

Formulating
“MORE”
INTO FOODS AND BEVERAGES

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Formulating “MORE” INTO FOODS AND BEVERAGES

Kyowa Hakko Bio fuels innovation of next-generation products with ingredients that provide functional benefits

Once a little-known concept among mainstream shoppers, functional foods, which are those foods and beverages with health benefits beyond basic nutrition, are concepts that today's consumers increasingly seek out for short- and long-term health and wellness benefits. Advancements in fermentation technology and biotechnology enable the manufacture and purification of high-quality functional ingredients that can be added to familiar foods, turning them into superfoods.

The International Food Information Council (IFIC) Foundation's *2016 Food and Health Survey* found that nearly half of consumers said that "weight loss/management" is a health benefit they are interested in getting from foods. About one-third of Americans listed "increased energy," "cardiovascular health," "healthy aging" or "digestive health."

Consumer insights from market research firm Canadean supports this trend towards wanting "more" from everyday foods. Research shows that consumers are more conscious of their health than ever before and aim to improve it proactively through healthy living, which includes healthy eating and drinking, rather than reactively through the use of conventional medicines. This health-consciousness, in conjunction with consumer willingness to experiment, explains the development of

innovative superfoods, everything from grain-based snack foods to grab-and-go yogurt drinks.

"The increasing trust that consumers have for formulations including superfood extracts is therefore widening the possibility for manufacturers to incorporate superfood ingredients within their products across several sectors," says Lia Neophytou, associate analyst at Canadean.

Kyowa Hakko Bio makes substantial contributions to the well-being of people around the world through an array of health-promoting biochemical substances. This includes various amino acids, nucleic acid-related substances, vitamins, bioactive substances and pharmaceutical products, as well as oligosaccharides and dipeptides. Many are generally recognized as safe (GRAS) for foods and beverages, while others are intended for the dietary supplement and pharmaceutical industries.

"As pioneers in the development and application of fermentation technology, we maintain an ongoing commitment to research, developing innovative new products and quality management," says Chikakuni Kotani, president and chief executive officer. "Our quality-first approach to doing business means that our customers receive reliable, high-quality products that perform as promised."

The booming brain health market

Rehydrate and recovery in sports nutrition

Opportunities to formulate foods and beverages that address heart health, immunity, metabolism and more



*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

CITICOLINE

SUPPORTS COGNITIVE HEALTH DURING AGING

Graying hair, wrinkles and expanding waistlines are all outward signs of getting older. More subtle indicators include forgetfulness, weak bones and sleeplessness. The 74-plus million baby boomers in the U.S.—about one-fourth of the population—are actively trying to defy these symptoms of aging, and in doing so, are seeking out foods and beverages that provide nutrients that support cognitive health.

According to the *2017 NMI Health & Wellness Trends in America* study from the Natural Marketing Institute, Harleysville, Pa., baby boomers are seeking out very specific health benefits in their foods and beverages. Improving heart health, strengthening bones, and memory and focus are some of the top drivers of purchase.

The latter is contributing to a brain and cognitive health market, which has been growing steadily since 2003. Ingredients such as citicoline are fueling innovation.

Citicoline is an organic molecule produced endogenously and found in every living cell. When consumed, it is broken down during intestinal absorption and, after passing through the blood/brain barrier, is reconstituted in the brain as citicoline. Citicoline is needed to build cell membranes throughout the body. Its cognitive health benefits have been studied repeatedly.

A review of citicoline supplementation studies with elderly subjects showed improvements in a wide range of cognitive and behavioral measures. This includes focus, attention, reaction time and mental energy.⁽¹⁾

To keep the brain healthy, it is paramount that it receive the fuel it needs to function at its best. Citicoline has been shown to assist.

Daniel Drubach, M.D, a neurologist at the Mayo Clinic, Rochester, Minn., states in his book *The Brain Explained* that the brain makes up only 2% of a person's body weight, yet it consumes roughly 20% of the body's energy when at rest.

"Citicoline helps keep the brain's metabolic activity at healthy levels," says Elyse Lovett, marketing manager at Kyowa Hakko. "The research indicates that it not only supports mental energy, but it also promotes focus and attention."

Citicoline is an important cellular building block that is synthesized into two types of compounds vital to healthy brain function. First there are phospholipids, which make up approximately 30% of brain tissue and are essential constituents of cell membranes. Because cell membranes have a very high turnover rate, these phospholipids must be continuously synthesized to ensure adequate function of cells.

