

# Nutritional OUTLOOK

Brain health targets: stress, sleep, healthy aging, esports, and more



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### Brain Health

Consumers of all ages have an incentive to buy and use brain health supplements. According to statistics from market research firm IRI, in 2019 sales of specialty supplements targeting brain health grew in sales by 24%, and those targeting sleep and mood grew by 16%. Reasons for purchasing brain health supplements range across age demographics.

For example, older adults might be interested in supporting their memory function and mitochondrial health, while younger folks might be more interested in energy, focus, and stress reduction. In fact, when listing reasons why they take supplements, 22% of respondents cited emotional wellbeing, and 16% cited maintaining and/or boosting energy levels. Both of these reasons trended significantly higher among millennials. As the industry continues to innovate, there is no shortage of novel ingredients that will help manufacturers meet these consumer needs.

### **Energy + Focus = Productivity**

L-theanine is a popular ingredient often featured in nootropic products to support focus and attention. As an active constituent found in tea, L-theanine is a natural complement to caffeine, which is also present in tea. While caffeine is commonly used as a functional energy ingredient in beverages, recent research shows how combining both caffeine and L-theanine in a functional beverage, for example, could affect the end user.

One study found that subjects taking the combination saw significant improvements in Rapid Visual Information Processing (RVIP) accuracy, reductions in mental fatigue ratings, as well as faster simple reaction time, faster numeric working memory reaction time, and improved sentence verification accuracy.<sup>1</sup>

“L-theanine can help counter some of the ‘jitteriness’ that people sometimes experience, especially when consuming larger amounts of caffeine,” explains Katie Ferren of Blue California (Rancho Santa Margarita, CA), which manufactures L-theanine ingredient L-Tea Active. In clinical research, for example, supplementation with L-theanine significantly reduced the effects of caffeine on subjects’ blood pressure.<sup>2</sup>

Some ingredients act similarly to caffeine, while being stimulant free. For example, a patent-pending proprietary *Mangifera indica* extract standardized to ≥ 60% mangiferin called Zynamite (distributed by PLT Health Solutions; Morristown, NJ) was found in an animal study to have similar effects on the central nervous system as caffeine.<sup>3</sup> Both Zynamite and caffeine act in similar ways on brain electrical activity, increasing long-term potentiation, which is a persistent strengthening of synapses based on recent patterns of activity, and is related to space- and time-dependent memory. Marketed to support mental energy, and endurance during physical fitness, the ingredient’s cognitive

and physical benefits can translate into a number of applications, from pre-workout to energy and focus.

Another ingredient marketed for sports and endurance called LJ100 (from HP Ingredients; Bradenton, FL) was recently found to support quality of life, mood, and stress.<sup>4</sup> In the study, subjects between the ages of 25 and 65 were given a combination of the branded tongkat ali ingredient and multivitamins, or placebo, for 24 weeks. The primary endpoints were quality of life measured with the 12-Item Short Form Health Survey (SF-12) questionnaire and with mood measured by Profiles of Mood States (POMS). The secondary endpoint, stress, was measured by a Multi-Modal Stress Questionnaire (MMSQ).

Results showed that those taking the combination exhibited significant improvements in quality of life, mood, and stress. These same subjects reported improvements in vigor, mental acuity and cognition, and emotional well-being.

Stress reduction is an important component of focus. “Healthy stress can help motivate someone,” says Ferren. “When it becomes too overwhelming, the stress can be dysfunctional and paralyzing for the individual, which impacts their ability to focus and pay attention.”

It’s not enough just to promote relaxation. L-theanine, for instance, can promote a calm and relaxed state while also maintaining alertness—a unique attribute, says Derek Timm, PhD, RDN, technical sales director, Taiyo International (Minneapolis, MN), which manufactures L-theanine ingredient Suntheanine. “When one is calm and alert, they are better able to focus and complete whatever task is at hand,” he states. “Several alternative relaxation and calming ingredients lead to drowsiness and decreased focus and attention.”

In a study of 34 healthy subjects between the ages of 18 and 40, supplementation with L-theanine in a functional beverage containing Blue California’s L-Tea Active was shown to reduce measures of subjective stress in response to a multitasking cognitive stressor an hour after administration.<sup>5</sup> Analysis of salivary cortisol also showed a significant reduction in salivary cortisol three hours after administration. This same study also used magnetoencephalography (MEG) analysis to measure brain activity. Results showed that subjects supplementing with L-theanine showed evidence of higher alpha wave activity, which is generally linked to a more relaxed mental state. According to the researchers, this activity was particularly apparent in subjects with higher trait anxiety.

A more recently published study conducted on 30 healthy subjects for four weeks found that L-theanine in the form of Suntheanine not only supported stress but also has the potential to support cognitive function.<sup>6</sup> In this study, results showed that four weeks of supplementation significantly reduced the following scores: Self-Rating Depression Scale, State-Trait Anxiety Inventory, and Pittsburgh Sleep Quality Index (PSQI). PSQI subscales showed significant improvements in sleep latency and daytime functioning after L-theanine supplementation. In measures of cognitive function, L-theanine

supplementation significantly improved scores from the Brief Assessment of Cognition in Schizophrenia (BACS) related to verbal fluency (especially letter fluency) and executive function scores. These scores were found to be most significant compared to placebo in subjects who demonstrated lower baseline functions.

