-3 fatty acids found naturally in seafood that are required for proper anti-inflammatory signaling. Supplementation, particularly with EPA, has been shown to reduce depression, but likely only in those with a low baseline intake of fatty fish and seafood that supplies the EPA and DHA being supplemented.

### Lion's Mane

Lion's mane mushroom (also called *Yamabushitake* or *Hericium* erinaceus) is a medicinal mushroom that has been extensively studied for its neurohealth properties [96]. Research has shown that lion's mane:

- Stimulates the production of Nerve Growth Factor (NGF) [97], which promotes neuronal growth, development, and regeneration [98].
- Restores levels of key neurotransmitters serotonin, noradrenaline, and dopamine in the brain (that are often suppressed due to chronic stress) [99].
- Reduces neuroinflammation [100].

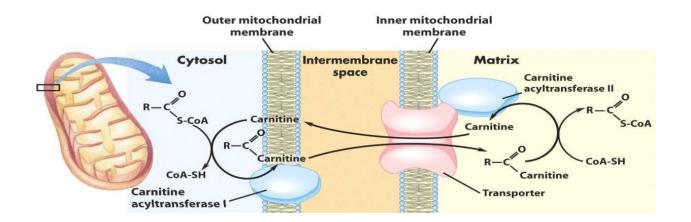
 Stimulates the expression of brain derived neurotrophic factor (BDNF), which plays a role in neuronal development, and helps in the formation of neuronal connections important for memory and cognition [101].

Studies in mice have demonstrated that these effects ultimately lend lion's mane cognitive-enhancing [102], neuroprotective [103], and mood-stabilizing properties [104].

In men with mild cognitive impairment, 3000 mg per day improved cognitive function by 12% over 16 weeks compared to placebo [105]. In overweight and obese adults, 1500 mg per day for 8 weeks reduced feelings of anxiety by 27% and feelings of depression by 39% [106].

## **Acetyl-L-Carnitine**

Our mitochondria cannot 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, where they can be used to produce energy.



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.

While complete carnitine deficiencies cause a host of nasty effects like liver and brain damage, weakness, and lethargy [107], even mild subclinical insufficiencies can cause problems. For example, a systematic review of 25 studies investigating the relationship between mitochondrial function and fatigue reported that carnitine deficits were one of the most common biomarkers linked to fatigue status [108].

Acetyl-L-Carnitine (ALCAR) is a special form of carnitine that hits two birds with one stone — it supplies the carnitine your mitochondria need to produce energy, and it provides an acetyl moiety that the mitochondria use to remain youthful and healthy.

Over 20% of mitochondrial proteins are reliant on these acetyl moieties to function properly, including those involved in antioxidant defenses and energy production [109]. In fact, one of the key changes in physiology associated with longevity is an increased acetylation of mitochondrial proteins [110].

For these reasons, some researchers have proposed that ALCAR should be considered a "mitochondrial rejuvenator" [111]. By virtue of increasing acetyl-CoA levels within mitochondria, ALCAR effectively increases antioxidant status, increases protein and membrane stability, enhances mitochondrial biogenesis, and reduces cell death.

To illustrate these benefits, one study on chronically fatigued older adults found that taking 4 grams of ALCAR daily over six months led to profound benefits to their wellbeing, including a 15% increase in cognitive function, 24% increase in physical function, and close to a whopping 50% reduction in mental fatigue, physical fatigue, and overall fatigue severity [112].



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

Through increasing mitochondrial acetylation and carnitine levels within the brain, ALCAR supplementation affects several parameters of brain health too:

- Improves mitochondrial function within brain cells.
- Increases acetylcholine signaling and improves learning capacity.
- Increases brain energy availability.
- Protects against β-amyloid neurotoxicity and reduces oxidative stress.

Accordingly, ALCAR can be a powerful ally in the fight against neurodegeneration and cognitive decline with aging (Pennisi et al. 2020). For example, a meta-analysis of 21 randomized, double-blind, placebo-controlled trials reported that 1.5–3 g/d of ALCAR significantly improved cognitive function assessed by a variety of

methods in older adults with mild cognitive impairment or early Alzheimer's disease [113].

