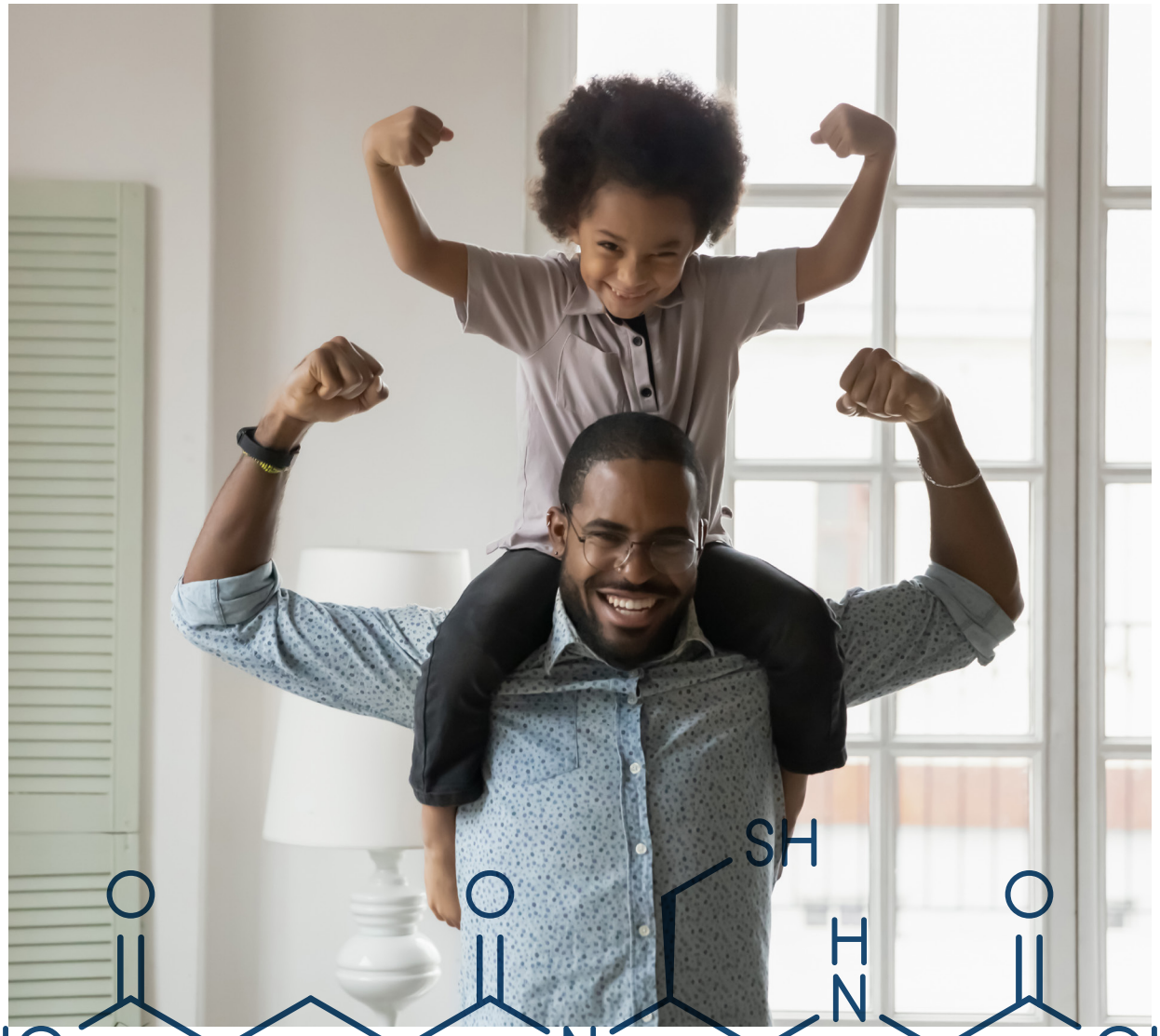
Mastering the Natural Products Market

Glutathione supports cellular wellness across immunity and more



WHAT'S INSIDE



3 Introducing the master antioxidant

4 Glutathione and cellular wellness

6 Healthy aging at the start of the day

7 Increased glutathione in the body equals greater benefit

7 The branded advantage of Setria® Glutathione

8 Glutathione: A competitive edge in sports nutrition

9 Market opportunities with Setria® Glutathione

11 Shining a light on skin health with glutathione

Introducing the *master* antioxidant



What is wellness? Some would say with good nutritional habits and an active lifestyle. That's easy to say, harder to accomplish. Life happens – pandemics hit, the pounds and stress pile on, we are stuck in place. External environments are also at play, as pollutants and toxins from our industrial needs and digital desires intrude upon both our physical and mental health.

