

Stress, Anxiety and Cognitive Function

Clinically proven natural alternatives for treating stress & anxiety and declining memory

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Evidence-Based Use of Supplements

ABSTRACT

Stress-related anxiety and mild cognitive impairment are common, related, and inadequately treated. Scientific data are increasingly demonstrating the power of nutrition to address these conditions. In addition to effectively preventing and treating anxiety and cognitive dysfunction, nutritional approaches have the added advantage of circumventing serious risks posed by other interventions. Here we discuss the realities of stress-related anxiety and mild cognitive impairment, including the limitations of conventional strategies to combat them. We also provide information on our current understanding of the relevance and potential of specific ingredients to promote mental health as it relates to anxiety and cognition.

Rates of chronic stress and cognitive decline are increasing rapidly, and unfortunately the solutions to these issues are not keeping pace.^{1,2} Complicating and exacerbating the problem is that stress and cognitive decline are inextricably linked. Finding new and better ways to prevent and treat stress, anxiety, and cognitive problems is critical, particularly as our older population, who is at a heightened risk for cognitive decline, is projected to soon outsize children for the first time in U.S. history.³

Anxiety Disorders and Cognitive Deficits are Prevalent and Linked

Anxiety Disorders

According to the National Institute on Mental Health (NIMH), 1 out of every 3 people will suffer from an anxiety disorder in their lifetime.⁴ Anxiety disorders are the most common mental illness in the U.S, with roughly 40 million Americans suffering from these disorders.⁵ Among adults, about 1 in 5 people have an anxiety disorder, whereas the prevalence is more than 1 in 4 for children between the ages of 13 and 18. Women are significantly more affected than men, developing certain anxiety disorders twice as frequently as their male counterparts.¹

Chronic stress and anxiety have detrimental effects on health. According to the American Psychological Association (APA), chronic stress is becoming a public health crisis, as adults are experiencing stress at growing rates. Though often unrecognized, the rise in adult stress has also been shown to be taking an increasing toll on children.¹ Not only are children more anxious than they used to be, but they are increasingly debilitated by this anxiety. Of adolescents experiencing anxiety, more than 8% are found to be severely impaired.⁴ If not treated properly, anxiety is chronic.⁵

Mild Cognitive Impairment

Stress and anxiety are common in those with mild cognitive impairment (MCI), which exists in 15% to 20% of people who are 65 and older.⁶ As with anxiety, MCI can be difficult for clinicians to identify and classify.^{7,8} Unlike anxiety, however, no treatments for MCI have been shown to be effective.⁹

MCI involves changes in cognition that are not severe enough to disrupt everyday activities but affect functioning enough to be noticed by the person experiencing MCI and those around them. As many as 15% of people with MCI progress to dementia each year, highlighting the importance of identifying and effectively treating MCI.¹⁰ Though having MCI increases the risk of developing Alzheimer's disease or another form of dementia, not everyone with MCI will go on to have dementia.^{11–14} Nonetheless, those who simultaneously suffer from both MCI and anxiety are more likely to develop dementia.¹⁵ It is therefore critical that we find ways to adequately address anxiety and cognitive dysfunction, not only to minimize their burden but also to prevent their progression and development into potentially more severe impairments.

The Reciprocal Relationship Between Stress and Cognition

Anxiety Can Derail Cognition

While stress is a part of everyday life, our ability to cope with stress is critical for avoiding maladaptive anxiety and associated health problems. Stress responses are triggered by cues and events that signal threats and occur as a way to promote mechanisms for coping that increase our likelihood for survival.¹⁶ Thus, while it is important to experience stress, an overreaction to stress or an inability to cope properly with the perception of stress can lead to pathological anxiety and a variety of mental and physical health problems.