It can also be a powerful ally against mood disorders like depression, with one meta-analysis of 12 randomized controlled trials showing that ALCAR significantly reduced depressive symptoms with an efficacy similar to antidepressant medications but with less side-effects [114]!

With all of this said, I'd like to tell you about our ultra-premium formula that we've designed specifically to boost brain health, and all that it encompasses -- from focus, to clarity, to mood support, to long-term brain health and neurotransmitter optimization. It's called UltraBrain and it includes most of the ingredients we just discussed.

## **INTRODUCING UltraBrain**

We created a premium, next generation brain supplement that's packed with the nutrition your brain needs to heal and function at its full power.

# ULTRABRAIN IS A FULL-SPECTRUM NOOTROPIC THAT:





- Restores your blood-brain barrier, keeping toxins OUT of your brain and letting IN key nutrients, like glucose and amino acids
- Increases mitochondrial function, ensuring they remain out of the cell danger response and stay in energy production mode
- Reduces inflammation and oxidative damage, helping your neurons fire more quickly and promoting proper cell function and communication
- Optimizes your entire brain, ensuring each part is working at maximum capacity
- Is safe and effective for everybody (and every brain), no matter the age or activity level
- Contains zero stimulants, junk, or fillers and uses only high quality, carefully sourced ingredients

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### UltraBrain is a full spectrum nootropic that:

- Restores your blood brain barrier, keeping toxins OUT of your brain and letting IN key nutrients, like glucose and amino acids.
- Increases mitochondrial function, ensuring they remain out of the cell danger response and stay in energy production mode.
- Reduces inflammation and oxidative damage, helping your neurons fire more quickly and promoting proper cell function and communication.

- Optimizes your entire brain, ensuring each part is working at maximum capacity.
- Is safe and effective for everybody (and every brain), no matter the age or activity level.
- Contains zero stimulants, junk, or fillers and uses only high quality, carefully sourced ingredients.



Buy Now
From US\$ 74

## THE PERFECT FORMULATION

### 15 Premium Ingredients in Effective Dosages

**Suggested Use:** Take 6 capsules per day. Use Ultrabrain 5 days a week and take 2 days off. (E.g. weekends off). Take UltraBrain with food, in one dose or two divided doses (e.g. 3 pills with breakfast and 3 pills with lunch). This is a potent supplement, so when initially starting, we suggest starting with only 2-3 pills per day and then working your way up to your optimal dose (up to 6 capsules per day), over the course of several days.

## Supplement Facts

Serving size: 6 capsules Servings Per Container: 25

Amount Pe	r Serving	%DV
Rhodiola Extract (Rhodiola rosea) (3% salidrosides and 1% rosavins)	<b>400</b> mg	**
Lion's Mane (Hericium erinaceus) (fruiting bodies)	<b>600</b> mg	**
Alpha-GPC (50%)	<b>150</b> mg	**
CDP-Choline (as Cognizin* Citicoline)	<b>150</b> mg	**
Bacopa Extract (Bacopa monnieri) (leaf) (standardized to 50% bacopa glycosides)	<b>300</b> mg	**
Ginkgo Extract (Ginkgo biloba) (24% flavone glycosides & 6% terpene lactones)	<b>250</b> mg	**
CognatiQ™ Whole Coffee Fruit Extract (Coffee Arabica)	<b>100</b> mg	**
Huperzine A (from Huperzia serrata whole plant extract)	<b>200</b> mcg	**
Acetyl-L-Carnitine	<b>600</b> mg	**
Saffron Extract (Crocus sativus) (2% safranal)	<b>30</b> mg	**
L-Theanine	<b>200</b> mg	**
Agmatine Sulfate	<b>500</b> mg	**
Polygala Tenuifolia (20:1 extract)	<b>125</b> mg	**
Tyrosine (as N-Acetyl-L-Tyrosine)	<b>300</b> mg	**
Magnesium (as Magnesium Taurate)	<b>60</b> mg	**

Cognizin® is a registered trademark of KYOWA HAKKO BIO CO., LTD.

