

Smart Ingredients for Brain Health

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The latest research on brain health ingredients indicates products are meeting consumer needs and offer significant opportunity for category growth.



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Brain health supplements are a growing market segment thanks to several recent research developments and the rise of age-related cognitive decline. One market report by Research and Markets states that the global brain health supplement market was worth \$2.3 billion (USD) in 2015, and worldwide sales of brain health supplements are projected to exceed \$11 billion (USD) by 2024.¹

This report points to an aging population of highly educated professionals as the driving force behind the growth in demand. In addition, increased awareness about the benefits of supplements for supporting concentration and memory among college students, scientists, and entrepreneurs has increased sales in this category, according to the firm.

Research and Markets also states that the largest sales channel for brain health products is online stores, which are outpacing drug stores and supermarkets in sales growth due to more variety in price points, more product launches, and a greater availability of private labels.

As demand for brain health ingredients grows, so does interest in research that demonstrates the value of new and established nutrients for promoting healthy brain function. New studies continue to demonstrate the specialized beneficial effects of various compounds on the brain, particularly for

memory and cognition support.

While there are too many brain health ingredients on the market to examine them all in one sitting, what follows is a shortlist of some popular ingredients with new studies that demonstrate their benefits. (Note that this list is by no means exhaustive, and is intended to be a sampling of some compelling recent studies.)

Omega-3s for Athletes

Omega-3 fatty acids, the class of polyunsaturated fatty acids typically used as metabolic regulators in dietary supplements, are also useful in cognitive supplement formulations.

Gretchen Vannice, RDN, head of Global Nutrition Education at Organic Technologies, the parent company of AlaskOmega (Coshocton, OH), says omega-3 fatty acids are essential to healthy brain function, and that supplements are an ideal delivery form given that most Americans do not consume enough omega-3 fatty acids in their diet.

Says Vannice, "90% of the omega-3 fats in the brain are DHA. In the adult brain, DHA is especially concentrated in gray matter and is enriched in brain cell membranes, where it directly influences functional processes like membrane fluidity, gene expression, myelination, neuroinflammation, neurotransmitter release, and more."

Vannice says that decades of research have demonstrated that high levels of omega-3 fatty acids are associated with better cognition, slower cognitive decline in older adults, improvements in episodic memory in women, and improvements in working memory in men.

Perhaps the most promising new brain health application of omega-3s is assisting athletes in recovering from traumatic brain injuries (TBIs). One randomized, double-blind, placebo-controlled clinical trial on DHA omega-3 fatty acid supplements followed 81 National Collegiate Athletic Association Division I football players for 189 days, the entire duration of the college football season. Participants were given 0, 2, 4, or 6 grams of DHA per day. The study tracked measures of mild traumatic brain injury, including changes in serum neurofilament light (NFL), which is a biomarker of axonal injury. Elevated serum NFL levels is a telltale sign of mild traumatic brain injury and is common among football players.²

This study found that supplementing with DHA attenuated axonal injury, particularly among starting players, who tend to have more playing time and physical contact, and are therefore more likely to suffer brain injuries.

"This was the first study to examine prophylactic use of omega-3 supplements in football players," Vannice notes. "While the study used DHA only, based on the literature, I can predict that equal or higher amounts of EPA would provide additional benefits not only for brain health, but also for physical health and recovery."

Extending the Shelf Life of Phospholipid Supplements

Phospholipids are naturally occurring lipids present in all cell membranes that contain at least one phosphate group. Phosphatidylserine (PS) is a type of phospholipid that signals phagocytes to begin apoptosis.³

Soft Gel Technologies, Inc. (Commerce, CA) President and CEO Steve Holtby says PS is an essential building block that works to stabilize the membranes of brain cells, thereby protecting brain cell activity and limiting cell deterioration. He also notes the ingredient's role in stimulating memory and cognition as well as regulating mood.

Says Holtby: "PS supplements have been demonstrated in clinical trials to improve memory, concentration, word recall, and mood in middle-aged and elderly subjects. For older adults with moderate cognitive impairment, PS has produced consistently modest increases in recall of word lists."