But where does wellness begin? It really starts at the cellular level. Science is constantly reminding us that our brains and biology are beholden to the cellular machinery that metabolizes and absorbs nutrients and fats and sugars, powering processes involving proteins and enzymes. Somehow it all works, according to the DNA blueprint, until it doesn't. The immune system breaks down under the assault of a virus or the constant barrage of cortisol spiking in response to the modern world. Unstable molecules called free radicals can damage DNA, cell membranes and other parts of cells.

This is where life and the inevitable decline toward the alternative happen. It is also where more and more consumers start their journey into improving their "healthspan," a lifetime of wellness, by supporting cellular health with natural products. In fact, one could argue that every major market category—immune health, brain health, digestive health, active mobility and even skin health—is one part of the healthy aging category.

"Post pandemic, consumers are seeking out new and innovative health products for daily use: A new way to achieve physical fitness, something that supports longevity, and a way to support and balance their immune system year-round," said Maria Stanieich, marketing manager for Kyowa Hakko USA.

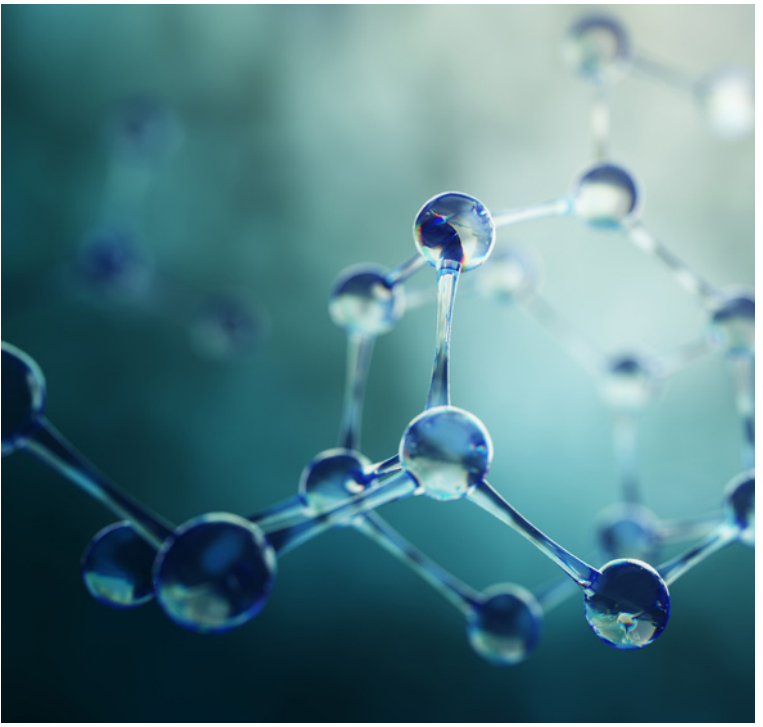
Kyowa Hakko is an international health ingredients manufacturer based in Japan that has developed a number of branded ingredients for the nutraceuticals market. Originally specializing in the commercial development of amino acids



> Glutathione, often referred to as the *'master antioxidant,'* may help support everything from immune, digestive, and brain function to detoxification and longevity.

compounds like glutathione, the company pioneered a proprietary fermentation process in the 1950s. One of the flagship ingredients in its portfolio today is Setria® Glutathione, a branded, clinically studied form of reduced glutathione (GSH).