Citicoline is also an important component of neurotransmitters, including acetylcholine, dopamine and noradrenaline. All of these compounds play a role in healthy brain function, including focus and attention.

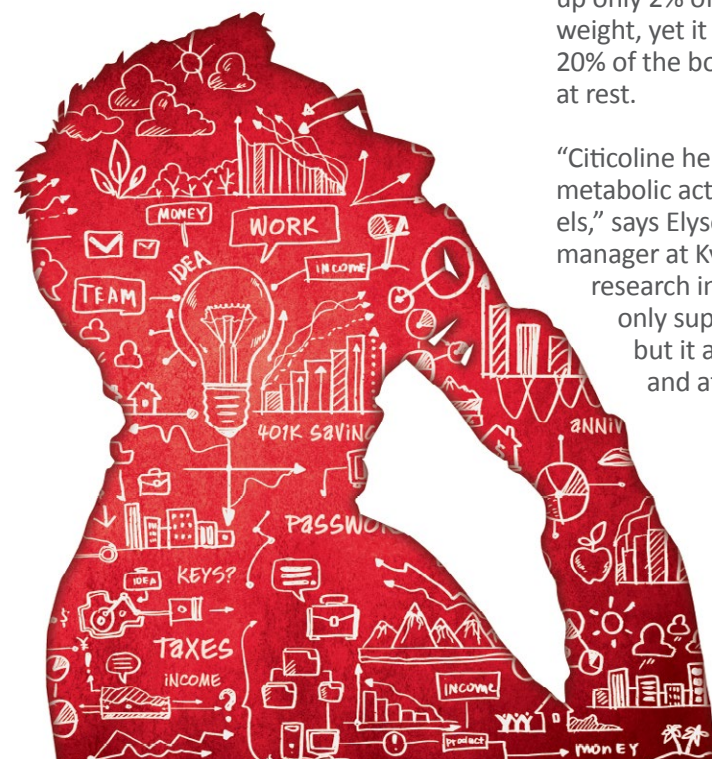
Cognizin® is Kyowa Hakko's branded form of pure, stable citicoline. It is produced by a patented fermentation process and contains no food additives, artificial flavors or preservatives, and thus complements today's clean-label trends. From a formulation perspective, Cognizin citicoline is stable in liquids and to high heat, while also being water soluble, rendering it easy to use in beverages and liquids. Because of its neutral to slightly acidic taste, it complements numerous product flavors.

"Cognizin achieved self-affirmed GRAS status in 2009 and is considered safe for food and beverage applications," says Ms. Lovett.

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Cognizin®

For the evolution of your mind®



CITICOLINE

SUPPORTS COGNITIVE HEALTH DURING AGING CONT.

"It is also a vegetarian and allergen-free ingredient, and is certified kosher."

Applications include beverages, breakfast cereals and bars, chewing gum and confections, dairy product analogs, frozen dairy desserts, milk and milk products, and processed fruits and fruit juices. Opportunities exist to formulate foods and beverages for baby boomers that address one or more of their aging concerns.

1. Secades, J.J., Lorenzo J.L., *Methods & Findings in Experimental & Clinical Pharmacology*, 2006; 27(Supplement B): 1–56.

CITICOLINE: THE BRAIN NUTRIENT

Citicoline is often called a brain nutrient because it supports levels of several important neurotransmitters that regulate cognitive function. It has also been shown to support the activity of nerves that respond to these neurotransmitters, helping to support the brain's learning and communication circuits.

A study published in 2008 in *NMR in Biomedicine* showed the effects of Cognizin® citicoline on brain cellular metabolism in humans. The study quantified the effects of citicoline on high-energy phosphate metabolites and constituents of cellular membrane synthesis in the frontal lobe of 16 healthy men and women. The data showed that citicoline improved frontal lobe bioenergetics and altered phospholipid cell membrane turnover. After six weeks of receiving citicoline, participants experienced an average 26% increase in phosphoetha-



What is citicoline?