Acute stress has detrimental effects on a variety of cognitive abilities, including executive functioning, the formation of and updating of memories, mental rotation and spatial memory, and hand-eye coordination.^{17–19} Experiencing anxiety can limit working memory capacity by, for instance, redirecting some of our attentional resources.²⁰ Indeed, if we are distracted by our anxieties, we simply have less brain power to devote to other tasks, especially cognitive tasks that require concentration. It is perhaps therefore not surprising that measurements using the Montreal Cognitive Assessment (MoCA) have found that compared to those without psychological distress, those experiencing such distress display higher levels of cognitive deterioration.²¹

These cognitive effects of stress are likely mediated by the stress hormone cortisol, the levels of which are inversely correlated with memory.²² When stress and cortisol concentrations are high, structural changes in areas of the brain that are important for memory and cognition – such as the hippocampus – can occur, leading to atrophy and associated memory disorders.^{23,24}

A poignant example of this relationship between stress and brain change-associated memory impairment is what occurs in those with post-traumatic stress disorder (PTSD). Magnetic resonance imaging (MRI) studies on patients with PTSD have revealed reduced hippocampal volume and weaker verbal memory in those with the disorder.²⁵

Research has also shown that a stroke victim undergoing cognitive training is more likely to improve in cognitive performance if the victim has lower levels of anxiety.²⁶ Based on data on neural activation patterns, it appears that those with lower anxiety also have more neural efficiency that accompanies their ability to improve their cognitive performance over time. Indeed, those who experience acute stress seem to require more brain activation in somatosensory cortices to perform as well as those without such stress.²⁷

Similarly, research on those with MCI has shown that between 35% and 85% of adults with the disorder also display neuropsychiatric symptoms, which often occur before cognitive decline.²⁸ In those who suffer from both MCI and anxiety, cognitive decline is more likely to occur at a faster rate.²⁹ In some patients, anxiety also increases with increasing cognitive decline, suggesting a bidirectional relationship between the conditions.²⁸

It should be noted that in cases of mild stress, short-term memory can be improved, as is often the case in high pressure contexts such as academic test taking. However, long-term stress and high intensity stress have the opposite effect, leading to cognitive disorders.³⁰

Cognitive Problems Can Lead to Anxiety

The way we respond to stress not only affects but also likely derives from aspects of our cognition. Our cognitive appraisal of our situation critically contributes to our stress response, as no cue or event is in itself stressful unless it is perceived that way.^{31,32} Thus, abnormal cognitive processing can lead to anxiety that is out of proportion with the existing threat or potential threat.

Research on both cognitive and neuropsychiatric disturbances suggests that these issues not only influence one another but that there may be common pathological pathways leading to anxiety and MCI.³³ Experts posit that in certain cases, anxiety is likely¹ a manifestation of neurodegeneration rather than the cause.³⁴

Given the way that abnormal cognitive processing can lead to anxiety while stress and anxiety can simultaneously disrupt cognitive performance, it is important that we find ways to prevent problems related to both cognition and stress. Unfortunately, difficulties related to anxiety and cognitive continue to grow, with virtually no new effective strategies for prevention or treatment being introduced.

CONVENTIONAL TREATMENTS

Pharmacological Interventions

Drugs for Stress and Anxiety

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are generally

considered first line treatments for anxiety disorders, particularly generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder, and PTSD. There is also evidence, though, that PTSD is not adequately addressed by current pharmacological or non-pharmacological options.^{35–40} This particularly troubling given that PTSD is thought to be the most extreme form of stress-induced anxiety.

Second line and other treatments for anxiety disorders include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), benzodiazepines, and anticonvulsants like gabapentin and pregabalin.⁴¹

Unfortunately, there are weaknesses and limitations associated with all the currently available drugs for managing stress and anxiety. For instance, a proportion of the population with anxiety is resistant to first line treatments, with some people actually experiencing enhancements in their anxiety upon starting these medications.⁴²

These first line options are also associated with adverse side effects including headache, nausea, stomach pain, sexual dysfunction, and difficulty sleeping.^{43,44} In addition, data have shown that SSRIs can lead to suicidal thoughts and behaviors, including in children, led the FDA to issue a warning regarding these drugs in October 2004.^{5,45} Drugs in this class have also been associated with negative outcomes when taken by pregnant women.^{46–50}

SSRIs are also associated with dangerous drug interactions, including interactions with recreational substances like alcohol as well as with drugs used to treat other conditions.^{51–53} For those who may want to discontinue use of SSRIs in favor of another drug may struggle with withdrawal.⁵⁴

