



Mood in the Time of COVID-19

In turbulent times, natural products are more sought-after than ever before by the stressed and the sleepless.

By Mike Montemarano
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The ways in which sleep, nutrition, and mood are inextricably connected has become one of the most prevalent dynamics that researchers, consumers, and product formulators in the nutritional products market have been gravitating toward for several years now.

Global statistics presented by leading health researchers characterize people in the U.S. and several other countries as more stressed, sleepless, and depressed.

Meanwhile, abundant data continue to ascertain that certain dietary patterns and nutritional deficiencies play a role in emotional well-being.

"The modern lifestyle, despite all of the commodities within our reach nowadays, can be truly exigent for our minds," Julia Díaz, head of marketing for Pharmactive, said. "This, along with the most recent research on nutrition, nutritional disorders, and their consequences, has resulted in new products designed to improve these conditions rising in popularity."

An estimated 30-40% of supplement consumers use nutritional products to address concerns about anxiety or stress,

with concerns over a lack of energy falling shortly behind, according to a recent National Health Interview Survey (NHIS). This survey also found "wellness" was a much more common driver to supplement use than "treatment," and approximately one in four supplement users reported feeling better emotionally as a result of their supplementation.

Nutritional psychiatry is beginning to emerge as a standalone field of research and practice, and while complementary treatments aren't intended to address severe psychiatric symptoms, a growing base of evidence supports nutritional intervention as a worthwhile complement to medical and other types of interventions for mood and sleep issues.

"From a practitioner's point of view, nutrition, stress, and exercise are the fundamental factors that need to be addressed

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prior to resorting to supplementation,” Mariko Hill, product development executive at Gencor, said. “If an individual is still having troubles with sleep or their mood once they have worked to optimize all of these factors, it is then recommended that they try some sort of supplementation.”

Because such an abundance of natural products and supplements can have an effect on mood or sleep patterns, a common definition of “mood” or “sleep” products is difficult to reach. All types of foods, beverages, supplements, aromatics, and more tout mood and sleep benefits, making this market segment very fragmented and ubiquitous.

The lion’s share of mood and sleep benefit claims have been applied to supplements over the years, however, Mintel market research reported these claims are beginning to penetrate into more conventional food products; about 5% of all product launches Mintel tracked in the food and beverage space had either a mood or sleep claim attached to them.

With many pharmaceutical and OTC remedies for sleep, the dietary supplements industry has largely responded with natural, drug-free alternative solutions, catering well toward consumers who fear grogginess and other side effects associated with drugs. Mintel reported that nearly half of adults indicated a lack of sleep contributes to their level of stress, and getting more sleep is the top 2020 health and wellness goal, according to the company’s research.

“More people are looking for natural, holistic alternatives to chemical, artificial, and synthetic therapies,” James Roza, chief scientific advisor for Layn Natural Ingredients, said. “Many botanicals are rolling out in new and novel delivery formats, including functional foods and beverages, gummies, chewable tablets, and liquids. We are rapidly innovating and scaling new ingredient solutions to deliver the benefits of botanical extracts in formats consumers prefer.”

“Years ago, the focus was primarily on the ability to fall asleep. Today, there is greater emphasis on the qual-

ity and quantity of sleep and how a good night’s rest can improve our well-being. That’s where CBD, adaptogens, and other calming herbs can be of great benefit,” Roza continued.

The mood and sleep domain, like virtually all segments of this industry, is also pressured to be sustainable in its practices, both environmentally and socially, Díaz said.

“It has proven to be a differentiating factor if the product remains 100% natural if it’s a nutritional-related product,” she noted. “They also need to be environmentally and socially responsible.”

Díaz said most mood and sleep products have one of four biomechanisms: oxidative stress reduction, interacting with inflammatory pathways in the nervous tissue, improving the balance of neurotransmitters produced, and offering nutrients associated with neuroplasticity.

“Multi-targeted products need to be developed to offer effective solutions to customers,” Díaz said. For example, “Af-ron saffron extract has been demonstrated in several clinical studies as a potent antioxidant with anti-inflammatory effects, which not only help balance key neurotransmitter levels, such as serotonin and dopamine, but also fight oxidative stress produced during anxiety and stress processes in the brain to protect it from damage.”