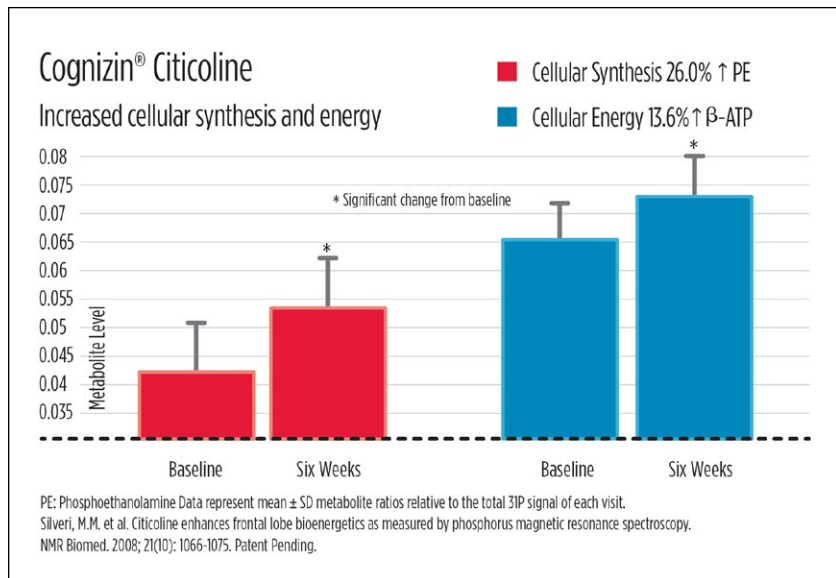
A naturally occurring nutrient found in the brain.



What does it do?

Citicoline increases an important substance in the brain called phosphatidylcholine that is critical for healthy brain function.

Visit www.cognizin.com to learn more about how citicoline improves cognitive function.



nolamine and a 13.6% increase in adenosine triphosphate.

The study also demonstrated that the area of the brain most affected by citicoline is the anterior cingulate cortex (ACC). The ACC is involved in cognitive functions such as focus and attention. The researchers concluded that citicoline supplementation may

help support cognitive health as we age by increasing energy reserves and utilization. It may also increase the amount of essential phospholipid membrane components needed to synthesize and maintain cell membranes.

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REHYDRATION FOR PEAK PERFORMANCE

Proper fueling of the body prior to, during and after exercise is paramount for peak performance and recovery. This includes fluid and electrolyte regulation.

During dehydration, fluids move from the plasma to both intracellular and extracellular spaces and then eventually back into circulation. Significant decreases in performance have been associated with even minor hypohydration (dehydration levels below perceptible thirst).(1)

Glutamine ingestion during acute dehydration stress is reported to support fluid and electrolyte absorption. Using a patented fermentation process, Kyowa Hakko developed Sustamine®, a dipeptide that has been shown to increase electrolyte and fluid



tides and amino acids must wait for a “transporter.” A transporter can carry either single amino acids or dipeptides through the cell barrier at once. By coupling for transport, dipeptides reduce time and energy needed for amino acid absorption.

Sustamine is stable to both heat and acid, is highly soluble and can function as a source of glutamine

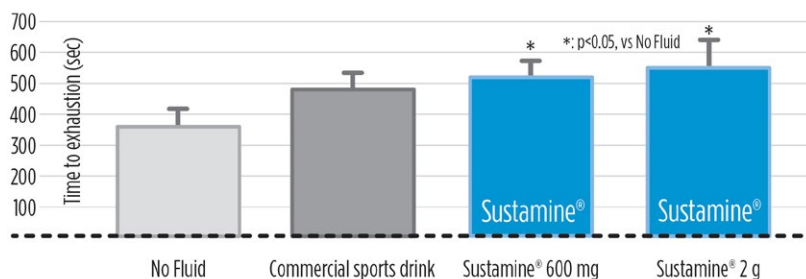
“Because Sustamine’s dipeptide form breaks down into free alanine and glutamine immediately upon entering the body, the benefits of Sustamine include glutamine’s ability to promote protein synthesis and stimulate immune action as well as L-Alanine’s ability to supply energy and promote healthy hydration,” says Elyse Lovett, marketing manager at Kyowa Hakko. “Sustamine is the only dipeptide backed by healthy human clinical results, and the only self-affirmed GRAS dipeptide of L-Alanyl-L-Glutamine for foods and beverages.”

Sustamine supports clean-label formulating. It is vegetarian, allergen-free, kosher and contains no additives or preservatives. It is also stable, soluble and taste-free. Unlike straight L-Glutamine, which begins to degrade when mixed with liquids, Sustamine’s unique dipeptide form resists degradation and ensures that the consumer receives the amount listed on the label. Sustamine is also stable in combination with other active ingredients, such as vitamins or electrolytes.