Considering these potential benefits, it's no surprise that L-theanine is breaking into the mainstream. The fastest-growing use has been in energy drinks to either support focus or antagonize the effect of caffeine, says Timm. "It is especially popular for the next generation of energy drinks that aim to provide focused energy and not just an energy jolt," he explains. "Another exciting new category, going beyond the standard energy drink, is the concept of beverages for accuracy. This is of strong interest to gamers, students, athletes, and those just looking to be more on their game."

The gaming category is a major opportunity many industry suppliers are actively seizing. Firms like Kemin (Des Moines, IA) and Nutrition 21 (Purchase, NY), for example, have both made pushes to position their ingredients to the Esports category.<sup>7</sup> Kemin's Neumentix spearmint extract, for example, has been shown in clinical research to support cognitive and physical performance, even under stress.

One study found that sleep-deprived volunteers from an elite counterterrorism unit showed significant improvements in executive function under stress, compared to placebo.<sup>8</sup> This was assessed by having participants shoot or not shoot a target on the basis of recognition after undergoing cognitive and physical stress. Prior to supplementation, all members of the placebo group engaged the correct target, whereas four out of five volunteers assigned to take the spearmint extract engaged the correct target. However, following supplementation and the high-risk operation, all volunteers who took the spearmint extract engaged the proper target, while only three of five subjects in the placebo group engaged the correct target.

In another study on Neumentix, researchers observed the effects of the spearmint extract by measuring physical performance with a Makoto Arena.<sup>9</sup> This is a 360-degree, multi-planar, game-like environment that closely mimics a sports environment, and it is designed to assess the link between cognitive function and physical performance. Results showed that compared to placebo, subjects taking the extract demonstrated statistically significant improvements in reaction time. These outcomes translate well to virtual reality gaming, which is growing in both consumer and competitive spaces, not to mention traditional athletics, like martial arts, for example.

A proprietary brain-health ingredient from Nutrition 21 called nooLVL (read "new level") was studied specifically on gamers.<sup>10</sup> In the double-blind, placebo-controlled study, 60 healthy subjects who spent more than five hours a week gaming were given either nooLVL or placebo for seven days. On day one and day seven, before and 15 minutes after dosing, subjects were given cognitive assessments, a mood questionnaire, and then played video games for 60 minutes. Immediately after gaming, these cognitive tests were repeated. Results showed that compared to the placebo group, the supplement

group had increased levels of perceived energy, decreased anger, decreased fatigue, and 66% fewer errors in cognitive tests.

Citicoline may also be a valuable addition to a gamer-focused product. For example, a study published in *The Journal of Attention Disorders* assessed the effects of a proprietary citicoline ingredient (Cognizin, manufactured by Kyowa Hakko; New York City, NY) on attention, psychomotor function, and impulsivity in healthy male adolescents.<sup>11</sup> Results showed that subjects taking citicoline exhibited significant improvements in attention, psychomotor speed, and impulsivity, compared to placebo. Considering that gaming is popular among adolescents, this study demonstrates efficacy on an important target audience. While parents may not be keen on products that encourage too much screen time, they might take solace in the benefits such a product might pose for learning and behavior.

### **Staying Sharp with Age**

While energy and focus are areas of cognitive health that present newer opportunities for dietary supplements among younger demographics, older adults are an important population because their brain health needs are more urgent. Taking dietary supplements to maintain brain health against age-related decline and to support facets of cognitive health such as memory can have an important impact on a person's quality of life.

“Baby boomers have become the primary age group for cognitive products,” says Lisa Riedell, senior director of marketing, Alfasigma USA Inc. (Covington, LA). “They want to maintain a high quality of life for as long as possible. Maintaining cognitive acuity, including memory and performance, is critical for this age group.”

Kyowa's Cognizin citicoline has been studied for its effects on memory in aging adults for some time now. A 1996 study, for example, found that supplementation with citicoline improved verbal memory in subjects between the ages of 50 and 85. The randomized, double-blind, placebo-controlled, parallel-group-design clinical study found that compared to placebo, supplementation only improved delayed recall related to logical memory for the subjects with relatively inefficient memories. These subjects were then recruited for a crossover study in which a higher dosage of citicoline was clearly associated with improved immediate and delayed logical memory.<sup>12</sup>

A more recent animal study on Cognizin found a potential synergistic benefit with omega-3 fatty acid docosahexaenoic acid (DHA), an important active component of fish oil, which many older consumers already take to support cardiovascular health.<sup>13</sup> Phospholipids, structural components of cellular membranes, play an important role as precursors to signaling pathways that modulate neuronal membrane function. Phosphatidylcholine is the most abundant cellular phospholipid, and citicoline along with DHA is an essential intermediate in the synthesis of phosphatidylcholine. In the study, mice with brain ischemia were treated with a combination of Cognizin citicoline and DHA, or each alone. Results showed that the combination significantly improved learning and memory ability compared to the ingredients independently.