Holtby says that early PS ingredients were extracted from the brains of cows, which presented potential dangers concerning the transfer of infectious diseases such as bovine spongiform encephalopathy. To resolve this risk, manufacturers like Soft Gel Technologies developed a means of extracting PS from soybeans and other plant sources.

However, delivery mechanism optimization presented further challenges. PS tends to degrade when stored in a soft gel, which makes it difficult to produce a PS supplement that appeals to older supplement users who have readily embraced soft gels as a delivery mechanism.

"To overcome this problem," Holtby explains, "we created a fluid dispersion PS material that has a greater stability. We've conducted stability and shelf-life studies, and we've found that the soft gel capsules maintain ingredient quality and level for a long period of time. Shelf-life studies performed by an independent laboratory for phospholipid analysis found that even after 24 months, the

material showed absolutely no degradation."

Citicoline May Hold Promise for Schizophrenia Patients

A naturally occurring cholinergic compound, citicoline promotes normal brain function and supports neuroprotective mechanisms by stimulating the production of phosphatidylcholine and acetylcholine in the brain.⁴

Clinical trials have examined citicoline as a therapy for addressing substance dependence, bipolar disorder, and traumatic brain injuries. Research is expanding into its benefits for schizophrenia patients.

One randomized, placebo-controlled trial followed 43 adult schizophrenia patients for 16 weeks.⁵

Before the trial, participants were assessed using the PANSS scale, which measures schizophrenia symptom severity. Individuals were assigned a score correlated to the sum of their ratings for five symptoms on the PANSS negative-symptom subscale. Participants in the experimental group received gradually increasing doses of citicoline, starting at 500 mg/day on the first day of the trial and ending with 2,000 mg/day by the beginning of the second week.

Over the course of the 16 weeks, both the placebo group (n=19) and the experimental groups (n=15) gradually lowered their PANSS scores. However, the experimental group scores decreased by one full standard deviation, whereas the placebo group scores decreased by only one half of a standard deviation.

While a follow-up double-blind clinical trial failed to replicate a statistically significant reduction in the experimental group's PANSS scores, it did find that citicoline had a significant effect on global functioning scores and free verbal recall.⁶

These studies are significant in that they found a therapeutic effect of citicoline on schizophrenia symptoms. Schizophrenia is a challenging condition to address. The negative symptoms of the disease in particular, such as apathy and avolition, are notoriously resistant to conventional therapies, partly because schizophrenia medications like haloperidol and risperidone tend to induce these symptoms in healthy individuals.⁷

The fact that the first study found a reduction in PANSS scores indicates that citicoline may hold promise in addressing the negative symptoms of schizophrenia. The study authors caution, however, "further study...is warranted in larger studies that will have greater (statistical) power."

Arginine Boosts Focus, Mental Acuity, and Problem-Solving Speed

Arginine is a well-studied amino acid frequently used in athletic and heart health supplements, but now, a silicon-bonded arginine variant is showing promise for cognitive applications. Double-blind, placebo-controlled human clinical trials have now found that arginine silicate is effective at improving mental acuity, cognitive function, and subjective feelings of mental energy.⁸

Jim Komorowski, chief science officer at Nutrition 21 (Purchase, NY), says a small daily dose of his firm's branded and patented arginine silicate complex Nitrosigine resulted in significant increases in feelings of energy in two clinical trials involving healthy participants.⁹

Both studies were double-blind, placebo-controlled crossover trials involving healthy subjects (n=16 and n=11, respectively). Experimental groups received 1.5 grams of Nitrosigine per day. Relative to the placebo groups, the experimental groups reported feelings of higher energy and performed better on cognitive tests.

Says Komorowski, "Nitrosigine supplementation also improved response time on a test of cognitive function, and after a single dose, Nitrosigine has been clinically shown to increase mental acuity and focus by 33% within 15 minutes. The impact on mental acuity also continues to build over time...Although studies on other nutrients may have reported some effects on brain function, those effects took weeks or months to develop."