While glutathione is an endogenous antioxidant that the body makes on its own and through diet, maintaining sufficient levels of this important amino acid compound can be challenging, according to Stanieich. **"A host of factors like poor diet, stress, pollution, toxins, and even aging deplete glutathione levels,"** she said. "As consumers seek to be more proactive in maintaining everyday health and quality of life, glutathione, often referred to as the 'master antioxidant,' may help support everything from immune, digestive, and brain function to detoxification and longevity."



GLUTATHIONE AND CELLULAR WELLNESS

That may seem to be an extraordinary number of claims, but glutathione is no ordinary antioxidant. It is tripeptide made up of three amino acids—cysteine, glycine and glutamic acid—that is produced in the cytoplasm of every cell in the human body. Like other antioxidants, it plays an important part in scavenging for free radicals.[1] Free radicals are the natural byproducts of cellular processes, such as metabolism and immune system responses. Environmental factors such as air pollution, tobacco smoke and alcohol can also generate free radicals.

If these unstable molecules accumulate in the body's cellular machinery unchecked, they can cause damage by stealing electrons from other molecules through the process of oxidation. This oxidative stress can play a major part in many chronic and degenerative diseases, from cancer and autoimmune disorders to cardiovascular and neurodegenerative diseases to aging itself.[2]

"I often compare this process to a pinball machine," Stanieich explained. "If you think of the free radical as the ball and the walls of the pinball machine as our cells and tissues, every time it wildly hits those walls, it is creating damage. That damage accumulates over time."

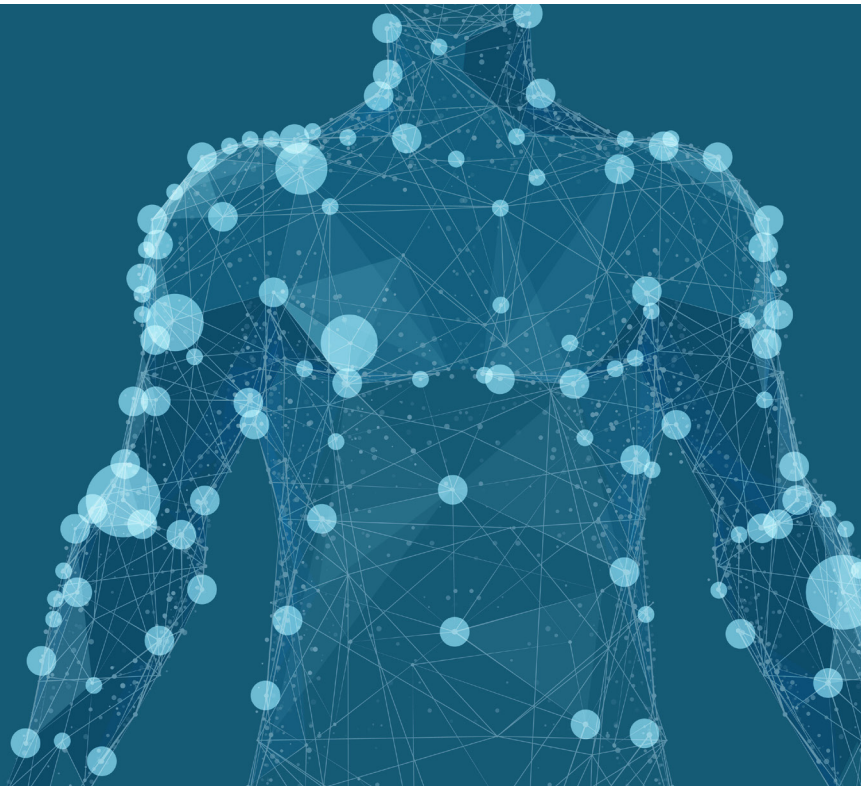
This is where antioxidants get involved. They work by donating electrons to free radicals, which shuts down the oxidation process. There are hundreds, if not thousands, of different antioxidants, each with its particular chemical behaviors and biological properties. The term "antioxidant" refers less to a type of substance but as the name for the chemical act of donating an electron.