Other Ingredients: Vegetable Capsules (cellulose).

† THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE OR PREVENT ANY DISEASE OR ILLNESS.

KEEP OUT OF THE REACH OF CHILDREN. DO NOT USE IF SAFETY SEAL IS DAMAGED OR MISSING. STORE IN A COOL, DARK PLACE. CONSULT YOUR PHYSICIAN IF YOU ARE PREGNANT OR LACTATING.

UB150C1221EBL

Manufactured For: Energy Blueprint Labs 249 S Hwy 101 Suite 410 Solana Beach, CA 92075 theenergyblueprint.com

# Why These Specific Nutrients?

We spent years combing through mountains of scientific studies, finding the ingredients *proven* to provide broad spectrum brain healing and support.

The result is a very carefully curated formulation that meets these unparalleled standards:

- Absolutely zero pseudo-science, fads, or false marketing. Pure science in every serving.
- Each ingredient is in its most potent, bioavailable form. Really nothing else can outperform these brain boosting compounds.
  - Effective dosages in each and every serving. 1 scoop a day [OR X AMOUNT OF PILLS] is everything you need to help reverse cellular dysfunction and supercharge your mental capacity.

The specific stack of ingredients in UltraBrain work together to stimulate your brain in multiple ways:



**Brain Clarity** | Improve your memory, concentration, and focus. Remove your mental fog and clouded thoughts.



**Brain Energy** | Boost your alertness, stamina, and energy. Accomplish mentally demanding tasks and not feel tired.



**Brain Strength** | Handle and recover from stress better. Bounce back faster. Become less fragile and anxious.



**Brain Balance** | Maintain an even, joyful mood that easily feels and appreciates pleasure. Eliminate depression and anxiety and be happy, optimistic, and grateful.



### **Buy Now**

From US\$ 74

UltraBrain was tormulated to give you your youthful,

# alert, energetic brain back.

The 18 science-backed ingredients – in effective dosages in each serving – will help heal your brain, allowing your cognitive function to reach its full potential.

Even after just a few daily doses, you'll notice dramatic improvements in your mental performance and will be able to:

- **Shut down neuroinflammation** and increase mitochondrial health in the brain, supercharging your brain cell communication and stopping brain-related fatigue.
- Repair neurotransmitter imbalances, positively impacting your cognitive function and learning, your mood and ability to feel joy, your sense of relaxation and calm, your stress response and tolerance, and your energy and wakefulness.
- Protect your blood-brain barrier, keeping toxins out of your brain and preventing negative immune reactions.
- Maintain steady blood sugar levels, which will greatly reduce brain fog and anxiety. UltraBrain not only has zero sugars but it also has the proper amount of protein to help regulate your glucose.
- **Regulate your appetite.** Eating less will reduce inflammation and cellular damage and thus boost your brain health.

- Minimize your caffeine dependence, so you can correct your cognitive function and mood and significantly raise your baseline energy levels.
- Develop metabolic flexibility, helping your body seamlessly switch from burning calories from food to tapping into stored sources of fuel (ie body fat) when needed. Your body's capacity to easily shift like this is important for maintaining proper brain function and energy levels.

When your brainpower is optimized like this, you will be better able to:

- Make decisions quickly so you can work more efficiently and get your to-dos done in much less time!
- Sleep soundly through the night so you can bounce out of bed without the *need* for coffee.
- Handle bad news and stressful situations without anxiety or worry. Confidently tackle your problems, big or small.
- Be clear headed and able to concentrate for long periods of time.
- Recall all the important details of your life with ease (and without the need for post-it notes).
- Complete mentally challenging tasks with plenty of energy to spare. Now is the time to crack open that non-fiction book.

Custom formulated with 15 power-packed nutrients, UltraBrain is the ONLY supplement you need to heal your brain and rewire it for lasting clarity, resilience, joy, and energy.