Other non-first line treatment options are classified as such because they pose significant risks related to safety and tolerability.⁴¹ For instance, in addition to their side effects, benzodiazepines also carry risks associated with dependence and withdrawal.⁵⁵ Current guidelines do not recommend addressing anxiety with benzodiazepines as first-line treatments because of the adverse side effects associated with these drugs.³⁹ In the context of addressing co-existing anxiety and cognitive deficits, it is also important to note that systematic meta-analyses have shown that long-term use of benzodiazepines is associated with cognitive dysfunction that persists even if benzodiazepine use is discontinued.⁵⁵

Drugs for MCI

Though treating reversible causes of MCI tends to have positive results, many cases of MCI do not emerge due to identifiable and reversible causes.⁵⁶ There are no pharmacological interventions for MCI that have been approved by the U.S. Food and Drug Administration (FDA).^{56,57} Given the role of acetylcholine in cognition, 3 cholinesterase inhibitors were developed and later approved by the FDA for the treatment of mild dementia due to Alzheimer's disease. These drugs include donepezil, galantamine, and rivastigmine.^{58,59}

Despite their modest benefits in this Alzheimer's disease population, research into the potential of cholinesterase inhibitors to treat those with MCI has yielded disappointing results.^{60,61} Given that the drugs do not appear to be effective and yet are associated with adverse side effects like diarrhea, nausea, hypotension, increased risk of falling, fatigue, and bradycardia, experts have concluded that there is no justification for using these drugs in those with MCI.⁶²

Non-Pharmacological Interventions

Cognitive Approaches

While engagement in intellectual and cognitively stimulating activities may help protect against MCI,⁶³ cognitive behavioral therapy (CBT) – a form of psychotherapy – can be an effective way to reduce anxiety and involves strengthening connections between cognitive and affective parts of the brain to improve emotion regulation.⁶⁴ Over the course of several weeks of CBT, people can learn skills to help them combat their anxiety.⁵ Though CBT is generally considered the gold standard form of psychotherapy, this status has recently been called into question because of weaknesses in the relevant research, including studies deemed low in quality.⁶⁵

TMS

Transcranial magnetic stimulation (TMS), more often used to treat depression, was approved by the FDA for use against obsessive-compulsive disorder (OCD) in 2018.⁶⁶ This technique leverages magnetic fields to influence aberrant activity in brain circuits that may underlie neuropsychiatric conditions. Research into the potential for TMS to effectively and safely treat other forms of anxiety, such as PTSD, is ongoing.

Meditation, Relaxation, and Breathing Techniques

Data have shown that meditation, as well as relaxation and breathing techniques, can counteract detrimental effects of psychological stress. These observations have led experts to suggest that these techniques be used as both first-line and supplemental treatments for stress and anxiety.^{67,68} Similarly, meditation has been deemed feasible even for older adults, and research has shown that meditation may be able to combat age-related cognitive decline.⁶⁹

Recent data suggest that mindfulness-based interventions are capable of not only reducing perceived stress and cognitive decline but also of affecting brain physiology. Specifically, researchers have observed increased functional connectivity, cerebral blood flow, and brain volume change following these types of interventions.⁷⁰ However, more data from stronger study designs are needed to determine the specific ways that meditation could help those suffering from anxiety and stress-related behavior.⁷¹

Acupuncture

Acupuncture may be a promising intervention for anxiety.⁷² Systematic reviews of the literature have shown that acupuncture therapy is effective and also associated with fewer side effects than conventional anxiety treatments.⁷³

Recent research has also shown that acupuncture therapy is a promising non-pharmacological method to treat patients with MCI, successfully improving their cognitive functioning.⁷⁴ Based on functional magnetic resonance imaging (fMRI) data, this effect may occur due to the ability of acupuncture to activate areas of the brain associated with cognition in those with MCI.⁷⁵ Based on the positive data collected on the impact of acupuncture, clinical trials aimed at optimizing acupuncture therapy for use in MCI are being pursued.^{76–79}

