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RESEARCH GUIDE
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Oral Availability of GLUTATHIONE

Does the research dispel previously held beliefs?

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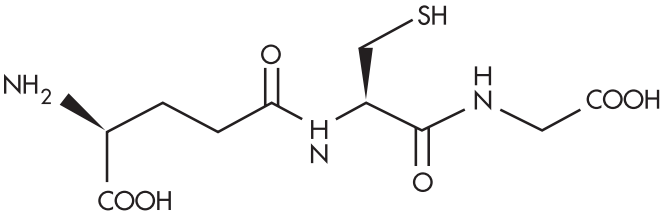
What is Glutathione?

Glutathione is a potent antioxidant compound and detoxifying agent that is produced in the cytoplasm of every cell of the human body. Because of its central role in detoxification, approximately 25% of all the body's glutathione resides in the liver alone. Glutathione is also concentrated in the kidneys and in mucosal secretions of the intestinal lining and lungs. It is present inside cells and in extracellular fluids.

Glutathione is a tripeptide molecule, composed of the amino acids glutamate, cysteine, and glycine. It exists in at least 4 different forms within the human body, including a reduced form, an oxidized form, a disulfide cysteine-containing form, and a protein-bound form. The pool of glutathione in the human body is constantly in flux, transforming between forms as well as being split into its components and synthesized again.

Structural Formula of Reduced Glutathione

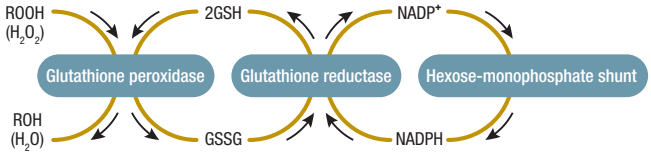


The reduced form of glutathione (GSH) is the biologically active form that has earned glutathione its reputation as the body's most important antioxidant. GSH contains a thiol group (—SH), making it an effective electron donor to neutralize lipid peroxides, hydrogen peroxide, and other reactive oxygen species.

> ***"Free radicals are a necessary waste product of cellular energy production, but our cells must rid themselves of this waste or succumb to the ravaging effects of oxidative damage. Glutathione acts in every cellular compartment—the cytosol, the nucleus, and the mitochondria, to quell the free radicals. Adequate glutathione is not just desirable, it is essential to the survival of each cell, making it essential to life itself."***
>
> **–Tina Kaczor, ND, FABNO**
> **(www.RoundTableCancerCare.com)**

The process of neutralizing free radicals, catalyzed by glutathione peroxidase, transforms reduced GSH into its oxidized glutathione disulfide (GSSH) form. GSSH is then recycled back to GSH with help from the enzyme glutathione reductase and electrons donated from the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH).

Antioxidant Action of Glutathione



The ratio of GSSH to GSH in the body serves as an important measurement of oxidative stress, or redox status. Higher levels of GSSH indicate greater oxidative stress, whereas higher levels of GSH indicate protection against toxins and oxidative damage. Because GSH provides the primary physiologic benefits of glutathione, any mention of glutathione for the rest of this document refers to the reduced form (GSH), unless otherwise specified.

Who Needs Glutathione?

More than 100,000 studies have been published related to the physiologic effects of glutathione. In broad terms, these studies have found glutathione to protect against oxidative stress, detoxify chemicals and toxins, boost immune function, and support healthy aging.

Glutathione has both inherent antioxidant activity as well as the ability to regenerate other antioxidants, including vitamins C and E. Glutathione is more than simply an electron donor, however. It also serves as a substrate to conjugate drugs, alcohol, pesticides, and carcinogens. Enzymatic conjugation, catalyzed by the enzyme glutathione-S-transferase, occurs in Phase 2 detoxification in the liver and in gastrointestinal mucosal secretions. Glutathione conjugation provides a mechanism to neutralize reactive toxins before they are able to damage body tissues. Glutathione also plays an important role in immune function, by stimulating natural killer (NK) cell function and promoting healthy function of T-cells and other white blood cells.