Glutathione not only performs this important cellular service itself, but it can regenerate other antioxidants, including vitamins C and E—hence the title of master antioxidant. It's also the body's chief detoxifying agent. About 25% of all the body's glutathione resides in the liver, with similarly high concentrations in other organs with detox functions such as the kidneys. Additionally, high concentrations of glutathione are also found in mucosal barriers of both the intestines and lungs in support of the immune system, where glutathione stimulates natural killer (NK) cell function and promotes healthy function of T-cells and other white blood cells.

According to glutathione researcher Dean P. Jones, PhD, of Emory University School of Medicine, the lungs, intestines, kidneys and some immune cells are able to benefit directly from glutathione. The liver benefits from added glutathione as well, but takes a different pathway; first breaking down the compound into its three component amino acids, which it absorbs and then recombines to make glutathione for the organ's function. In fact, glutathione is so important for liver function that if the body goes 24 hours without food, it will "steal" the precursors from muscles to maintain liver glutathione.[3]

Scientists believe that the high level of metabolic activity required to produce glutathione underscores its importance to cellular wellness.[4] Other researchers have noted that GSH plays a pivotal role in reducing oxidative stress, maintaining redox balance, enhancing metabolic detoxification and regulating immune function.[5]

Glutathione not only performs this important cellular service itself, but it can regenerate other antioxidants, including vitamins C and E—hence the title of master antioxidant.



Healthy aging at the start of the day



The benefits of glutathione to healthy aging are well documented. As the master antioxidant, it scavenges free radicals and recycles other important antioxidants such as vitamins C and E. It is a key molecule in detoxification, quickly binding to toxins and removing them from the body. It supports the immune system and many other cellular functions.

While the active, reduced form of glutathione (GHS) is made in the body as well as consumed through the diet, many factors can reduce levels of this important molecule and rob the body of its benefits.

Diet is a key factor. A Mediterranean-style diet that emphasizes fresh fruits and vegetables is best for helping maintain optimal glutathione levels. However, most Western-style diets rely heavily on processed foods, which largely destroy glutathione. In addition, chronic conditions such as obesity and diabetes are associated with depleted levels of glutathione.[6,7] Smoking and drinking are also linked to oxidizing glutathione and causing oxidative stress.[8,9]

While it is possible to change diet, habits and lifestyle to some extent, there is one factor directly connected to lower glutathione levels that no one can change—getting older.

Glutathione status generally begins to weaken around age 45 and declines precipitously after age 60.[10] It is believed that we are not able to make as much glutathione as we age because of less enzyme activity and lower efficiency of the cellular signals that trigger glutathione synthesis.

The amount of one's lifetime spent in good health, also called their healthspan, is inextricably linked to elevated levels of glutathione. In one study, older individuals who were in good health—for example, had lower levels of cholesterol, blood pressure and body mass index—had higher levels of glutathione compared to those considered to be in poor health or suffered from chronic diseases such as arthritis, diabetes or heart disease.[11] Another study of 87 healthy women aged 60 to 103 years found that high-blood glutathione concentrations were characteristic of long-lived women who were in excellent physical and mental health.[12]

Glutathione levels also appear to rise and fall naturally during a 24-hour period, based on a study that sampled blood plasma levels of 63 people between the ages of 18 and 86. Researchers at Emory University found the lowest concentrations in the morning hours. In addition, there were more pronounced differences between the glutathione peaks and valleys in people over age 60, who are more vulnerable to oxidative stress in general.[13]

While the healthy aging market is relatively modest at about $650 million, as of 2021, there is a huge amount of interest in finding ways to extend healthspan, according to the *Nutrition Business Journal (NBJ)*. The publication went on to say, "That means there is always potential for a breakout star if the science holds up long enough for a brand to find traction."[14]

INCREASED GLUTATHIONE IN THE BODY EQUALS GREATER BENEFIT

The challenge for products formulating with GSH is that the prevailing wisdom until fairly recently was that the body could not easily absorb it when taken orally. Clinicians believed the sheer molecular size of glutathione alone would prevent the body from absorbing it, leading to alternative delivery methods, including nebulizers, transdermal creams, and intravenous injections.[15]