That's because each of the ingredients are scientifically proven to tackle all types of brain dysfunction.

Take it each day and heal damaged cells, reduce neuroinflammation, and repair faulty communication.

Take it each day and experience renewed mental strength and vitality – that you haven't felt in years.





### References

 Wang J, Wu X, Lai W, Long E, Zhang X, Li W, et al. Prevalence of depression and depressive symptoms among outpatients: a systematic review and meta-analysis. BMJ Open.

#### 2017;7:e017173.

- 2. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016. p. 1545–602.
- 3. Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. BMC Psychiatry. 2014;14:107.
- 4. Hidaka BH. Depression as a disease of modernity: explanations for increasing prevalence. J Affect Disord. 2012;140:205–14.
- 5. Boubekri M, Cheung IN, Reid KJ, Wang C-H, Zee PC. Impact of windows and daylight exposure on overall health and sleep quality of office workers: a case-control pilot study. J Clin Sleep Med. 2014;10:603–11.
- Figueiro MG, Steverson B, Heerwagen J, Kampschroer K, Hunter CM, Gonzales K, et al. The impact of daytime light exposures on sleep and mood in office workers. Sleep Health. 2017;3:204–15.
- 7. Kaida K, Takahashi M, Haratani T, Otsuka Y, Fukasawa K, Nakata A. Indoor exposure to natural bright light prevents afternoon sleepiness. Sleep. 2006;29:462–9.
- 8. Kaida K, Takahashi M, Otsuka Y. A short nap and natural bright light exposure improve positive mood status. Ind Health. 2007;45:301–8.
- 9. Yasukouchi A, Maeda T, Hara K, Furuune H. Non-visual effects of diurnal exposure to an artificial skylight, including nocturnal melatonin suppression. J Physiol Anthropol. 2019;38:10.
- 10. Winthorst WH, Roest AM, Bos EH, Meesters Y, Penninx BWJH, Nolen WA, et al. Seasonal affective disorder and non-seasonal affective disorders: results from the NESDA study. BJPsych Open. 2017;3:196–203.
- 11. Cobb BS, Coryell WH, Cavanaugh J, Keller M, Solomon DA, Endicott J, et al. Seasonal variation of depressive symptoms in unipolar major depressive disorder. Compr Psychiatry. 2014;55:1891–9.
- 12. Rosen LN, Targum SD, Terman M, Bryant MJ, Hoffman H, Kasper SF, et al. Prevalence of seasonal affective disorder at four latitudes. Psychiatry Res. 1990;31:131–44.
- 13. Persons JE, Coryell WH, Solomon DA, Keller MB, Endicott J, Fiedorowicz JG. Mixed stateand suicide: Is the effect of mixed state on suicidal behavior more than the sum of its parts?

Bipolar Disord. 2018;20:35-41.

- 14. Yang AC, Huang NE, Peng C-K, Tsai S-J. Do seasons have an influence on the incidence of depression? The use of an internet search engine query data as a proxy of human affect. PLoS One. 2010;5:e13728.
- 15. Schwartz PJ. Chris Cornell, the Black Hole Sun, and the Seasonality of Suicide. Neuropsychobiology. 2019;78:38–47.
- 16. Campbell PD, Miller AM, Woesner ME. Bright Light Therapy: Seasonal Affective Disorder and Beyond. Einstein J Biol Med. 2017;32:E13–25.