Exercise

Though the data are limited, there is evidence that exercise can provide a cost-effective way to address both anxiety and cognition.^{57,80} For instance, data point to a role of physical activity in improving subjective memory impairments and to yoga in relieving stress and anxiety.^{81,82} A comprehensive

meta-analysis covering 15 cohort studies showed that the risk of cognitive decline was 38% greater in sedentary people than in those who were physically active.⁸³ It is thought that these advantages occur because exercise stimulates the blood to take nutrient and oxygen rich blood to the brain, reduce cortisol levels, and protect against cardiovascular disease.⁸⁴

However, when it comes to anxiety, it is unclear whether exercise can achieve the same impact as psychopharmaceuticals.⁸⁵ Though exercise appears to confer mental benefits, our understanding of exactly if and how exercise can be preventative or therapeutic is incomplete due to a lack of solid data from randomized controlled trials.⁸⁰

Diet

Adequate nutrition is known to be critical for optimizing brain function, including for preventing cognitive decline and improving cognitive capacity.⁸⁶ Cognitive impairments are observed less frequently in those who follow a Mediterranean diet, rich in plant-based foods, whole grains, fish, nuts, and monosaturated fats.⁸⁷ In addition, consuming and staying on a Mediterranean diet has been shown to reduce the rate of cognitive decline in MCI.⁸⁸

Combining approaches

Data increasingly suggest that combining different types of strategies to combat MCI may be more effective than using individual interventions alone. A recent meta-analysis found that not only were combined cognitive-physical interventions associated with improvements in the performance of daily activities as well as in mood, but that these benefits occurred at equal levels in those with MCI and in patients with dementia.⁸⁹

A multicomponent therapy referred to as MAKES (an acronym for Motor, Activities of daily living, Cognitive, Social) has been shown to be effective in improving cognition in a wide range of patients, ranging from those suffering from MCI to those with moderate dementia.⁹⁰ Specifically, MAKES was associated with improvements in performance on the Mini-Mental State Examination (MMSE) and the Erlangen Test of Activities of Daily Living (ADL) in Persons with Mild Dementia or Mild Cognitive Impairment (ETAM), as well as improvements in neuropsychiatric symptoms.

CLINICALLY DOCUMENTED SUPPLEMENTS

Given that MCI has no pharmacological treatments and accordingly, interventions are shifting to diet and exercise as ways to combat cognitive deficits,⁵⁶ supplements offer a particularly important opportunity to address MCI. Similarly, nutritional strategy and supplementation have been deemed an effective way to treat anxiety and anxiety-related disorders with the added benefit of avoiding the risks associated with other treatment options.^{91–96}

The challenge is thus to determine the best ingredients and the details of the formulations to optimize treatment for or prevention of these challenges that arise within the brain. Below is information on research into ingredients that hold promise for addressing stress, anxiety, and cognition.

Ashwagandha Extract

The nootropic potential of ashwagandha extract, also known as *Withania Somnifera*, and its health benefits as a supplement have been widely demonstrated through

scientific research.⁹⁷ This compound has been shown to reduce anxiety through its impact on a variety of anxiety tests including the Hamilton Anxiety Scale, the Beck Anxiety Inventory, and the Perceived Stress Scale.⁹⁸ Research on ashwagandha has helped to clarify its benefits for anxiety in specific contexts as well, including during alcohol withdrawal.⁹⁹

The extract has been shown not only to substantially reduce cortisol levels but also the stress and weight gain associated with cortisol release.^{100,101} Studies on the extract have supported ashwagandha as a safe and effective intervention for stress that is not associated with adverse events.^{100,101}

In addition to its beneficial effects in contexts of stress and anxiety, ashwagandha can also enhance memory. It has been shown to improve cognition across different age groups, in those with obesity-induced cognitive impairments, and in those with bipolar disorder. Some of the specific cognitive domains in which ashwagandha has demonstrated benefits include: auditory-verbal working memory, reaction time, and social cognition.^{102–104}

Ashwagandha may also help with information processing, attention, and executive functioning in those with MCI.¹⁰⁵ A recent review that included a comprehensive look at the impact of ashwagandha on cognition even argued that the substance should be considered in the development of therapies for Alzheimer's disease.¹⁰⁶