The Quarantine Blues

It is becoming abundantly clear that day-to-day life under the persistent threat of COVID-19 is adversely affecting the sleep patterns and mental well-being of a sizeable portion of Americans. It can be expected that problems associated with sleep and emotional wellness, which were already a chart-topping consumer demand, will continue to be a rising health priority.

“Any outcome related to the pandemic, whether it is being kept in isolation, or the loss of a loved one, is certainly impacting the lives and mental health of millions of people around the world,” said Hill, at

Gencor. “Given the dire need for support, the dietary supplement industry has an opportunity to step in and provide solutions for the growing mental health crisis, whether that takes the form of mood, stress, weight management, or immunity.”

In a survey conducted by Sleep Standards, 50.2% of Americans stated that COVID-19 complications have affected their sleep patterns negatively, a phenomenon most prevalent among Millennials (60%), though it’s less prevalent among Gen X (22%), Gen Z (11%)—who are less likely to be working yet—and Baby Boomers (6%) who are more likely to be retired.

“Teenagers are one of the most vulnerable targets of stress, since they are the hardest hit from a mental health standpoint,” Díaz said. “Necessities widely vary among different age groups, however, when it comes to mental health, brain performance, or sleep aid products, there is a uniform tendency to consume naturally sourced ingredients, preferably botanical.”

A study conducted by the University of British Columbia and published in the *Journal of Gerontology: Psychological Sciences* yielded similar findings. Adults over the age of 60 who were surveyed experienced notably greater emotional well-being and felt less stressed and threatened by the pandemic despite a greater objective vulnerability and mortality rate associated with the virus. Furthermore, adults in this age bracket were more likely to report experiencing positive remote social interactions, at a rate of 75% in their daily surveys.

The American Psychological Association found that almost eight in 10 Americans said COVID-19 is a significant source of stress; government response to COVID-19 is a significant stressor for 66% of adults. Nearly as many (63%) reported the thought of the U.S. reopening is causing them stress.

On the pharmaceutical end, according to the America’s State of Mind Report, the number of antidepressant, anti-anxiety, and anti-insomnia medication prescriptions filled increased by 21% from February to March this year. Previously, the use

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—Jeremy Appleton, ND, PLT Health Solutions

of anti-anxiety and anti-insomnia medications was on a steady decline from 2015 to 2019, down 12% and 11.3%, respectively.

“While making the public aware of services that are available to them is important, it’s incumbent upon us to take charge of our own health,” Roza said. “Dietary supplements can play a significant role in enabling us to regain balance in our lives while staving off or mitigating the assaults caused by stress and anxiety on our immune systems.”

“The coronavirus pandemic has already precipitated a mental health crisis in the United States,” said Jeremy Appleton, ND, director of medical and scientific affairs at PLT Health Solutions. “Anxiety and depression are rising, and the country is ill-prepared to deal with the consequences. As far back as May, experts warned of a historic wave of mental health problems, including depression, substance abuse, post-traumatic stress disorder, and suicide. We need to use every tool and resource available to us to combat this crisis and prevent it from worsening.”

Mood Must-Haves

Several of the standard vitamins and minerals necessary for a wide range of health applications have, in several studies, shown themselves to have important neuroprotective benefits. Though some of the research is preliminary, deficiencies in

key vitamins and minerals including the B complex, vitamin D, zinc, magnesium, and selenium appear to be correlated with lowered emotional states, and worsened outcomes in clinical psychiatric settings.

Of the hundreds of mechanisms with which it is involved in the human body, magnesium is well-known for its critical role in cognitive function, and its protective effect against depression. One of the most prominent studies on this examined magnesium intakes of 8,894 adults, and found that low magnesium intake placed people at a 22% greater risk of developing depression. Additionally, researchers cited notable correlations between treatment-resistant depression and magnesium deficiency (*Journal of the American Board of Family Medicine*, 2015).

The eight essential B vitamins that make up the vitamin B complex have been evaluated in several prominent studies, which have provided evidence that each of the B vitamins plays a role in improving cognition and regulating nervous system response to mitigate stressors. B12 in particular helps metabolize both serotonin and melatonin more efficiently, signifying that deficiencies may have something to do with disruptions in mood or sleep patterns.