- 17. Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry. 2005;162:656–62.
- 18. Even C, Schröder CM, Friedman S, Rouillon F. Efficacy of light therapy in nonseasonal depression: a systematic review. J Affect Disord. 2008;108:11–23.
- 19. Al-Karawi D, Jubair L. Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials. J Affect Disord. 2016;198:64–71.
- 20. Lam RW, Buchanan A, Clark CM, Remick RA. Ultraviolet versus non-ultraviolet light therapy for seasonal affective disorder. J Clin Psychiatry. 1991;52:213–6.
- 21. Veleva BI, van Bezooijen RL, Chel VGM, Numans ME, Caljouw MAA. Effect of ultraviolet light on mood, depressive disorders and well-being. Photodermatol Photoimmunol Photomed.
- 2018;34:288-97.
- 22. Zhu D-M, Zhao W, Zhang B, Zhang Y, Yang Y, Zhang C, et al. The Relationship Between Serum Concentration of Vitamin D, Total Intracranial Volume, and Severity of Depressive Symptoms in Patients With Major Depressive Disorder. Front Psychiatry. 2019;10:322.
- 23. von Känel R, Fardad N, Steurer N, Horak N, Hindermann E, Fischer F, et al. Vitamin D Deficiency and Depressive Symptomatology in Psychiatric Patients Hospitalized with a Current Depressive Episode: A Factor Analytic Study. PLoS One. 2015;10:e0138550.
- 24. Woo YS, Kim S, Jeong J-H, Jung Y-E, Kim M-D, Bahk W-M. Vitamin D Deficiency/Insufficiency among Inpatients with Depressive Symptoms. Clin Psychopharmacol Neurosci. 2019;17:121–4.
- 25. Vellekkatt F, Menon V. Efficacy of vitamin D supplementation in major depression: A meta-analysis of randomized controlled trials. J Postgrad Med. 2019;65:74–80.
- 26. Askalsky P, Iosifescu DV. Transcranial Photobiomodulation For The Management Of Depression: Current Perspectives. Neuropsychiatr Dis Treat. 2019;15:3255–72.
- 27. Schiffer F, Johnston AL, Ravichandran C, Polcari A, Teicher MH, Webb RH, et al. Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety. Behav Brain Funct. 2009;5:46.
- 28. Consensus Conference Panel, Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, et al. Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society on the Recommended Amount of Sleep for a Healthy Adult: Methodology and Discussion. J Clin Sleep Med. 2015;11:931–52.
- 29. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. DialoguesClin Neurosci. 2008;10:329–36.
- 30. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011;135:10–9.

31. Rahman SA, Shapiro CM, Wang F, Ainlay H, Kazmi S, Brown TJ, et al. Effects of filtering visual short wavelengths during nocturnal shiftwork on sleep and performance. Chronobiol Int.

#### 2013;30:951-62.

- 32. Shechter A, Kim EW, St-Onge M-P, Westwood AJ. Blocking nocturnal blue light for insomnia: A randomized controlled trial. J Psychiatr Res. 2018;96:196–202.
- 33. Mortazavi SAR, Parhoodeh S, Hosseini MA, Arabi H, Malakooti H, Nematollahi S, et al. Blocking Short-Wavelength Component of the Visible Light Emitted by Smartphones' Screens Improves Human Sleep Quality. J Biomed Phys Eng. 2018;8:375–80.
- 34. Scott J, Langsrud K, Vethe D, Kjørstad K, Vestergaard CL, Faaland P, et al. A pragmatic effectiveness randomized controlled trial of the duration of psychiatric hospitalization in a trans-diagnostic sample of patients with acute mental illness admitted to a ward with either blue-depleted evening lighting or normal lighting conditions. Trials. 2019;20:472.
- 35. Moylan S, Eyre HA, Maes M, Baune BT, Jacka FN, Berk M. Exercising the worry away: how inflammation, oxidative and nitrogen stress mediates the beneficial effect of physical activity on anxiety disorder symptoms and behaviours. Neurosci Biobehav Rev. 2013;37:573–84.
- 36. Seo D-Y, Heo J-W, Ko JR, Kwak H-B. Exercise and Neuroinflammation in Health and Disease. Int Neurourol J. 2019;23:S82–92.
- 37. Erickson KI, Miller DL, Roecklein KA. The aging hippocampus: interactions between exercise, depression, and BDNF. Neuroscientist. 2012;18:82–97.
- 38. Ernst C, Olson AK, Pinel JPJ, Lam RW, Christie BR. Antidepressant effects of exercise: evidence for an adult-neurogenesis hypothesis? J Psychiatry Neurosci. 2006;31:84–92.
- Dey S, Singh RH, Dey PK. Exercise training: significance of regional alterations in serotonin metabolism of rat brain in relation to antidepressant effect of exercise. Physiol Behav. 1992;52:1095–9.
- 40. Bender T, Nagy G, Barna I, Tefner I, Kádas E, Géher P. The effect of physical therapy on beta-endorphin levels. Eur J Appl Physiol. 2007;100:371–82.
- 41. Mastorakos G, Pavlatou M, Diamanti-Kandarakis E, Chrousos GP. Exercise and the stress system. Hormones . 2005;4:73–89.
- 42. Deslandes A, Moraes H, Ferreira C, Veiga H, Silveira H, Mouta R, et al. Exercise and mental health: many reasons to move. Neuropsychobiology. 2009;59:191–8.
- 43. Ashdown-Franks G, Firth J, Carney R, Carvalho AF, Hallgren M, Koyanagi A, et al. Exercise as Medicine for Mental and Substance Use Disorders: A Meta-review of the Benefits for Neuropsychiatric and Cognitive Outcomes. Sports Med. 2020;50:151–70.
- 44. Morres ID, Hatzigeorgiadis A, Stathi A, Comoutos N, Arpin-Cribbie C, Krommidas C, et al. Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. Depress Anxiety. 2019;36:39–53.
- 45. Gordon BR, McDowell CP, Hallgren M, Meyer JD, Lyons M, Herring MP. Association of Efficacy of Resistance Exercise Training With Depressive Symptoms: Meta-analysis and Meta-regression Analysis of Randomized Clinical Trials. JAMA Psychiatry. 2018;75:566–76.