1. Hoffman, J.R., Stavsky H., Falk B.: The effect of water restriction on anaerobic power and vertical jumping height in basketball players. *International Journal of Sports Medicine*, 1995, 16:214-218.

Sports performance benefits

Improved time to exhaustion during high-intensity, one-hour treadmill run



Rehydration with Sustamine®, at both high and low doses, significantly improved time to exhaustion compared to no-hydration.

uptake across the intestines by increasing ion transport through the intestinal mucosal cells.

Sustamine consists of two amino acids (L-Alanine and L-Glutamine) connected by a peptide bond. Smaller than a complete protein, the dipeptide Sustamine is absorbed faster than individual amino acids. To get into cells, dipep-

tidal amino acids must wait for a transporter. Because of these properties, Sustamine is used in clinical nutrition as a source of glutamine without the problems of poor stability in liquids and low solubility that are associated with free glutamine. There's also opportunity to create sports nutrition products to assist with fluid and electrolyte regulation, while also delivering additional health benefits.

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L-CITRULLINE SUPPORTS CIRCULATION FOR IMPROVED HEALTH AND WELLNESS

Nitric oxide is a behind-the-scenes player when it comes to health and wellness. It is produced by the endothelial cells lining the arteries and penetrates the underlying smooth muscles, acting as a potent vasodilator to relax the arteries. Therefore, nitric oxide supports normal oxygen and blood circulation throughout the body, contributing to total well-being.

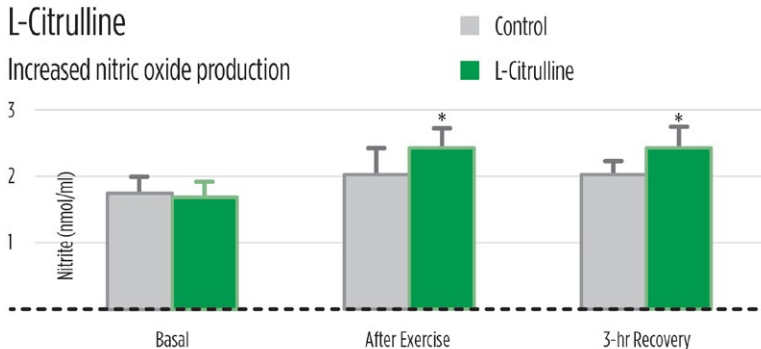
The most common way to increase nitric oxide is through exercise. When active, the muscles require more oxygen, in response, the heart works faster to supply the muscles with blood. The lining in the arteries releases nitric oxide into the blood, which relaxes and widens the vessel wall, allowing for more blood to pass through.

Another way to increase nitric oxide is through diet, most notably by consuming the amino acids L-Arginine and L-Citrulline. These amino acids are found in a number of plant-based foods including dark cocoa and watermelon. Another option is to consume functional foods.

"L-Citrulline is a non-essential amino acid that previously was thought of as just an intermediate metabolite," says Elyse Lovett, marketing manager at Kyowa Hakko. "However, over the past decade, research on L-Citrulline has dramatically increased due to the

L-Citrulline

Increased nitric oxide production



Sureda et al., Eur J Appl Physiol (2010). Modified

In a human study, male cyclists were supplemented with L-Citrulline or a placebo. Nitric oxide production was measured as nitrite plasma concentration. Nitrates in the plasma were significantly increased after the cycling stage in the supplemented group and maintained high during recovery.

(Suede A., Cordova A., Ferrer M.D. L-Citrulline-malate influence over branched chain amino acid utilization during exercise. *European Journal of Applied Physiology*. 110:341-51, 2010.)

understanding and importance of its metabolism."

Research shows that L-Citrulline is converted to L-Arginine in the body, leading to increases in both L-Arginine and nitric oxide. Increased production of nitric oxide promotes vascular dilation, which improves oxygen and blood circulation throughout the body. L-Citrulline is also expected to relieve muscle fatigue through ammonia elimination. Antioxidant action and cardiovascular support action are also known.

Unlike most other amino acids, L-Citrulline is not a component of dietary proteins; therefore, everyday foods cannot be a direct source of L-Citrulline to the body. As a result, interest in this nutrient is emerging in various applications for improving health and wellness.

In 2014, Kyowa Hakko self-affirmed its L-Citrulline as GRAS. Manufactured in the U.S. using a proprietary fermentation process, L-Citrulline is an ultra-pure amino acid that is preservative-free, allergen-free and contains no artificial flavors or colors. The company markets it as a food ingredient for use at levels of 275 milligrams of L-Citrulline per serving in various food products, such as beverages and beverage bases; grain products and pastas; and milk products.