Resveratrol Supports Memory in Healthy Individuals and Those with Cognitive Decline

A naturally occurring polyphenol commonly found in grapes and berries, resveratrol is most well known as an anti-aging ingredient. Gene Adamski, national sales manager at Evolva (Reinach, Switzerland), and his colleagues Angela Tsetsis and Ernesto Simon say that resveratrol protects grapes from harsh environmental conditions, and that the compound has a similar effect in humans by promoting healthy aging at a cellular level.

Evolva's team says that resveratrol supports a balanced inflammation response in the brain and improves cerebral blood flow, which results in mood and cognition benefits.

Recent human studies indicate that regular resveratrol intake can support brain function in both patients with Alzheimer's disease and normal, healthy individuals. One randomized, double-blind,

placebo-controlled trial gave varying doses (500 mg/day to 2 grams/day) of resveratrol to 119 patients with Alzheimer's disease for 52 weeks. This clinical trial found that relative to a placebo, resveratrol resulted in an improvement in Alzheimer's Disease Cooperative Study Activities of Daily Living Scale scores, changed AD biomarker trajectories, modulated neuroinflammation, and induced adaptive immunity.¹⁰

A second randomized clinical trial found that 75 mg of resveratrol given twice per day for 14 weeks improved performance on verbal learning and semantic memory tasks and boosted blood flow in the brains of 80 healthy postmenopausal women.¹¹

The Evolva team says that these studies showcase the mood-boosting and cognitive-enhancing properties of resveratrol and also serve as a jumping-off point for investigations into resveratrol's long-term health effects: "The same research group is conducting a bigger follow-up study where they investigate the effects of Veri-te resveratrol in cerebrovascular function, cognitive performance, and bone health."

Blueberry Extract Supports Episodic Memory in Older Adults

Wild blueberry extract (*Vaccinium corymbosum*) is a polyphenol-rich supplement that supports healthy blood pressure levels. In addition, Dan Souza, nutrition and health category manager for the branded blueberry product ThinkBlue by Naturex (Avignon, France), says wild blueberry extract has been clinically shown to improve episodic memory in senior citizens.

One randomized, double-blind, placebo-controlled human trial on the effects of ThinkBlue-branded blueberry extract involved 120 healthy participants between 65 and 80 years of age. This six-month study followed a group of seniors who consumed 111 mg of ThinkBlue per day.

After three months, Souza says, participants in the experimental group saw a 7% improvement in episodic memory. After six months, participants saw a six-point drop in systolic blood pressure. This study is slated for publication at the end of 2017.

Souza says that these findings are significant because they demonstrate a clear opportunity to resolve an ongoing challenge that seniors face: the degradation of episodic memory.

He states, "Episodic memory, the memory of personally experienced events, shows the greatest degree of age-related decline. There's robust and growing literature illustrating the cognitive health benefits of wild blueberries, but until now, there hasn't been a compliance-friendly, clinically substantiated dose of wild blueberry for nutritional supplement applications."

Souza also notes that past studies were conducted using much higher doses (at least 10 grams per day), whereas the ThinkBlue study showed a statistically significant improvement in episodic memory with a much smaller dose of just 111 mg per day.

The evidence also suggests that blueberry supplementation can improve verbal learning skills, and that the ingredient's effects on memory apply both to short- and long-term memory.

Cécile Frémont, the communications manager for Activ'Inside (Libourne, France), says blueberry's high concentration of polyphenols, anthocyanins, flavonols, and phenolic acids make it an ideal brain supplement, particularly for older adults with memory issues.

In one randomized, double-blind, placebo-controlled clinical trial, 215 healthy adults between the ages of 60 and 70 received 300 mg of Activ'Inside's branded Memophenol grape/blueberry extract or a matching placebo twice per day for six months. According to Frémont, participants were assessed on the Verbal Recall Memory (VRM) test and the Paired Associates Learning (PAL) test, which evaluate short-term working memory and long-term episodic memory, respectively.