There is mounting evidence that impaired glutathione synthesis, dysfunctional glutathione metabolism, or glutathione depletion may be implicated in the etiology and progression of a wide range of chronic diseases. For example, polymorphisms in glutathione peroxidase appear to increase the risk for coronary

heart disease and stroke; levels of GSH are substantially lower in the substantia nigra of patients with Parkinson's disease; diminishing levels of GSH are associated with age-related cataracts, glaucoma, and macular degeneration; and glutathione depletion may be implicated in the pathogenesis of cancer.

Conditions that are thought to benefit from therapies that boost glutathione levels include cardiovascular disease, pulmonary disease, liver disease, neurodegenerative disease, immune disorders, chronic infections, and metabolic disorders.

> ***"One of the most surprising benefits I have discovered with the use of glutathione in my practice is the positive impact it has had with women suffering from symptoms of hormone imbalances, including PMS, hot flashes, mood disorders like depression and anxiety, inflammation, sleep disturbances, low libido, and weight gain. I will use it alone or in some cases paired with bioidentical hormone therapies to provide optimal results for our patients."***
>
> **–Gina Nick, NMD**
> **(www.DrGina.com)**

Even for individuals who are generally healthy, the body's need for glutathione increases at certain times and under certain conditions. The demand for glutathione increases, for example, in response to stress, weight gain, poor lifestyle choices, and normal aging. Glutathione can also become depleted by increased exposure to medications, toxins, heavy metals, solvents, pesticides, or alcohol. If glutathione or its precursors are not supplied from the diet on a routine basis, the body will begin to sequester amino acid precursors from the muscle. Animal studies suggest that even short periods of fasting, such as overnight, are enough to deplete glutathione levels, resulting in levels being lowest in the morning.

The essential nature of glutathione may suggest that boosting endogenous levels would benefit all patients and conditions, but this is not necessarily the case. In cases of advanced cancer or chemotherapy, for example, boosting glutathione levels may be contraindicated. Whereas glutathione protects against oxidative damage that may lead to cancer, high levels of glutathione can paradoxically have the opposite effect during cancer treatment.

> ***"There is a small, but growing body of evidence that high levels of antioxidants such as vitamin E and NAC, and by inference, perhaps glutathione, may support the viability of metastatic cancer cells. There are also animal studies which have found increased chemoresistance during antioxidant administration. However, to date, human trials have failed to find a reduction in treatment response when glutathione or other antioxidants are used concurrently with oxidative chemotherapeutics. As the body of literature on glutathione in the context of active malignancy is small and contradictory, some caution is warranted. Generally, I do not supplement glutathione during chemotherapy with curative intent or in individuals with active metastatic disease. I do supplement glutathione when my goal is to restore cellular antioxidant capacity in patients who are at risk of cancer, who have a personal history of cancer, or who are receiving palliative conventional treatment and suffering from quality of life issues for which glutathione may be helpful."***
>
> **–Lise Alschuler, ND, FABNO**
> **(www.DrLise.net)**

What are Glutathione Precursors and Cofactors?

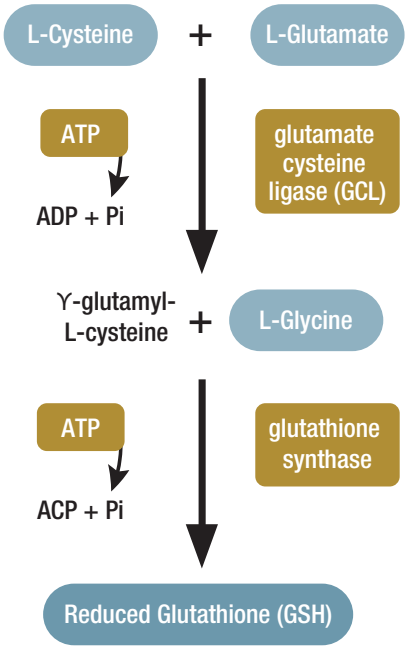
Glutathione is endogenously produced and therefore not considered an essential nutrient from the diet. It is critical, however, that the body receives a constant supply of either glutathione itself or its precursors in order to maintain adequate levels.

Glutathione is naturally occurring in fresh meats, dairy, fruits, and vegetables, and studies suggest that higher intakes of dietary glutathione correlate with a lower risk of some cancers. Glutathione is destroyed by most methods of food processing, however, and epidemiological studies report that modern diets typically provide negligible amounts.