- 46. Mammen G, Faulkner G. Physical activity and the prevention of depression: a systematicreview of prospective studies. Am J Prev Med. 2013;45:649–57.
- 47. Bartolomucci A, Leopardi R. Stress and depression: preclinical research and clinical implications. PLoS One. 2009;4:e4265.
- 48. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301:386–9. 49. Flügge G. Dynamics of central nervous 5-HT1A-receptors under psychosocial stress. J Neurosci. 1995;15:7132–40.
- 50. Tafet GE, Idoyaga-Vargas VP, Abulafia DP, Calandria JM, Roffman SS, Chiovetta A, et al. Correlation between cortisol level and serotonin uptake in patients with chronic stress and depression. Cogn. Affect. Behav. Neurosci. 2001. p. 388–93.
- 51. Yao Y, Zhao S, Zhang Y, Tang L, An Z, Lu L, et al. Job-related burnout is associated with brain neurotransmitter levels in Chinese medical workers: a cross-sectional study. J Int Med Res. 2018;46:3226–35.
- 52. Goyal M, Singh S, Sibinga EMS, Gould NF, Rowland-Seymour A, Sharma R, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med. 2014;174:357–68.
- 53. Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. Lancet. 2015;386:63–73.
- 54. Lopresti AL, Drummond PD. Saffron (Crocus sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. Hum Psychopharmacol. 2014;29:517–27.
- 55. Bukhari SI, Manzoor M, Dhar MK. A comprehensive review of the pharmacological potential of Crocus sativus and its bioactive apocarotenoids. Biomed Pharmacother. 2018;98:733–45. 56. Khaksarian M, Behzadifar M, Behzadifar M, Alipour M, Jahanpanah F, Re TS, et al. The efficacy of Crocus sativus (Saffron) versus placebo and Fluoxetine in treating depression: a systematic review and meta-analysis. Psychol Res Behav Manag. 2019;12:297–305.
- 57. Tóth B, Hegyi P, Lantos T, Szakács Z, Kerémi B, Varga G, et al. The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis. Planta Med. 2019;85:24–31.
- 58. Yang X, Chen X, Fu Y, Luo Q, Du L, Qiu H, et al. Comparative efficacy and safety of Crocus sativus L. for treating mild to moderate major depressive disorder in adults: a meta-analysis of randomized controlled trials. Neuropsychiatr Dis Treat. 2018;14:1297–305.
- 59. Hausenblas HA, Saha D, Dubyak PJ, Anton SD. Saffron (Crocus sativus L.) and major depressive disorder: a meta-analysis of randomized clinical trials. J Integr Med. 2013:11:377–83.
- 60. Panossian A, Wikman G, Sarris J. Rosenroot (Rhodiola rosea): traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine. 2010;17:481–93.