Vitamin D, a nutrient which some researchers have estimated is at deficient levels in over 1 billion people, is hypothesized to play a role in neuroprotection, as

well. Cross-comparisons between sunlight therapy and vitamin D, which is absorbed through a hormonal reaction in response to sunlight exposure, have examined and compared effects on seasonal affective disorder (SAD) a form of periodic emotional lows that emerge seasonally, usually at the onset of winter. Another large-scale study on obese but otherwise healthy men, published in the *Journal of International Medicine*, found that increased serum levels of vitamin D improved in the Beck Depression Inventory, a widely-used psychometric self-evaluation.

Zinc is a cofactor of hundreds of enzymes, many of which play a part in the neurotransmitter activity in the central nervous system. In depressed patients, low serum zinc is considered a possible biomarker for resistance to antidepressant drugs, and studies have found that supplements of zinc result in statistically significant improvements to sleep time, especially when combined with other nutrients.

Natural Zzs

Many prescription and OTC solutions to disrupted sleep patterns were once heralded for their potency, however, consumer preferences today are beginning to skew toward more natural alternatives, according to multiple market research firms.

While melatonin remains the top

seller in the nutraceutical sleep market as a drug-free sleep solution, representing a near-entirety of ingredient sales in the sleep supplements category, it's noteworthy that the market is becoming more sophisticated with formulations that offer compounding benefits to mood, stress, and other cognitive issues. This approach allows consumers to personalize their sleep aid regimen with a stack of natural ingredients.

Amid a growing consumer base that uses supplements to improve sleep (from 11% to 19% according to CRN's 2019 Consumer Survey), people are gravitating toward more natural, clean-label attributes, echoing broader market trends.

A common driving factor for purchasing combination herbs, adaptogens, lavender, L-Theanine, and other products is that conventional sleep supplements like melatonin haven't been studied for standalone mood benefits. Additionally, adaptogens like ashwagandha and Rhodiola, and amino acids such as L-Theanine, have been studied for their potential to affect mood positively as well. For this reason, many new melatonin product launches feature additional ingredients known to be effective during long-term supplementation to complement the acute, short-term benefits that melatonin provides at bedtime.

CBD

The importance that consumers place on cannabidiol (CBD) as a non-psychoactive botanical extract for mood and sleep benefits certainly cannot be understated.

While CBD is still experiencing some rough regulatory waters, the ingredient has captivated many consumers seeking to improve their emotional states and sleep patterns. According to FMCG Gurus, 9% of global consumers said they currently use CBD products, and 40% reported they would be willing to do so.

While much of the research on the benefits of CBD is preliminary, and involves doses much higher than consumer-grade, certain human and animal studies have yielded evidence that the

effects of CBD oil may result in reductions in anxiety and sleep disorders. One study, for example, found some notable human results; six weeks of daily supplementation with a commercially-available CBD oil was able to significantly improve assessed mood, sleep quality, and enjoyment of life in a group of 65 overweight but otherwise healthy men compared to a placebo in which no improvements were observed (*The Center for Applied Health Sciences*, 2019).

There remain a significant portion of skeptics who believe it's too early to make any assumptions on CBD's efficacy.

"CBD, albeit having little to no scientific evidence, is gaining a lot of attention within the millennial demographic for its 'stress relieving' properties. This drug, as recently classified by the European Commission, is likely only rising in popularity due to its association with the psychoactive drug marijuana," according to Hill.

The leading benefits of mood and sleep, combined with the tidal wave of stress caused by the COVID-19 pandemic, lead market researchers to believe that the next few years will be an extension of the CBD springboard. Technavio projected that CBD is poised to grow by \$3.52 billion over the next four years, at a CAGR of over 32%, though post-COVID analysis suggests this may be an underestimate.

While most CBD products are standalone oil extracts, many sleep and mood

supplements include ingredient stacks featuring CBD in tandem with other formulations. Roza, for example, reported that Layn is working on several mood, stress, and sleep multiherbals, including a CBD, sea buckthorn, and resveratrol formulation.

Additionally, wide varieties in CBD oils can be achieved, using unique combinations of cannabinoids and terpenes, the two primary types of ingredients found in full-spectrum hemp extracts. As these unique phytochemicals become more researched, formulators will inevitably offer products tailored to meet specific benefits.

Contenders to watch for those in the CBD business are other products which beneficially interact with the same receptors as CBD, including Palmitoylethanolamide (PEA), Hill said. While the etymology behind "cannabinoid" is directly tied to the cannabis plant, recent research has identified plenty of cannabinoids that exist naturally in other plants that won't face the same level of regulatory trouble. Examples include black pepper extract, ginger, Echinacea, and kava. Other synthesized ingredients are able to act upon the receptors of the cannabinoid system, as well.