That opinion changed in 2015 with the publication of a study in the European Journal of Nutrition. Researchers at Penn State University conducted the first long-term, randomized, placebo-controlled trial of oral glutathione supplementation using Setria® Glutathione. A total of 54 healthy, nonsmoking adults received a placebo or oral GSH at a dosage of 250 mg or 1000 mg per day for six months. The Penn State team tested GSH levels in whole blood, plasma, red blood cells, lymphocytes (a type of white blood cell) and exfoliated buccal mucosal cells from the inner linings of the cheek at baseline and after one, three and six months.[16]

The study showed that when glutatione is taken orally daily over a longer period of time, we can increase glutathione levels and the detailed results of the study were astounding. Glutathione levels increased significantly from baseline in whole blood and red blood cells at three months and six months at both dosages. After six months, taking 250 mg glutathione per day increased glutathione levels by 17% in whole blood and by 29% in red blood cells. The participants in the group taking 1000 mg per day increased their glutathione levels by 31% in whole blood, 35% in red blood cells and 250% in buccal cells.[17]

One trend that was observed in the research was the ratios of oxidized glutathione to reduced glutathione, a measure of oxidative stress, dropped at six months at both dosages. Plus, NK cellular toxicity, a measure of the immune system's ability to combat infections, increased more than two-fold from baseline to three months



in the high-dose group. In other words, the study with Setria® Glutathione indicated reduced oxidative stress markers, which is an indicator of cellular health.[18] The study was also noteworthy for what it didn't find: any sign that oral supplementation with glutathione inhibited the body's natural ability to produce the antioxidant compound. Some experts had raised concerns that glutathione supplementation may suppress endogenous production.[19]

Improved bioavailability can also help a brand's bottom line: A survey of 200 consumers by veteran industry consultant and ingredient branding expert Steve Hanson, CEO of Phoenix-based CEO of Nutrasocial, found that about 75% of supplement users said they would pay 10% or more for vitamins or supplements that were better absorbed.[20] Ultimately what is key is that supplement actions should be scientifically verifiable.

THE BRANDED ADVANTAGE OF SETRIA® GLUTATHIONE

The clinical evidence establishing the excellent efficacy and bioavailability of Setria® Glutathione is the hallmark of a branded ingredient from Kyowa Hakko.

"Often branded ingredients do represent quality, science and efficacy," vnoted Stanieich. "In the case where Kyowa Hakko creates a branded product, it



is because we have research to support its efficacy that is unique to that material and worth protecting by branding."

Consumer surveys time and again underscore the fact that people trust branded ingredients over their generic counterparts. For instance, a 2020 study of more than 2,000 U.S. adults by the Council for Responsible Nutrition (CRN) found that supplement users preferred branded ingredients 2X over generic ones. A follow-up study by CRN in 2021 noted that about three-quarters of consumers between 18 and 54 years old are more likely to have confidence in supplements with branded ingredients than those with generic ones. In addition, 63% of those same consumers are willing to pay more for products with branded ingredients because they believe they are more effective and better quality.

A November 2021 report in the Nutrition Business Journal (NBJ) noted that brands choose to work with branded ingredients for transparency and quality as much as the science. One quoted expert noted that consumers more often reach for products made with branded ingredients "knowing the ingredients included are both clinically efficacious and consistent in quality."[21]

Cutting-edge formulations with clinically studied ingredients will resonate with consumers, according to Stanieich. "There will continue to be a demand for scientifically proven and clinically safe ingredients to attract and build trust as consumers are using a range of supplements to ensure they are getting the necessary ingredients to fortify and manage their health," she said. "Branded ingredients provide education and empowerment for those seeing supplements as there is supporting science around how these ingredients help them to stay healthy and live their best lives—an important resonating factor with this audience."

Glutathione: A *competitive edge* in sports nutrition

Healthy aging, immune support and cellular detox are obvious market categories for Setria® Glutathione. One less obvious but equally relevant category is sport nutrition, a market worth more than $60 billion.[22]

Nitric oxide (NO) is an essential molecule for human metabolism, with research suggesting that it both enhances athletic performance and post-workout recovery.[23] Safe supplements that can boost NO levels are the holy grail for hard-charging athletes.