In addition to its ability to promote the formation of dendrites on cells of the brain,¹⁰³ the positive effects of ashwagandha on cognition appear to also occur through its antioxidant properties. Its ability to quench free radicals help ashwagandha to protect the brain against environmental toxins.¹⁰⁷ This neuroprotective effect may allow it to play a role in the reversal of pathologies related to Alzheimer's disease and Parkinson's disease.^{97,108}

The modulation of the immune system is another way that ashwagandha may confer benefits to the brain. Ashwagandha fights inflammation and cell death,¹⁰⁹ and it has been shown to suppress reactive gliosis and the production of inflammatory cytokines like TNF- α , IL-1 β , IL-6.¹¹⁰ It also appears to activate the PI3/AKT pathway and thereby promote cell survival and plasticity.¹⁰⁴

Ascorbic Acid

Ascorbic acid, more commonly referred to as vitamin C, is a vital antioxidant and has been implicated in the promotion of healthy brain aging.^{111,112} For instance, vitamin C supplementation has been deemed safe and effective for reducing anxiety levels in human patients.¹¹³ Specifically, it has been shown to be capable of achieving acute anxiolytic effects in people with anxiety as measured through the State-Trait Anxiety Inventory (STAI) and the Visual Analogue Mood Scale (VAMS), as well as in animal models.^{114,115}

Its anxiolytic effects have also been demonstrated in specific patient groups, such as in those with type 2 diabetes.¹¹³ A study on 42 high school students, given either 500 milligrams (mg) of vitamin C daily or a placebo showed that only those who took vitamin C supplements displayed significantly lower anxiety based on testing with the Beck Anxiety Inventory after 14 days.¹¹⁶

Research suggests that the decrease in anxiety level observed in those treated with vitamin C supplements may occur through a reduction in oxidative damage that vitamin C achieves through its antioxidant properties and by modulating the nitric oxide system.^{113,117,118} It may also attenuate harmful cortisol activity that increases in response

To stress, as well as other stress responses.¹¹⁷ For example, high-dose sustained release vitamin C may help to improve anxiety by combatting the increased blood pressure that accompanies stress.¹¹⁹

In addition to stress and anxiety, vitamin C deficiency has also been linked to age-related cognitive decline and cognitive deficits that occur in patients with schizophrenia.^{120,121} Consistent with these findings are data that suggest that vitamin C supplementation can improve cognitive abilities like memory.¹²² Research in this area has suggested that vitamin C supplementation may help to mitigate the cognitive impairments that can accompany menopause.¹²³

The specific mechanisms by which vitamin C may improve memory are not well understood, but the vitamin has a variety of beneficial effects on the central nervous system that could help explain the cognitive improvements that are observed with vitamin C supplementation. For instance, in addition to its ability to scavenge reactive oxygen species, vitamin C contributes to neuronal maturation and differentiation, angiogenesis, proper neurotransmission, and the formation of myelin.^{111,120}

Bacopa Monnieri

Bacopa monnieri, commonly referred to as bacopa, has long been used in formulations aimed at treating anxiety, memory loss, poor cognition, and loss of concentration.^{124,125} Some of the anxiolytic effects that have been demonstrated with bacopa include improvements in mood and reduced cortisol levels.¹²⁶ Reductions in anxiety and heart rate have been observed in people taking 300 mg per day of bacopa orally.¹²⁷ Bacopa supplementation has been shown to be well-tolerated.¹²⁵

Bacopa, however, is perhaps even better known for its cognitive benefits. One meta-analysis of 9 studies covering over 500 subjects supported the idea that bacopa improves cognition, particularly in the area of attention.¹²⁸ Another meta-analysis pointed to the potential of bacopa to help with free recall memory.¹²⁹

It has been suggested that bacopa's safe improvement of cognition may be particularly pronounced in older individuals.¹³⁰ Indeed, in a study where older adults were provided with 300 mg per day of oral bacopa supplementation for 12 weeks, those taking the supplements were found to display greater cognitive improvements than those taking placebo, including enhanced performance on the Rey Auditory Verbal Learning Test (AVLT).¹³⁰