Relative to the placebo group, subjects who received Memophenol recalled 60% more words on the VRM test and had significantly fewer errors on the PAL test. Study authors concluded that Memophenol supplementation reversed eight years of cognitive degradation, Frémont explains.

Frémont says this and other studies show that some brain health ingredients are more effective when formulated in blends: "Ten studies have been performed with a scientific R&D approach using this same framework, and they've revealed that grape and blueberry compounds are better absorbed when consumed in a specific ratio that boosts the cognitive properties of each single ingredient."

Botanicals Promote Dendritic Growth

Botanical brain health supplements, whether single-ingredient products or blends, have a variety of beneficial effects on the brain.

Deanne Dolnick, science director at TR Nutritionals (Alpharetta, GA), says botanical products like Gingko biloba extract and Bacopa monnieri extract are among the most popular brain health botanicals on the market, and for good reason.

"Ginkgo biloba extract has been the gold standard in brain health botanicals for a very long time," says Dolnick. "It's still popular for supporting memory and cognitive function, as well as increasing blood flow and reducing inflammation."

Dolnick says bacopa is also an important brain health supplement due to its ability to repair damaged neurons and restore degraded synaptic activity.

Until a few years ago, it was unknown whether the dendrites of neurons could repair themselves.¹² Now, researchers have confirmed through animal studies that bacopa induces dendritic proliferation and promotes neuron communication.¹³

Bacopa also has anti-inflammatory properties that may have applications for a variety of central nervous system disorders, as demonstrated in a recent in vitro study involving microglial cells grown from mice.¹⁴

This study examined the effects of bacopa infusions, teas, and alkaloid extracts (made from 10 grams of powdered bacopa extract) on cell cultures, specifically the neurotoxic M1 microglia and the neuroprotective M2 microglia. After administration, the infusion and a high-concentration alkaloid extract significantly inhibited the release of TNF-alpha and had an anti-inflammatory effect.

Dolnick says this study is significant because it demonstrates that *Bacopa monnieri* "inhibits the release of inflammatory cytokines from microglial cells and inhibits enzymes associated with inflammation in the brain."

Spearmint a Popular Brain Supplement for Athletes

Spearmint (*Mentha spicata/Mentha viridis*) has been shown to support memory, attention, planning, and reasoning when administered in high doses.¹⁵

Kim Colletti, global cognition product manager for Kemin (Des Moines, IA), says spearmint strains bred to be high in polyphenols have beneficial effects on focus as well as working memory, which processes new stimuli and uses recent memories to solve problems. Colletti says polyphenols like those in spearmint have been found in studies to reduce oxidative stress, boost acetylcholine levels, promote neurogenesis, and have neuroprotective properties.

Colletti points to a recent randomized, double-blind, placebo-controlled clinical trial on Kemin's branded spearmint supplement Neumentix Phenolic Complex that involved 142 healthy, active men and women in their late 20s. The experimental group received a daily 900-mg dose of Neumentix, and participants were assessed using computerized cognitive test batteries after 0, 7, 30, and 90 days.

Says Colletti, "The participants taking Neumentix had significantly higher scores in sustained attention after 30 days of supplementation, and these improvements were still present after 90 days. These findings build on earlier work and further emphasize the uniqueness of this special ingredient."

Ashwagandha Reduces Mental Stress and Enhances Neurotransmitter Effects in Studies

Ashwagandha (*withania somnifera*) is an adaptogenic herb commonly used in Ayurvedic medicine.

Bruce Abedon, PhD, vice president of scientific and regulatory affairs for NutraGenesis (Brattleboro, VT), says ashwagandha also supports normal memory function and cognition in addition to reducing cortisol levels in human clinical trials.

Abedon says that the glycowithanolide bioactives present in ashwagandha can also inhibit the enzymes that break down neurotransmitters, thereby extending the duration of neurotransmitter effects.

"For example, ashwagandha helps to inhibit acetylcholinesterase, an enzyme that breaks down acetylcholine. Acetylcholine is active in the hippocampus, which is associated with memory and learning. So, reduced degradation of acetylcholine can produce cognitive benefits (by enhancing memory and learning)."