Polyphenol-rich extracts derived from grapes and blueberries have a growing library of evidence supporting their use in cognitive health formulations. Given their fruit origin, they also have a functional advantage for use in foods and beverages as well as recognition by consumers.

In a study published in *Biological Sciences*, 215 healthy subjects between the ages of 60 and 70 years of age were randomized to receive either 600 mg per day of a polyphenol-rich extract from grape and blueberry (Cerebelle from Diana Food; Hasbrouck Heights, NJ) or placebo for six months.<sup>14</sup> Subjects were given a CANTAB Paired Associates Learning (PAL) test, a visuospatial learning and episodic memory test, as well as a Verbal Recognition Memory (VRM) and Spatial Span (SSP) working memory test, at baseline and 24 weeks.

There were no significant changes in primary outcomes in the placebo and experimental group, but subjects taking the extract did see significant improvements in VRM-free recall compared to baseline and placebo group. Researchers then stratified subjects into four quartiles based on cognitive performance at baseline. Results showed that the quartile with the lowest performance at baseline experienced the most significant improvements in primary and secondary outcomes, compared to placebo.

A study of a different polyphenol-rich extract ingredient from grape and blueberry (Memophenol from Activ'Inside; Beychac-et-Caillau, France) published in *Antioxidants* also saw positive results.<sup>15</sup> In the study, 30 healthy students were randomized to consume either 600 mg of Memophenol or a placebo. Ninety minutes after intake, cognitive assessments were conducted for one hour. These assessments included Serial Three Subtraction task (STS), Rapid Visual Information Processing task (RVIP), and subjective ratings using Visual Analogue Scale (VAS).

Results showed that consumption of Memophenol was associated with a 2.5-fold increase in STS variation net scores, compared to placebo. The STS task requires participants to count quickly and accurately backwards in threes from a given random starting number between 800 and 999 presented on a screen. The task aims to evaluate subjects' working memory and attention levels. A serial seven subtraction task was also performed but showed no significant improvements.

## **Healthy Aging**

Healthy aging as a category represents a more holistic approach to combatting age-related decline, within which cognitive health is an important factor. It represents a major opportunity for manufacturers as well. For example, Natural Alternatives International (NAI; Carlsbad, CA) recently introduced a slow-release version of its patented beta-alanine ingredient CarnoSyn, called SR CarnoSyn. The new slow-release version focuses primarily on the healthy aging market rather than the sports nutrition space, a market in which the original CarnoSyn ingredient is already well known.<sup>16</sup>

The amino acid beta-alanine supports the synthesis of muscle carnosine in the body, which acts as a buffer against lactic acid to delay the onset of muscle fatigue. Carnosine

levels decline as people age; therefore supplementation reduces the risk of sarcopenia. As an antioxidant, beta-alanine also helps fight glycation. Glycation leads to the accumulation of advanced glycation endpoints, which damage brain cells and function.

Ingredients touting mitochondrial health benefits are a big part of the healthy aging space. “Through the body’s regulation of healthy mitochondria and the removal of dysfunctional mitochondria, brain activities such as memory and learning may be improved,” says Shoji Matsukawa, vice president of Mitsubishi Gas Chemical, manufacturer of BioPQQ, a branded pyrroloquinoline quinone ingredient. “Importantly, the healthiness of mitochondria can affect not only brain functions but so many other functions as well, especially associated with aging, so it is important to have consumers conscious of the importance of mitochondrial health.”

“BioPQQ has been proven to activate mitochondrial biogenesis—a process critical to healthy cell activity in which clusters of mitochondria divide and multiply,” explains Matsukawa. “As we get older, mitochondrial function begins to decline, leading to the deterioration of brain health as well as the heart and other vital organs. But by reenergizing the mitochondria, BioPQQ can fuel cellular activity, providing more efficient energy production.”<sup>17</sup>

Another ingredient that supports mitochondrial health and, in turn, cognitive health, is MitoCarn from Alfasigma USA Inc. The ingredient is an acetyl-L-carnitine (ALC) form of L-carnitine. “As nerve growth factors in the brain decline, so do acetyl-L-carnitine and acetylcholine levels,” explains Alfasigma’s Riedell. “As a result, mitochondria tend to lose their efficiency. This loss of efficiency contributes to common complaints related to aging, including loss of memory, learning, recall, and cognition.”

MitoCarn, says Riedell, penetrates the blood/brain barrier to deliver nutrients directly to the brain. “The molecules may help to increase healthy blood flow and support wide-ranging functions that contribute to healthy cognition, including help with managing oxidative damage, support of mitochondrial function, and maintaining healthy neurotransmitter activity,” she continues. “MitoCarn may also help to minimize cellular waste during the ATP process. Antioxidants are critical in helping to reduce damage caused by free radicals or reactive oxygen species and other toxic residue byproducts.”