- 61. Panossian A, Hamm R, Wikman G, Efferth T. Mechanism of action of Rhodiola, salidroside, tyrosol and triandrin in isolated neuroglial cells: an interactive pathway analysis of the downstream effects using RNA microarray data. Phytomedicine. 2014;21:1325–48.
- 62. Zhong Z, Han J, Zhang J, Xiao Q, Hu J, Chen L. Pharmacological activities, mechanisms ofaction, and safety of salidroside in the central nervous system. Drug Des Devel Ther.

2018;12:1479-89.

- 63. Ma G-P, Zheng Q, Xu M-B, Zhou X-L, Lu L, Li Z-X, et al. Rhodiola rosea L. Improves Learning and Memory Function: Preclinical Evidence and Possible Mechanisms. Front Pharmacol. 2018;9:1415.
- 64. Li Y, Pham V, Bui M, Song L, Wu C, Walia A, et al. Rhodiola rosea L.: an herb with anti-stress, anti-aging, and immunostimulating properties for cancer chemoprevention. Curr Pharmacol Rep. 2017;3:384–95.
- 65. Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmström C, Panossian A. Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. Nord J Psychiatry. 2007;61:343–8.
- 66. Bangratz M, Ait Abdellah S, Berlin A, Blondeau C, Guilbot A, Dubourdeaux M, et al. A preliminary assessment of a combination of rhodiola and saffron in the management of mild-moderate depression. Neuropsychiatr Dis Treat. 2018;14:1821–9.
- 67. Cornford EM, Oldendorf WH. Independent blood-brain barrier transport systems for nucleic acid precursors. Biochim Biophys Acta. 1975;394:211–9.
- 68. Dobolyi A, Juhász G, Kovács Z, Kardos J. Uridine function in the central nervous system. Curr Top Med Chem. 2011;11:1058–67.
- 69. Cansev M. Uridine and cytidine in the brain: their transport and utilization. Brain Res Rev. 2006;52:389–97.
- 70. Agarwal N, Sung Y-H, Jensen JE, daCunha G, Harper D, Olson D, et al. Short-term administration of uridine increases brain membrane phospholipid precursors in healthy adults: a 31-phosphorus magnetic resonance spectroscopy study at 4T. Bipolar Disord. 2010;12:825–33. 71. Wurtman RJ, Cansev M, Ulus IH. Synapse formation is enhanced by oral administration of uridine and DHA, the circulating precursors of brain phosphatides. J Nutr Health Aging.

2009;13:189-97.

- 72. Wurtman RJ, Cansev M, Sakamoto T, Ulus I. Nutritional modifiers of aging brain function: use of uridine and other phosphatide precursors to increase formation of brain synapses. Nutr Rev. 2010;68 Suppl 2:S88–101.
- 73. Neary JT, Rathbone MP, Cattabeni F, Abbracchio MP, Burnstock G. Trophic actions of extracellular nucleotides and nucleosides on glial and neuronal cells. Trends Neurosci.

1996;19:13-8.

- 74. Pooler AM, Guez DH, Benedictus R, Wurtman RJ. Uridine enhances neurite outgrowth in nerve growth factor-differentiated PC12 [corrected]. Neuroscience. 2005;134:207–14.
- 75. Kondo DG, Sung Y-H, Hellem TL, Delmastro KK, Jeong E-K, Kim N, et al. Openlabel uridine for treatment of depressed adolescents with bipolar disorder. J Child Adolesc Psychopharmacol. 2011;21:171–5.
- 76. Uzbay TI. The pharmacological importance of agmatine in the brain. Neurosci Biobehav Rev. 2012;36:502–19.
- 77. Wang W-P, Iyo AH, Miguel-Hidalgo J, Regunathan S, Zhu M-Y. Agmatine protects against cell damage induced by NMDA and glutamate in cultured hippocampal neurons. Brain Res. 2006;1084:210–6.
- 78. Chang C-H, Wu H-T, Cheng K-C, Lin H-J, Cheng J-T. Increase of beta-endorphin secretion agmatine is induced by activation of imidazoline I(2A) receptors in adrenal gland of rats.