The cognitive benefits of bacopa, however, appear to extend beyond the elderly. For instance, a study on middle-aged adults, aged 40 to 65 years, showed that bacopa improved retention of new information in this population.¹³¹ Research has also demonstrated cognitive benefits of bacopa in specific patient groups, such as those with schizophrenia and hypoxia-induced memory impairments.^{132,133}

Other studies have shown that 320 mg of bacopa is sufficient for improving cognitive performance.^{126,127} One of these studies showed that improvements in multitasking tests like the Letter Search and Stroop tasks occurred within just 1 hour of bacopa consumption.¹²⁷

Bacopa is neuroprotective, mitigating brain oxidative stress and combatting inflammation, and also capable of inhibiting the release of cytokines like TNF- α and IL-6.^{124,132,134,135} In schizophrenia, bacopa appears able to improve cognition by attenuating the enhanced N-methyl-D-aspartate (NMDA) density that may occur in the prefrontal cortex of the brain in this group of patients.¹³⁶

Huperzine A

Huperzine A has been shown to safely improve performance on memory tasks in animal models, as well as in clinical trials.^{137–140} Based on preclinical and clinical research, huperzine A appears capable of improving cognition in specific patient sets, including those with schizophrenia, dementia, amnesia, diabetes, acute hyperbaric hypoxia, and hypoxic-ischemic encephalopathy.^{141–146}

Huperzine A has been widely implicated in the treatment of Alzheimer's disease, based largely on its ability to improve cognitive performance in those with mild to moderate Alzheimer's disease.^{140,147,148} A new study specifically showed that Huperzine A helps to reduce cognitive and task switching deficits in Alzheimer's patients.¹⁴⁹

Research has demonstrated that Alzheimer's disease patients who took huperzine A medication for 8 weeks showed cognitive improvements in task switching, whereas another study found that 8 to 12 weeks of huperzine A improved Mini-Mental State Examination results in Alzheimer's disease patients.^{149,150} Yet another study, conducted on 50 Alzheimer's disease patients taking 0.2 mg of huperzine A daily for 8 weeks, showed that huperzine A led to improvements in the patients' performance on several tasks related to cognition and memory.¹⁵¹

The cognitive benefits of huperzine A may be at least partly due to its ability to suppress the overexpression of inflammatory factors like tumor necrosis factor-alpha (TNF-alpha) and the overphosphorylation of JNK and p38 mitogen-activated protein kinases MAPKs).^{138,152} In addition to reducing neuroinflammation, huperzine A is also capable of combatting oxidative stress.^{137,145} It also inhibits acetylcholinesterase.^{139,150} It has been suggested that huperzine A may protect against the death of brain cells that results from actions of the neurochemical glutamate.¹³⁹

Investigation into the effects of huperzine A in specific patients helps to clarify the mechanisms by which it provides cognitive benefits and the different ways it may achieve these effects in distinct contexts. Its improvement of cognitive symptoms in dementia, for instance, may be due to its ability to affect cholinergic dysfunction and cerebral blood flow.¹⁵³

Following ischemia, huperzine A has been shown not only to improve memory, but also to reduce neuronal degeneration and partially restore hippocampal choline acetyltransferase.¹⁵⁴ Studies on diabetes-induced cognitive decline suggest that huperzine A improves cognition by reducing oxidative stress, inflammation, and cell death, and by modulating BDNF.^{144,155}

Pyridoxal-5-Phosphate

Pyridoxal-5-phosphate, more commonly referred to as vitamin B6, contributes to a variety of neural processes by acting as a cofactor for several enzymes.¹⁵⁶ The production of serotonin, a chemical implicated in anxiety, is one process for which vitamin B6 acts as a cofactor, and low serum concentrations of vitamin B6 have been implicated in higher levels of anxiety, panic attacks, and hyperventilation attacks.^{157,158}

Vitamin B6 is also implicated in cognition. Studies have shown that older adults with lower levels of vitamin B display faster rates of cognitive decline than those with higher levels of vitamin B.¹⁵⁹ The adverse effects of low vitamin B levels on cognition appear worse in certain contexts, such as in older people or in those who smoke.¹⁶⁰ Vitamin B has also been shown to combat memory impairment in animal models of specific illnesses, such as in

tmnpneumococcal meningitis.¹⁶¹

The glutamatergic neurotransmitter system contributes critically to learning and memory,¹⁶² and NMDA receptors for glutamate appear to be functionally altered by vitamin B deficiency. These observations suggest that vitamin B could contribute to the integrity of the brain's cognitive systems.¹⁶²