One double-blind, placebo-controlled crossover human clinical trial followed 20 healthy subjects for 43 days. Subjects took 250 mg of NutraGenesis' branded ashwagandha product Sensoril twice per day for 14 days, and were evaluated on cognitive function tests of reaction time, digital system substitution, digit vigilance tasks, and card sorting tests on day 15. After a 14-day washout period, the subjects crossed over to the opposite group for another 14 days.¹⁶

Subjects taking the ashwagandha supplement scored significantly higher on measures of psychomotor performance, working memory, reaction time, and information processing ability compared to the placebo group.

Abedon says that this study demonstrates the effectiveness of ashwagandha as a cognitive supplement: "This study shows that Sensoril is effective at multiple doses, in multiple populations,

when assessed both subjectively and objectively using validated test measures."

According to Abedon, NutraGenesis's branded and patented ashwagandha product Sensoril differs from traditional ashwagandha in that it has standardized to contain over 10% glycowithanolides, whereas the concentration of this component in traditionally prepared ashwagandha can vary.

Curcumin Clears Amyloid Plaque and Neutralized Free Radicals

A linear diarylheptanoid extracted from the dried rhizomes of the *Curcuma longa* plant, curcumin is often used as a brain health supplement for its mood-stabilizing and stress-reducing properties. Now, research suggests that curcumin may play an important role in supporting a balanced immune response and clearing amyloid plaque in the brain.

In a recent double-blind randomized crossover clinical trial, 30 obese participants (BMI >30) with varying degrees of comorbid anxiety and depression received 1 gram of curcumin per day (or a corresponding placebo) for 30 days. After a two-week washout period, subjects crossed over to the alternate condition for an additional 30 days.

Participants were assessed on their anxiety and depression using the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory at 0, 4, 6, and 10 weeks.

The study found that curcumin supplementation was associated with a statistically significant ($p<0.05$) reduction in mean BAI scores relative to a placebo.¹⁷

Shaheen Majeed, president of Sabinsa Worldwide (East Windsor, NJ), says this and other studies demonstrate the impressive brain health benefits of curcumin: "Several recent studies have demonstrated that curcumin can help restore equilibrium by improving mood, regulating stress and anxiety, and protecting the brain against aging and neurodegenerative diseases like Alzheimer's."

Lutein Benefits Memory and Academic Performance in Children

A naturally occurring terpenoid, lutein is commonly used as a supplement for the eye and skin health markets. As a brain health supplement, lutein is typically used to prevent age-related cognitive decline.

Kemin's Global Manager of Vision Products Ceci Snyder says lutein is the predominant carotenoid in the brains of children and older adults.

"In children, lutein makes up more than half of the brain's total carotenoids, which indicates that lutein plays a role in brain development. Higher brain levels of lutein are also related to better cognitive function in older adults."

Snyder speaks of one recent clinical trial involving 40 children between ages seven and 10. In this randomized, parallel-design clinical trial, participants were assessed for aerobic fitness via a modified Balke treadmill protocol and completed a task to measure relational memory performance. Participants were also assessed for macular pigment optical density (MPOD) and adiposity.¹⁸

The study found that higher levels of aerobic fitness and MPOD were correlated with fewer memory errors, and that MPOD accounted for a significant amount of the variance in memory performance. Snyder says this study is important because it demonstrates the importance of lutein throughout life. She states, "Lutein appears to help maintain brain health and function by protecting the brain from oxidative stress and inflammation."

OmniActive (Morristown, NJ) Vice President of Global Marketing Lynda Doyle says lutein is also a potent antioxidant that boosts academic performance and prevents age-related cognitive decline. While the exact mechanism of action remains unclear, Doyle says the current rationale is that lutein has anti-inflammatory and antioxidant properties.