Clinical efforts to boost glutathione levels in the body have historically focused not on directly supplying glutathione but rather on increasing endogenous production by providing precursor molecules and cofactors. To understand the reasoning behind precursor and cofactor supplementation, we need to review the biochemical pathways involved in glutathione production.

The endogenous synthesis of glutathione takes place in 2 steps: first is the formation of a dipeptide from l-glutamate and l-cysteine and second is the addition of l-glycine to form the tripeptide, glutathione. The first step is catalyzed by glutamate cysteine ligase (GCL) and requires either magnesium or manganese as enzymatic cofactors. The second step is catalyzed by glutathione synthase. Both steps are dependent on a steady source of energy in the form of ATP.

Glutathione Synthesis



The first step of this process is the rate-limiting step, and the 2 most important variables thought to affect the rate of GSH synthesis are enzymatic activity of GCL and availability of cysteine. Because cysteine is understood to be the rate-limiting substrate of glutathione production, supplementation with n-acetyl cysteine (NAC) has traditionally been a foundational approach to boosting endogenous glutathione synthesis.

NAC is the standard of care, for example, for the treatment of acetaminophen toxicity because of its ability to replenish hepatic glutathione levels. NAC has also been evaluated as a way to boost glutathione in patients with cystic fibrosis and HIV/AIDS. Despite the widespread use of NAC as an antioxidant, however, this approach assumes that the patient will effectively convert NAC to glutathione—a biochemical process that relies on adequate enzymatic function of GCL, adequate magnesium or manganese as cofactors, a steady supply of ATP, and additional substrates.

In addition to NAC supplementation, a variety of additional strategies are commonly implemented to boost endogenous glutathione production. These strategies are based on an understanding that glutathione production does not occur in isolation. Both steps of glutathione synthesis, for example, are ATP-dependent, meaning that any form of mitochondrial dysfunction or energy depletion will also impair glutathione production. In addition, cysteine not only comes from dietary sources but also can be endogenously produced from methionine via the transsulfuration pathway. The transsulfuration pathway, in turn, relies on availability of sulfur groups, proper function of methylation pathways, B vitamin metabolism, and other cofactors.

> ***"There are multiple precursors and cofactors involved in glutathione production—not just NAC. Patients also need sufficient glutamic acid, magnesium, selenium, riboflavin, and more. Simply consuming NAC is usually not sufficient. Ideally, taking a reduced form of glutathione can be extremely important when the goal is protecting cells from oxidative stress."***
>
> **–Geo Espinosa, ND, LAc (www.DrGeo.com)**

Because of the synergistic aspect of the numerous biochemical pathways either directly or indirectly influencing glutathione production, strategies to boost endogenous synthesis involve supplementation with nutrients to support a myriad of metabolic pathways. Selenium is given as a cofactor for glutathione peroxidase; alpha-lipoic acid is given to support mitochondrial function and energy production; B vitamins are given to support methylation pathways and transsulfuration; whey protein is given as a source of precursor amino acids; and cruciferous vegetables are recommended as a dietary source of sulfur. Additional nutrients commonly administered to support glutathione metabolism include vitamin C, vitamin E, milk thistle, and beef liver.

Why Use Preformed Glutathione?

The foods and supplements that are routinely used to boost endogenous glutathione production offer a variety of health benefits in their own right. The challenge for the practitioner becomes prioritizing what supplementation is most critical and most helpful. Depending on a patient's genetics, disease processes, and environmental exposures, even the best efforts

to provide precursor molecules and cofactors may not effectively optimize glutathione production. This is because genetic polymorphisms or chronic disease states can alter enzymatic function in ways that hinder glutathione production or glutathione metabolism, despite excellent nutrient intake.

Rare genetic polymorphisms have been identified that influence the activity of GCL, for example, and these polymorphisms have been associated with certain cancers. Impairments in GCL activity that are unrelated to polymorphisms have also been observed in a wide range of metabolic conditions, including aging, diabetes, cholestasis, alcoholic liver disease, schizophrenia, neurodegenerative disorders, inflammatory bowel disease, HIV, and cancer.

Even if the GCL enzyme is working well, evidence suggests that the second step of glutathione synthesis (catalyzed by glutathione synthase) can be diminished in certain tissues or under stressful situations. Liver disease, methylation defects, and other errors of metabolism can also directly or indirectly impair glutathione production.