Pantothenic Acid

Oral pantothenic acid, also known as pantothenate or vitamin B5, appears to protect against both anxiety and cognitive decline.^{163,164} As such, diets rich in pantothenic acid have been suggested to improve psychological disorders.¹⁶⁵

The benefits that vitamin B has for the brain may be related to its role in the synthesis of acetylcholine, which is used by the brain for cognitive processes including memory encoding and concentration.¹⁶⁴ Acetylcholine appears to be important for brain plasticity, which allows for the formation of new connections between brain cells. Without these new connections, we cannot make new memories or learn new skills. Vitamin B5 appears to be particularly important in the link between brain plasticity and age-related memory loss.

Vitamin B5 likely confers its benefits through mechanisms other than those related to acetylcholine as well. For instance, according to experts, those who consume less vitamin B5 also have more inflammatory biomarkers, so vitamin B5 may help to combat problematic inflammation that inhibits healthy brain functioning.¹⁶⁶ U.S. Food and Drug Administration (FDA) guidelines recommend 5 mg daily of vitamin B5, which has been determined to be a safe dose.¹⁶⁴

Ginkgo Biloba

Ginkgo biloba is thought to act a cognitive enhancer and appears to be specifically involved in improving cognition in stressful contexts, or in other words, acting as an anti-stress buffer for cognition. ^{167,168} Consistent with this notion, preclinical research has shown that the extract can reduce stress-induced memory deficits.¹⁶⁹ This protective effect applies to different types of memory, including spatial memory and recall.^{170,171}

There is also evidence for the cognitive benefits of Ginkgo biloba when anxiety is not considered. For instance, though MCI and dementia are likely associated with stress-related anxiety, studies focused on MCI and dementia patients – but not specifically on their anxiety – have found benefits of Ginkgo biloba.

A recent meta-analysis of eight randomized controlled trials on the effects of Ginkgo biloba in dementia patients found that the substance improved cognitive functioning as well as daily life activities in these patients.¹⁷² According to a recent systematic review, the benefits of Ginkgo biloba extract in people with dementia occur when the extract is taken at doses of 200 mg per day for 5 months or more.¹⁷³

A 2016 review and meta-analysis covering 21 trials involving the use of Ginkgo biloba in MCI and Alzheimer's disease found that compared to Alzheimer's disease and MCI patients taking medicine for their cognitive challenges, those taking Ginkgo biloba in combination with their medicine saw greater improvements in their performance on the MMSE and in ADL scores.¹⁷⁴ These differences were apparent 24 weeks into using Ginkgo biloba.

Ginkgo biloba appears to confer its protective benefits by improving the survival of relevant neurons,¹⁷⁵ and its

benefits appear to extend beyond the cognitive to the psychiatric as well. A randomized, double-blind, controlled trial also showed that a Ginkgo biloba extract reduced anxiety in elderly patients who were suffering from cognitive decline.¹⁷⁶ Other studies corroborate the anxiolytic-like effect of Ginkgo biloba extract.¹⁷⁷

Phosphatidylserene

Phosphatidylserine is critical for proper neuronal functioning,¹⁷⁸ and it has been shown to reduce stress, to improve memory, and to preserve cognition in older adults.^{179–181} A study that provided people with 400 mg of soy-derived phosphatidylserine demonstrated that this phosphatidylserine supplementation led to improvements in cognitive performance in just 14 days, as measured by the Serial Subtraction Test (SST).¹⁷⁹

Another study found that 300 mg of soy-derived phosphatidylserine taken for 6 months improved cognitive functions in elderly patients who had complained of memory deficits.¹⁸⁰ Many of these improvements were seen in the domain of verbal recall. A study on almost 60 patients with Alzheimer's disease showed that phosphatidylserine improved vocabulary and picture matching scores.¹⁵¹