L-citrulline is an amino acid that stimulates NO production, which causes vasodilation. This helps improve the delivery of more oxygen and nutrients to the muscles, therby reducing fatigue and enhancing exercise performance.[24] The powerful antioxidant glutathione improves endothelial function and nitric oxide bioavailability.[25] What would happen if a product combined the two ingredients into one formulation?

Researchers in the United States and Japan answered that question with a 2015 study published in the Journal of the International Society of Sports Nutrition. The team rigorously tested the hypothesis through a multi-phase experiment that involved human cells, an animal model and human subjects. Each phase reinforced the hypothesis that the combination of glutathione and L-citrulline would potentially enhance workout performance and recovery, culminating in a gold-standard clinical trial.

The double-blind, placebo-controlled phase of the study recruited 60 healthy, resistance-trained men aged 18 to 30 who were randomly divided into four treatment groups for a seven-day period. Each group took either a placebo,

MARKET OPPORTUNITIES WITH SETRIA® GLUTATHIONE

PubMed lists nearly 3,000 clinical trials involving glutathione, helping clinically establish the master antioxidant as an important nutrient in a variety of health categories. It is the obvious choice for brands formulating in the $200 million liver/detox market[27] thanks to its ability to remove toxins before they are even absorbed by the cells. In addition, brands working with Setria® Glutathione specifically can create formulations for some of the biggest, fastest-growing markets in the natural products industry.

Immune health

Immune health has obviously been at the top of the list for many consumers over the last few years, and market analysts do not see that changing anytime soon, even if the category's 2020-21 meteoric growth has come back to earth. Immune products will be among the top three categories for consumers in 2023, according to a consumer survey conducted by New Hope's NEXT Data & Insights research consulting group. More than a third of U.S. consumers say they plan to purchase a product for immune health in the coming year.[28] NBJ estimates the immunity market sits at about $5.5 billion in the United States alone.[29]

In the 2015 study, Setria® Glutathione demonstrated it could help fortify the immune system by stimulating the activity of NK cells. In addition to boosting NK cell activity, glutathione plays a central role in the proper function of T-cell lymphocytes (white blood cells), the frontline soldiers of the immune system[30]

1000 mg of Setria® glutathione, 2000 mg of L-citrulline or a combination of 200 mg of Setria® glutathione and 2000 mg of L-citrulline orally. Researchers found that the Setria® glutathione/L-citrulline combination significantly increased NO levels in the blood compared to placebo. In addition, they reported that at 30 minutes after exercise, this group was the only one to present such a striking improvement over the control group.[26]

Based on those results, Kyowa Hakko released Setria® Performance Blend, a novel combination of L-citrulline and its branded glutathione, in 2017.

"From everyday detox, mental performance, energy boost and immune support along with active nutrition to support muscle health, athletes are seeking to increase or maintain overall health and wellness," said Maria Stanieich, marketing manager for Kyowa Hakko USA, adding "Setria Performance Blend may enhance the synthesis."



Brain health

Brain health is also among the top three categories for consumers this year, according to the NEXT survey, driven partly by post-pandemic stress and lingering COVID brain fog, among other factors. The category broke $1 billion for the first time in 2020 and is expected to pass $1.5 billion by 2025, according to NBJ, despite the lack of a star ingredient[31] Yet.

Roughly 10% to 20% of reduced glutathione is contained in the mitochondria in neural cells, so some of the newest published studies on glutathione involve brain research.[32] That's probably because GSH depletion in the brain is a common finding in patients with neurodegenerative diseases. Such research suggests that glutathione plays an important role in counteracting oxidative stress in the brain, linked to these cognitive disorders.[33]

Claims and dosages

Whatever category brands choose to explore, Setria® Glutathione offers manufacturers a plethora of structure-function claims for these and other market applications:

- ☑ Boosts the body's natural defense system*
- ☑ Helps your body fight oxidative stress*
- ☑ Promotes healthy aging and overall health*
- ☑ Replenishes your body's primary defense system*
- ☑ Supports liver health by eliminating harmful toxins*
- ☑ Stable when exposed to stomach acid for enhanced absorption*
- ☑ Provides intracellular antioxidant support*
- ☑ Benefits cellular detoxification*
- ☑ Supports a healthy immune response*

In regards to dosage amounts in formulations, scientists in the 2015 Richie et al paper found efficacious effects with a daily dose as small as 250 mg, with more pronounced results in the group taking 1000 mg per day.[34] The wide range enables manufacturers to appeal to a wide variety of consumers looking for low-dose supplements or maximum-strength formulations.