Science is just beginning to touch the surface of the complexity involved in glutathione regulation in the human body. Some patients might effectively regulate glutathione levels while others might not. An alternative to supplementing precursors and cofactors is to provide preformed glutathione in its tripeptide form. If we can provide patients with a bioavailable and physiologically active form of reduced glutathione, we can bypass the myriad of potential metabolic errors that can interfere with its production.

> ***"Endogenous glutathione production is determined by genetics as well as the environmental influences in and around the cells. This means there are a lot of unknowns regarding whether someone can achieve the increase of glutathione production that is assumed to happen with precursor supplementation. Simply put, giving glutathione itself removes the chance that a given patient is someone who cannot efficiently produce it from NAC."***
>
> **–Tina Kaczor, ND, FABNO (www.RoundTableCancerCare.com)**

The reason to provide preformed glutathione rather than its precursors and cofactors is not a new concept in medicine. It is analogous to the need to supplement preformed vitamin A, rather than beta-carotene, in patients who have low thyroid function. It is analogous to the need to supplement 5-methyltetrahydrofolate rather than folic acid in patients with polymorphisms that affect B vitamin metabolism.

Science is uncovering more and more conditions that are accompanied by impaired glutathione synthesis or faulty glutathione metabolism. Direct supplementation with preformed glutathione provides a therapeutic option that bypasses metabolic errors and offers antioxidant protection to the patients who need it most.

Challenging the Myth of Oral Glutathione Absorption

For decades, the prevailing belief of clinicians and researchers has been that oral glutathione has little to no systemic availability. The sheer molecular size of glutathione was thought to preclude its absorption, and intestinal γ–glutamyl transpeptidase was known to enzymatically split glutathione into its amino acid constituents within the lumen of the small intestine.

Clinicians have taken a variety of approaches to circumvent the challenge of glutathione absorption, including administration of glutathione via nebulizers, transdermal creams, and intravenous injections. Unfortunately, these approaches can be cumbersome, impractical, and inaccessible to many patients. Research has continued, therefore, to find a way to deliver bioavailable glutathione via oral administration.

Human clinical trials assessing the bioavailability of oral glutathione are few, and 2 small clinical trials have reported negative results. The first of these studies was published in 1992, by Witschi and colleagues at the University of Bern, Switzerland. Researchers administered a single 3-gram dose of glutathione to 7 healthy volunteers, measured plasma levels of glutathione and its precursor amino acids over 4.5 hours, and concluded that "the systemic availability of glutathione is negligible in man." These results have been challenged by some researchers because glutathione is rapidly removed from the plasma by tissues such as the liver and kidney, bringing into question the relevance of a plasma measurement after a single glutathione dose. Also, the blood level response was extremely variable from subject to subject. While 4 did not show increases, 3 did, so the conclusions may be over generalized.

The second study was published in 2011, by Allen and Bradley at Bastyr University in Seattle, WA. This randomized, double-blind, placebo-controlled trial evaluated the effect of oral GSH administered at a dosage of 1000mg per day for 4 weeks. The trial involved a total of 40 healthy participants. The conclusion of this study was that oral administration of glutathione had no significant effect on biomarkers of oxidative stress, including erythrocyte levels of reduced and oxidized glutathione. The methodology of this study, however, has been questioned by Dr. John Richie at Penn State University. In publication of his subsequent study, Richie states, "GSH and GSSG measurements did not account for possible differences in erythrocyte volume and number, which can significantly impact GSH levels. In addition, erythrocytes were not directly acidified immediately after collection, but rather after an initial hemolysis step which can greatly decrease the stability of both GSSG and GSH and lead to inaccurate measurement."