"PEA is an emerging player in the sleep segment with influence on the endocannabinoid system (ECS)," Hill said. "The ECS has a role in many fundamental physiological processes such as sleep, pain, and mood. Thus, by acting on various receptors



in the ECS, also known as the 'entourage effect,' PEA has slowly been emerging in various sleep formulations. Gencor has conducted numerous gold-standard studies on its branded PEA, Levagen+, particularly in the areas of managing discomfort and exercise recovery."

Botanicals

There is a long list of herbs, fruiting bodies, and mushrooms which have been increasingly researched for mood and sleep benefits over the past several years, fueled in part by the demand for more clean-label, natural solutions that fit into the attributes consumers seek.

Adaptogens, including maca, *Rhodiola rosea*, *Ginkgo biloba*, and ginseng, each contain unique phytochemicals specific to each plant, which enable those plants to survive harsh environmental stressors. These compounds are evidenced to modulate a number of hormonal and enzymatic processes in ways that clinical research suggests may improve human reactions to external stressors. One of the most notable features of these botanical products is their demonstrated propensity to lower cortisol, the primary stress hormone that, at elevated levels, is a marker for frequent waking. It's also associated with increased blood pressure and weight gain.

"Numerous studies have demonstrated

that stress left unmanaged can contribute to serious health problems. Stress triggers the brain to release cortisol into the bloodstream. Many consumers have become aware of this connection and are looking for natural solutions to support healthy mood, manage stress, and aid with quality sleep. And they are looking for long-term solutions for self-care and without unwanted side effects," Roza said.

Mood can also be impacted by targeting another stress hormone corticosterone, Roza said, such as through the use of resveratrol, which inhibits the expression of the enzyme PDE-4.

Several other botanical ingredients contain antioxidant compounds that can pass through the blood-brain barrier; and others are shown to modulate certain inflammatory biomarkers. It is believed that these potent phytochemicals can improve mood by protecting the brain from free radicals and inflammation, and clinical trials continue to put them to the test in an array of mood and sleep evaluations.

Many herbal/botanical ingredients with established benefits to mood often work at least in part by addressing inflammation, according to Appleton.

"Inflammation and mood are related by multiple mechanisms of action, ranging from the modulation of the gut-brain axis by the intestinal microbiota to bioactive enzymes and peptides. PDE4 inhibitors are

perhaps the best-known modulators of inflammation," Appleton said. "Connections between mood and inflammation have been approached by formulators in specialty channels, like the healthcare practitioner channel, but to a large extent the complexity of these connections eludes product development teams formulating for the larger consumer product goods space. This is partly owing to the difficulty in connecting inflammation and mood claims, which require different types of evidence and structure-function language."s

Neurochemicals

A number of ingredients have been shown to be directly involved with synthesis and activity of neurotransmitters by crossing the blood-brain barrier.

GABA's benefits represent a cross-section between healthy aging, cognitive function, mood, and sleep benefits. Studies have shown that GABA, the most abundant neurotransmitter in the brain, induces a shorter duration of time before falling asleep, and lengthens time spent in non-REM sleep. GABA is inhibitory, meaning it helps regulate nervous system reactions to stressors. Supplementation in studies has resulted in significant reductions in blood pressure, and self-reported reductions in stress. Several supplements also feature a number of ingredients believed to effect GABA activity positively, including amino acids and herbs such as kava, American ginseng, and passionflower.

Another leading neurotransmitter building block is 5-HTP, a precursor to the neurotransmitters serotonin and melatonin. Research suggests it aids the body in its natural production of serotonin, and while there is not enough scientific evidence to support its use for any medical condition, research indicates it can increase serotonin levels, improve mood as measurable by a number of evaluations, and improve sleep quality and duration.

"In regard to stress and anxiety, serotonin reuptake inhibitor (SSRI) receptors have an influence on mood states of in-



dividuals,” Hill said. “Ingredients that act on these receptors are commonly found in nootropic-related products due to their ability to increase the mood enhancing hormone serotonin.”

The Gut-Brain Axis

There is a growing base of evidence suggesting that gut health plays a role in nutrition in ways much more pronounced than currently understood; and it has been driving some of the most groundbreaking research within the mood and sleep nutrition market.