"The more you learn and understand about all the good that glutathione does in our body, the more you think everyone should be using this—or at least consuming it at the highest amounts through our diets first and foremost," said Stanieich. "But, of course, supplementing is a great method to ensure you have enough—sort of like an insurance plan to your diet."

> "The more you learn and understand about all the good that glutathione does in our body, the more you think everyone should be using this—or at least consuming it at the highest amounts through our diets first and foremost,"



Shining a light on *skin health* with glutathione



The healthy aging benefits of glutathione extend to the beauty-from-within category, a market valued at about $1.4 billion by the Nutrition Business Journal.

A number of peer-reviewed studies have already established the ability of the amino acid compound to brighten skin. For example, in a randomized, double-blind, two-arm, placebo-controlled study, 60 participants received either 500mg of reduced glutathione (GSH) in two divided doses orally or a placebo for four weeks. At the end of the study period, the melanin, or skin pigment, decreased significantly for the glutathione group at six sites tracked by the experiment. Supplementation with glutathione also affected the number of UV spots.[35]

It is believed that glutathione affects skin pigmentation in several ways. First, it inhibits tyrosinase, an enzyme involved in producing melanin[36] Second, GSH appears to promote the stimulation of the pheomelanin pathway, which is associated with lighter skin color.[37] Finally, as a powerful antioxidant, it reduces free radical damage from exposure to UV rays and other pollutants.

More recent clinical research specifically on Setria® Glutathione has demonstrated that GSH may also reduce fine lines and wrinkles, as well as improve skin elasticity.

The 2017 randomized, double-blind, placebo-controlled, parallel, three-arm study involved 60 women who either took 250 mg daily of reduced glutathione (Setria®), 250 mg of oxidized glutathione or a placebo for three weeks.

Results showed that women receiving the glutathione supplements tended to have lower melanin index and UV spots compared to placebo. Both glutathione groups also showed improvements in skin elasticity. The paper is the first to show the effectiveness of a lower dose of glutathione for brightening skin.[38]

"This study on Setria glutathione suggests that when taken orally, Setria may decrease melanin production, lightening dark skin in individuals with Fitzpatrick skin types IV and V," said Dr. Rachel Nazarian, MD, Fellow of the Academy of Dermatology, when the study was originally released. "Given oral glutathione's regulatory properties on melanogenesis and pigment production in the skin, this safe, reduced dosing may also help decrease the melanin index in individuals with darker skin tones."