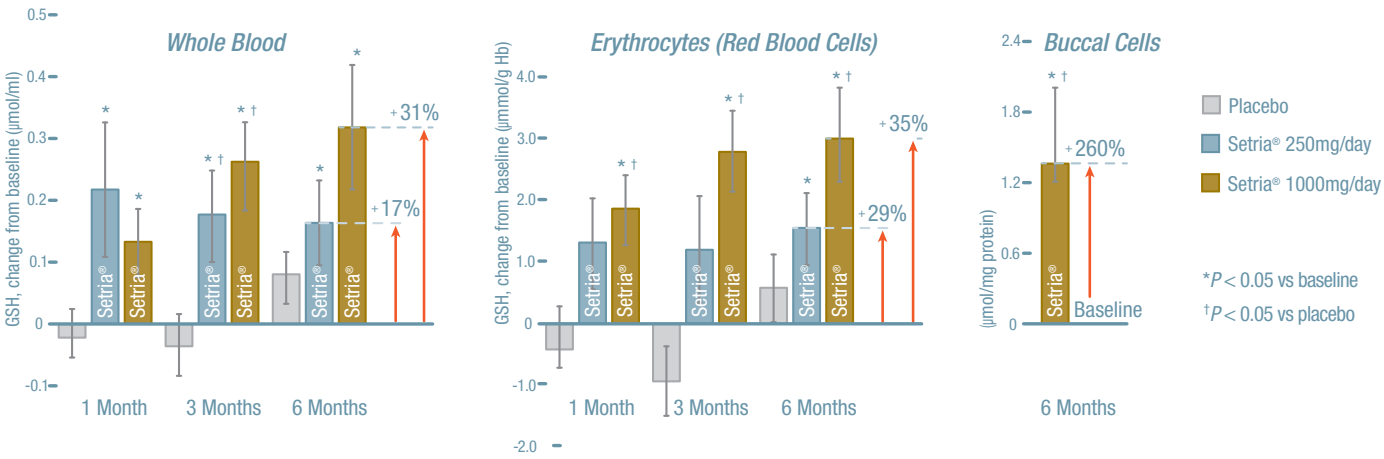
It might seem that the results of the 2 studies described above would put to rest the question of intestinal glutathione absorption, establishing once and for all that it simply does not occur. But mechanistic studies and now a more recent human clinical trial suggest otherwise—that glutathione can, indeed, be absorbed through the human intestinal lining and can effectively improve systemic antioxidant status.

Evidence that glutathione might be absorbed through the intestines began with animal and mechanistic studies in the late 1980s and early 1990s. Researchers found that oral intake of GSH increased plasma levels of GSH in mice and that administration of GSH was more effective at achieving this result than administration of its precursors. It was discovered in 1985 that glutathione was transported across human buccal mucosa *in vivo*, and in 1997, researchers at the University of Firenze, Italy, discovered GSH-specific transporter molecules in human intestinal epithelial cells. Evidence began to build that glutathione could, indeed, be absorbed through the human gastrointestinal tract.

Then, results of a study reported in a 2015 publication of the *European Journal of Nutrition* dramatically challenged the prevailing belief about the oral availability of glutathione. The study, conducted by Dr. John Richie and his colleagues at Penn State University, was the first long-term, randomized, placebo-controlled trial of oral glutathione supplementation. A total of 54 healthy, non-smoking adults were randomized to placebo or oral GSH at a dosage of 250mg or 1000mg per day for 6 months. GSH levels were tested in whole blood, plasma, erythrocytes, lymphocytes, and exfoliated buccal mucosal cells at baseline and after 1, 3, and 6 months. Ratios of oxidized to reduced glutathione (GSSH:GSH) were calculated to evaluate redox status. After a 1-month washout period, levels were tested for a final time.

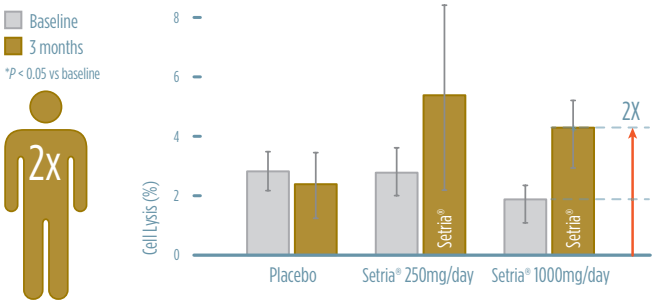
The results of this study were unprecedented. Glutathione levels increased significantly from baseline in whole blood and erythrocytes at 3 months and 6 months at both dosages. After 6 months, taking 250mg glutathione per day increased glutathione levels by 17% in whole blood and by 29% in erythrocytes. Taking 1000mg glutathione per day increased glutathione levels by 31% in whole blood, by 35% in erythrocytes, and by 250% in buccal cells.