One double-blind, placebo-controlled clinical trial on 59 healthy subjects between 18 and 25 years of age measured the effects of carotenoid supplementation on a variety of markers such as antioxidant concentration, inflammation, and brain-derived neurotrophic factor (BDNF), a neurotrophin associated with learning, memory, and higher cognitive processes.¹⁹

This study found that relative to the placebo group, lutein supplementation significantly improved antioxidant and BDNF levels, and significantly decreased inflammation markers.

Doyle says that these results demonstrate lutein's importance not only as an underlying anchor of healthy brain function, but also as a useful supplement for supporting day-to-day brain functioning. Says Doyle, "BDNF is one of the most important compounds in the brain. It plays an essential role in central nervous system development, neural plasticity, and cognitive function. Our research shows that increasing BDNF levels with lutein supplementation is correlated with improvements in processing speed, composite memory, and sustained attention."

Magnesium Sets the Clock Back on Aging Brains

There's no shortage of vitamins and minerals that contribute to brain health, but one of the most essential is magnesium.

Jennifer Gu, PhD, chief science officer at AIDP (City of Industry, CA), says magnesium is an essential cofactor in more than 300 biochemical reactions, including nerve and brain function. She notes that magnesium is a critical brain health supplement for aging adults, particularly Baby Boomers.

"Our memory, reasoning, and cognitive functions peak at age 25," Gu says. "After that, the area of the brain associated with complex thinking and decision-making starts to shrink, and our neural and synaptic function decreases."

Gu says that the brain's capacity for critical thinking shrinks by 50% between 25 and 80 years of age, and that over time, brain cells have more and more difficulty relaying signals.

The results, she says, include a variety of conditions including decreased cognition, poor memory, reduced attention span, poor sleep quality, and anxiety. Gu believes, however, that magnesium supplements can restore old neurons to their previous state and boost synaptic function.

A recent randomized, double-blind, placebo-controlled, parallel-design human clinical trial examined the effects of a branded magnesium L-threonate supplement (labeled MMFS-01) on 44 subjects aged 50–70 with mild age-related cognitive impairment.

Subjects took 25 mg/kg/day of the magnesium supplement (or a corresponding placebo) for 12 weeks. Measurements included plasma, urine, and intracellular magnesium levels, as well as tests of visual search and attention, motor speed, working memory, recognition, and association.²⁰

The experimental group exhibited a significant increase in magnesium secretion, as well as an improvement in performance speed on the Trail Making Test, Part B, and an improvement in overall cognitive ability. The placebo group did exhibit a training effect on several of the tasks; however, after applying statistical controls, the study authors concluded that magnesium L-threonate improves cognitive ability.

Gu says these results are an incredible breakthrough, as they have demonstrated that magnesium supplementation can undo years of cognitive aging:

"One of the most striking outcomes of this study was that supplementation led to a 10% increase on TMT-B scores, and that the improvement in participants' cognitive ability was equivalent to a brain that is nine years younger."

NutraScience Labs (Farmingdale, NY) Vice President of Contract Manufacturing Vincent Tricarico feels the brain health category has seen a variety of recent innovations, with vitamin and mineral manufacturers eyeing specialty formulations based on well-vetted ingredients.

Says Tricarico: "Across all of the brain formulations we're currently working with, vitamin C, B-complex vitamins, magnesium, and calcium are the top ingredients sought by our clients. Most of the formulas we've seen have been crafted with a combination of specialized—and usually trademarked—ingredients, with a greater presence of specialty herbs than in the past."

Brain Health Category Still Rich Ground for Innovators

With new research identifying positive brain health effects of a variety of nutritional ingredients, there's no shortage of opportunities for companies to begin developing specialized and enriched formulations for brain health products. Memory and cognition supplements, in particular, are in high demand among working professionals, athletes, students, and seniors. As category growth continues, further research will undoubtedly examine new and growing applications for these ingredients and formulations, making brain health a smart niche for manufacturers and distributors alike.

Also read:

[Latest Studies on Brain-Health Nutraceuticals](#)

[2016 Ingredient Trends to Watch for Food, Drinks, and Dietary Supplements: Brain Health Ingredients](#)

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