References

1. Galano A and Alvarez-Idaboy JP. "Glutathione: mechanism and kinetics of its non-enzymatic defense action against free radicals." RSC Adv, 2011,1, 1763-1771.
2. Pham-Huy LA, He H and Pham-Huy C. "Free Radicals, Antioxidants in Disease and Health." Int J Biomed Sci. 2008 Jun; 4(2): 89–96.
3. Jones DP. "The Health Dividend of Glutathione." Natural Medicine Journal 3(2), February 2011.
4. Pizzorno J. "Glutathione!" Integr Med (Encinitas). 2014 Feb; 13(1): 8–12.
5. Minich DM and Brown BI. "A Review of Dietary (Phyto)Nutrients for Glutathione Support." Nutrients. 2019 Sep 3;11(9):2073.
6. Vincent HK et al. "Oxidative stress and potential interventions to reduce oxidative stress in overweight and obesity." Diabetes Obes Metab. 2007 Nov;9(6):813-39.
7. Samiec PS et al. "Glutathione in human plasma: decline in association with aging, age-related macular degeneration, and diabetes." Free Radic Biol Med. 1998;24(5):699-704.
8. Moriarty SE et al. "Oxidation of glutathione and cysteine in human plasma associated with smoking." Free Radic Biol Med. 2003;35(12):1582-88.
9. Yeh MY et al. "Chronic alcoholism alters a systemic and pulmonary glutathione redox status." Am J Respir Crit Care Med. 2007;176(3):270-76.
10. Lang CA et al. "Low blood glutathione levels in health aging adults." J Lab Clin Med. 1992;120(5): 720-25.
11. Julius M et al. "Glutathione and morbidity in a community-based sample of elderly." J Clin Epidemiol. 1994;47(9):1021-26.
12. Lang CA et al. "High blood glutathione levels accompany excellent physical and mental health inwomen ages 60 to 103 years." *J Lab Clin Med*. 2002;140(6):380-81.
13. Blanco RA et al. "Diurnal variation in glutathione and cysteine redox states in human plasma." Am J Clin Nutr. 2007 Oct;86(4):1016-23.
14. NBJ 2022 Condition Specific Report.
15. Cook S. "Oral Availability of Glutathione." Natural Medicine Journal, 2017.
16. Richie, JP et al. "Randomized controlled trial of oral glutathione supplementation on body stores of glutathione." Eur J Nutr. 2015 Mar;54(2):251-63.
17. Ibid.
18. Ibid.
19. Cook S. "Oral Availability of Glutathione." Natural Medicine Journal, 2017.
20. Schultz H. "Consumers willing to pay more for bioavailability enhancements, consultant says." NutraIngredients-USA. March 27, 2016.
21. Rejcek P. "Beyond the clinicals." NBJ 2021 Supply Chain Issue. November 2021.
22. NBJ 2022 Sports Nutrition and Weight Management Report.
23. Oral O. "Nitric oxide and its role in exercise physiology." J Sports Med Phys Fitness. 2021 Sep;61(9):1208-1211.
24. Valaei K, Mehrabani J and Wong A. "Effects of L-citrulline supplementation on nitric oxide and antioxidant markers after high-intensity interval exercise in young men: a randomized controlled trial." Br J Nutr. 2021 Jun 17;1-23.
25. Prasad A et al. "Glutathione reverses endothelial dysfunction and improves nitric oxide bioavailability." J Am Coll Cardiol. 1999 Aug;34(2):507-14.
26. McKinley-Barnard S et al. "Combined L-citrulline and glutathione supplementation increases the concentration of markers indicative of nitric oxide synthesis." J Int Soc Sports Nutr. 2015; 12: 27.
27. NBJ 2022 Condition Specific Report.
28. NBJ 2022 Trends Issue. December 2022.
29. NBJ 2022 Condition Specific Report.
30. Richie, JP et al. "Randomized controlled trial of oral glutathione supplementation on body stores of glutathione." Eur J Nutr. 2015 Mar;54(2):251-63.
31. NBJ 2022 Condition Specific Report.
32. Iskusnykh IY, Zakharova AA and Pathak D. "Glutathione in Brain Disorders and Aging." Molecules. 2022 Jan 5;27(1):324.
33. Dwivedi D et al. "Glutathione in Brain: Overview of Its Conformations, Functions, Biochemical Characteristics, Quantitation and Potential Therapeutic Role in Brain Disorders." Neurochem Res. 2020 Jul;45(7):1461-1480.
34. Richie, JP et al. "Randomized controlled trial of oral glutathione supplementation on body stores of glutathione." Eur J Nutr. 2015 Mar;54(2):251-63.
35. Arjinpathana N and Asawanonda P. "Glutathione as an oral whitening agent: a randomized, double-blind, placebo-controlled study." J Dermatolog Treat. 2012 Apr;23(2):97-102.
36. Nagapan TS et al. "Oral supplementation of L-glutathione prevents ultraviolet B-induced melanogenesis and oxidative stress in BALB/c mice." Exp Anim. 2019; 68(4): 541–548.
37. Watanabe F et al. "Skin-whitening and skin-condition-improving effects of topical oxidized glutathione: a double-blind and placebo-controlled clinical trial in healthy women." Clin Cosmet Investig Dermatol. 2014 Oct 17;7:267-74.
38. Weschawalit S et al. "Glutathione and its antiaging and antimelanogenic effects." Clin Cosmet Investig Dermatol. 2017 Apr 27;10:147-153.