Neurosci Lett. 2010;468:297-9.

- 79. Freitas AE, Egea J, Buendía I, Navarro E, Rada P, Cuadrado A, et al. Agmatine induces Nrf2 and protects against corticosterone effects in hippocampal neuronal cell line. Mol Neurobiol. 2015;51:1504–19.
- 80. Freitas AE, Egea J, Buendia I, Gómez-Rangel V, Parada E, Navarro E, et al. Agmatine, by Improving Neuroplasticity Markers and Inducing Nrf2, Prevents Corticosterone-Induced Depressive-Like Behavior in Mice. Mol Neurobiol. 2016;53:3030–45.
- 81. Arndt MA, Battaglia V, Parisi E, Lortie MJ, Isome M, Baskerville C, et al. The arginine metabolite agmatine protects mitochondrial function and confers resistance to cellular apoptosis. Am J Physiol Cell Physiol. 2009;296:C1411–9.
- 82. Battaglia V, Grancara S, Satriano J, Saccoccio S, Agostinelli E, Toninello A. Agmatine prevents the Ca(2+)-dependent induction of permeability transition in rat brain mitochondria.

Amino Acids. 2010;38:431-7.

- 83. Piletz JE, Aricioglu F, Cheng J-T, Fairbanks CA, Gilad VH, Haenisch B, et al. Agmatine: clinical applications after 100 years in translation. Drug Discov Today. 2013;18:880–93.
- 84. Xu W, Gao L, Li T, Shao A, Zhang J. Neuroprotective Role of Agmatine in Neurological Diseases. Curr Neuropharmacol. 2018;16:1296–305.
- 85. Chen GG, Almeida D, Fiori L, Turecki G. Evidence of Reduced Agmatine Concentrations in the Cerebral Cortex of Suicides. Int J Neuropsychopharmacol. 2018;21:895–900.
- 86. Shopsin B. The clinical antidepressant effect of exogenous agmatine is not reversed by parachlorophenylalanine: a pilot study. Acta Neuropsychiatr. 2013;25:113–8.
- 87. Schmidt M, Butterweck V. The mechanisms of action of St. John's wort: an update. Wien Med Wochenschr. 2015;165:229–35.

- 88. Ng QX, Venkatanarayanan N, Ho CYX. Clinical use of Hypericum perforatum (St John's wort) in depression: A meta-analysis. J Affect Disord. 2017;210:211–21.
- 89. Apaydin EA, Maher AR, Shanman R, Booth MS, Miles JNV, Sorbero ME, et al. A systematic review of St. John's wort for major depressive disorder. Syst Rev. 2016;5:148.
- 90. Linde K, Berner MM, Kriston L. St John's wort for major depression. Cochrane Database Syst Rev. 2008;CD000448.
- 91. Chrubasik-Hausmann S, Vlachojannis J, McLachlan AJ. Understanding drug interactions with St John's wort (Hypericum perforatum L.): impact of hyperforin content. J Pharm Pharmacol. 2019;71:129–38.
- 92. Burdge G. Alpha-linolenic acid metabolism in men and women: nutritional and biological implications. Curr Opin Clin Nutr Metab Care. 2004;7:137–44.
- 93. Mocking RJT, Harmsen I, Assies J, Koeter MWJ, Ruhé HG, Schene AH. Metaanalysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. Transl Psychiatry. 2016;6:e756.
- 94. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr. 2009;28:525–42.
- 95. Wani AL, Bhat SA, Ara A. Omega-3 fatty acids and the treatment of depression: a review of scientific evidence. Integr Med Res. 2015;4:132–41.