Preclinical studies have shown that phosphatidylserine improves hippocampal inflammation injury and decreases cholinesterase,¹⁵¹ which could help explain its beneficial effects on the brain. According to the Natural Medicine Comprehensive Database, 100 mg taken 2 to 3 times each day represents the therapeutic dose for phosphatidylserine when used for failing memory.¹⁷⁸ A recent review found that humans can efficiently absorb 300 to 800 mg of this substance daily.¹⁸²

Alpha glycerylphosphorylcholine

Alpha glycerylphosphorylcholine, also referred to as choline alfoscerate, has been implicated in anxiety and cognition. Specifically, research has revealed an inverse relationship between choline alfoscerate concentration and anxiety levels,¹⁸³ suggesting that choline alfoscerate deficiency can cause or exacerbate anxiety, whereas choline alfoscerate supplementation may alleviate anxiety symptoms.

Choline alfoscerate has also been shown to be effective in improving cognitive functioning, including memory in dementia and stroke patients.¹⁸⁴ A study on patients with mild to moderate dementia who were given 400 mg of choline alfoscerate 3 times each day for 180 days showed that the intervention improved cognitive symptoms, as measured with the MMSE, Alzheimer's Disease Assessment Scale (ADAS-Total), and Clinical Global Impression (CGI).¹⁸⁵

This supplement has demonstrated good tolerability among patients and is currently being studied in clinical trials funded by the National Institutes of Health for its potential benefits on the brain and cognition.^{185,186} Like vitamin B5, choline alfoscerate appears to provide neural benefits through its interaction with acetylcholine systems of the brain. Specifically, it appears able to increase brain levels of acetylcholine, particularly in the hippocampus, which is vital for memory and cognition.¹⁸⁷

Salvia Officinalis Extract

Salvia officinalis is a perennial plant that is native to the Mediterranean area.¹⁸⁸ More commonly known as sage, it has been used to improve memory for centuries.¹⁸⁹ Since it was initially used, much research on sage has supported its value in enhancing cognition as well as in improving mood. Compared to control conditions, even just the aroma

of sage has been shown to lead to better memory outcomes.¹⁹⁰ Data have also helped to reveal the mechanisms by which sage leads to better cognitive performance and boosts health and well-being.

It has been suggested that sage can contribute to the treatment of Alzheimer's disease because of its ability to protect the brain against Ab-induced toxicity.¹⁹¹ One study on the effects of sage in patients with mild to moderate Alzheimer's disease showed that compared to a placebo, 4 months of a fixed dose of sage led to better cognitive functioning as well as lower levels of agitation.¹⁹²

The cognitive advantages of sage have not only been observed in those with cognitive deficits but also in healthy people. A randomized, placebo-controlled, double-blind study on the effects of sage on cognitive performance in healthy older adults showed that a 333 mg dose of sage led to better attention as well as significantly more memory enhancement and memory performance than did placebo.¹⁹³ Even in young healthy people, sage has been repeatedly shown to improve both mood and mnemonic performance following just single dose administrations.¹⁹⁴

Though other species of *Salvia* have also shown promise from a cognitive perspective, *Salvia officinalis* appears unique in its ability to provide a combination of enhancements to both cognitive performance and mood.¹⁹⁰ It also has anti-anxiety and anti-depressive effects.¹⁹⁵

In addition to acting as an antioxidant and combating inflammation, sage also appears to work through its inhibition of cholinesterase, as well as through its effects on amyloid- β and neurotrophins.^{194–198} According to researchers, the data on the effects of sage on cognition are consistent with improved stimulus processing or memory consolidation that likely works in a dose-related manner.¹⁹³

CONCLUSION

Given that stress-related anxiety and cognitive dysfunction are on the rise and often co-exist, there is an urgent need to address each condition and any overlapping underlying mechanisms. Current therapeutic interventions are limited by efficacy and safety concerns, and emerging data are pointing to the critical role of nutrition in these disorders. Supplemental formulations that leverage what we know about how nutritional ingredients can prevent or combat anxiety and cognitive impairment offer new opportunities for people to boost their mental health in a safe, noninvasive, and cost-effective way.

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