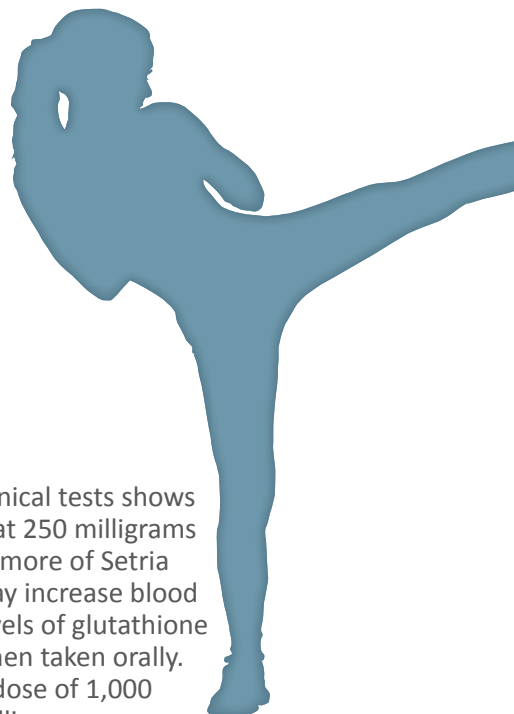
Nitric oxide is best known for its cardiovascular benefits, making L-Citrulline a suitable ingredient for functional foods targeted to aging consumers. Athletes and bodybuilders are also attracted to sports nutrition products supplemented with L-citrulline, as the nitric oxide produced facilitates the removal of exercise-induced lactic acid build-up. This reduces fatigue and recovery time.



KYOWA L-Citrulline
Kyowa Quality®

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GLUTATHIONE PROTECTS CELLS FROM OXIDATIVE STRESS



Dietary antioxidants are gaining traction among health-conscious consumers, as these powerful molecules are associated with reducing cellular damage in the body. Antioxidants help the body fight off damage from free radicals, which like to wreak havoc on the body by causing cells to grow and reproduce abnormally. Free radicals result from oxidation, a natural process that occurs when we digest food, exercise or simply breathe. Living in environments with pollution, radiation and cigarette smoke also increases free radical production.

The more free radicals in the body, the greater the potential for cellular damage. That's because once free radicals form, they can start a chain reaction, damaging healthy cells, which



can lead to premature aging. Antioxidants terminate these chain reactions by being oxidized themselves, reducing free radical damage.

More than 100,000 published studies have shown that glutathione plays a central role in managing overall health. Kyowa Hakko uses a patented fermentation process to produce Setria® Glutathione, a highly absorbable tripeptide that can help replenish the body with numerous bodily processes, including detoxification, antioxidant protection and immune system fortification.

Clinical tests show that 250 milligrams or more of Setria may increase blood levels of glutathione when taken orally. A dose of 1,000 milligrams may enhance the body's normal immune cell function.

Setria is recommended as a dietary supplement. It is a pure ingredient that is stable to temperature and humidity. Setria contains no additives, artificial flavors or preservatives, and is allergen-free, vegetarian and kosher.

PANTETHINE SUPPORTS HEART HEALTH

Maintaining heart health is important to everyone. A balanced diet and regular exercise helps keep the heart healthy; however, sometimes stresses at home or work challenge even the most dedicated consumer to stick to a heart-healthy regime.

Isolated and purified compounds such as the pantethine can assist. This derivative of pantothenic acid (vitamin B5) has been shown to help maintain balanced cholesterol levels, thus having a positive impact on heart health.



Pantesin® is Kyowa Hakko's branded form of pure, stable pantethine. It is an effective ingredient for use in dietary supplements and nutritional formulations for cardiovascular health.

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About Kyowa Hakko BIO and Kyowa Hakko USA

Kyowa Hakko USA is the North and South American office for Kyowa Hakko Bio Co. Ltd., an international health ingredients manufacturer and world leader in the development, manufacturing and marketing of pharmaceuticals, nutraceuticals and food products. Kyowa is the maker of branded ingredients including Cognizin® Citicoline, Lumistor® L-Hydroxyproline, Pantesin® Pantethine, Setria® Glutathione, as well as Sustamine® L-Alanyl-L-Glutamine. For more information, visit www.kyowa-usa.com.



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Kyowa's L-Citrulline is a Kyowa Quality® ingredient

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