There are many pathways by which certain species of probiotic bacteria interact with the nervous system, through the release of neurotransmitters, hormones, enzymes, and other compounds at which certain levels are associated with better mental health outcomes. It’s noteworthy, for example, that 90% of serotonin within the human body is synthesized within the gut, which is itself lined with neurons. While these neurons mostly help aid the process of digestion, the theory is that they influence emotional and sleep states as well.

Of the millions of bacteria located in the digestive tract, two probiotic genera have been the most extensively researched for effects on mental health and sleep. This special group of probiotics, recently dubbed “psychobiotics,” have been garnering significant intrigue with a steady rise of researchers conducting gene sequencing in hopes of finding new beneficial bacteria.

Lactobacillus and *Bifidobacterium* appear to have the most backing at this point, though there is plenty of research underway in a race to identify, evaluate, and patent other types. Pro- and prebiotics are often combined for their synergies in newer formulations, in addition to a host of other beneficial herbs, amino acids, and more.

Hill said that targeted nutritional endpoints for probiotics present unique challenges, beyond that which is typical in the nutritional space.

“There is still a lot more research need-

ed to be produced and published, particularly on the specific end-benefits,” Hill said. “Thus, brands must be specific when formulating and marketing their product, especially in terms of dose, type, and timing of the bacterial strain used for a particular target market.”

“Several clinical trials have now documented effects, or lack thereof, of certain probiotics for mood disorders,” Appleton said. “When considering probiotics for support of mood and stress, formulators should consider that probiotics within the same genus and species can have strain-specific and unique characteristics. Therefore, the efficacy of psychobiotics, as with all probiotics, should be considered strain-specific unless proven otherwise.”

Enzymes, peptides, and prebiotics, which play a role in nutritional uptake and the proliferation of beneficial bacteria, also interact with the gut-brain axis.

Research has shown that dozens of brain-gut peptides, including cholecystokinin, ghrelin, substance P, neuropeptide Y, melatonin, and opioid peptide can significantly mitigate the development of mood disorders (*Biomedical Research*, 2017). Many of the peptides found in the brain which are associated with mood benefits can be synthesized into supplement form, whereas the levels of others can be augmented through the intake of other nutrients.

“As solid scientific research continues to grow, consumers will remain focused on microbiome-boosting solutions, such as fiber sources (as Fructo-oligosaccharides) the most extended products on the market nowadays,” Díaz said. “The key is to understand how relevant the gut-brain axis is on regulating our bodies, having a direct impact on our sleep quality, nutrients absorption, immune system performance, hormonal system, etc.”

Conclusions

The mood and sleep market in the world of nutraceuticals is a dynamic, vast, and fragmented one, packed with unique benefits and nuanced mechanisms of action

in which no one ingredient category is quite the same as any other.

The increasing popularity of new delivery formats, and the fact that chart-topping priorities of mood and sleep are slated to become even more important—especially to young people—suggest this market segment has nowhere to go but up in tandem with any research that identifies the unique roles nutrients can play in the closely intertwined areas of mood, stress, and sleep.

Compared to other nutraceuticals, products in the sleep and mood categories offer immediately tangible benefits.

“The consumer experience of a product is another area that points to an enhanced role for cognitive support,” said Steve Fink, vice president of marketing for PLT Health Solutions. “For example, how do you know if your preventive immune support product is working? Because when it’s actually working for you, nothing happens. You don’t get sick. You don’t feel worse. But you also don’t necessarily feel better. If you formulate a cognitive support ingredient into an immune product, you do feel better. This leads to a more positive reaction to the product, greater compliance, and often more success.”

Formulators in a number of different categories can benefit from natural mood enhancer ingredients, Fink noted, in areas such as sports nutrition and weight management in which consumers might take weeks or months to reach a nutritional goal. PLT’s Zembrin, a *Scelietium tortuosum* ingredient formulated for weight management also has the added benefits of short-term improvements to cognitive flexibility, executive function, and mood, as demonstrated by multiple studies including MRI evaluations and psychometric tests.

Fink said that, among consumers PLT surveyed, 70% of people are expressing interest in adding cognitive support ingredients across a broad range of categories, signifying that as these types of ingredients are formulated in novel ways, they’ll receive overwhelmingly positive reception. 