Glutathione Levels after Oral Supplementation



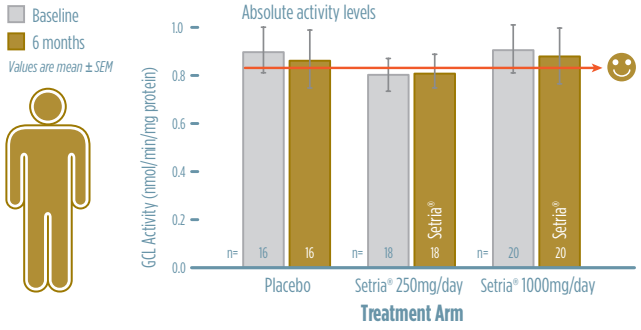
In addition to the absolute increases in glutathione, ratios of GSSH:GSH decreased at 6 months in both dosage groups, indicating a decrease in oxidative stress. In addition, NK cell cytotoxicity increased more than 2-fold from baseline to 3-months in the high-dose group.

NK Cell Activity after Glutathione Supplementation



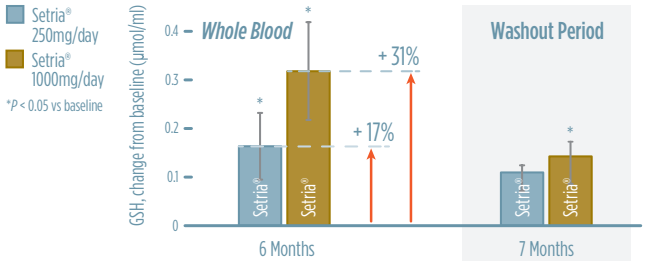
Oral supplementation of glutathione at either dosage did not inhibit the body's endogenous production of glutathione, as indicated by no change in glutathione cysteine ligase (GCL) activity—the rate-limiting enzyme of glutathione production. This is an extremely important finding, as some experts have raised concerns that glutathione supplementation may suppress endogenous production.

GCL Activity After Glutathione Supplementation



The observed increases in glutathione levels in this study were dose-dependent and time-dependent, and levels returned to baseline after supplementation was discontinued for 1 month.

Glutathione Levels after Washout Period



The conclusion of this landmark study was that oral supplementation of glutathione is an effective way to increase body stores of glutathione, decrease oxidative stress, and boost immune function without suppressing endogenous glutathione production when taken for 6 months.

Form Follows Function

The 2015 study of oral glutathione supplementation was conducted with Setria®, provided by Kyowa Hakko USA, Inc. Setria® is a branded form of reduced glutathione that is manufactured using a patented fermentation process. It provides reduced glutathione that has been clinically shown to increase glutathione levels within the body. Setria® is manufactured in compliance with Good Manufacturing Practice (GMP) standards and meets specifications of the new USP monograph. It is delivered in a vegetarian and allergen-free form, with no additives, preservatives, or artificial flavors. The study described above demonstrates, without a doubt, that Setria® offers a way to boost glutathione levels with oral supplementation.

> ***"The research on absorbability thus far with Setria® is indisputable. And it is backed by one of the most respected glutathione scientists in the country: John Richie, PhD from Penn State."***
>
> **–Geo Espinosa, ND, LAc**
> **(www.DrGeo.com)**

Research has established glutathione as one of the body's most important molecules to combat oxidative stress, neutralize toxins, support immune function, and reduce the risk of chronic disease. The widespread belief that glutathione cannot be absorbed through the gastrointestinal tract has led clinicians to rely on foods and precursor molecules to boost endogenous glutathione production. Defects in metabolic pathways required for endogenous glutathione synthesis, however, may limit the efficacy of this approach in aging patients or in those with chronic disease.

Results of the first long-term human clinical trial of oral glutathione supplementation challenge the assumption that oral glutathione cannot be absorbed. Oral glutathione (Setria®), administered at a dosage of 250mg or 1000mg per day, effectively increases body stores of glutathione, offering patients and clinicians hope for a new approach to glutathione therapy.

About the Author

Sarah Cook, ND, is a freelance medical writer who has a certificate in biomedical writing from the University of the Sciences in Philadelphia. Her naturopathic doctorate is from the Southwest College of Naturopathic Medicine in Tempe, AZ. She has previous experience in clinical practice, supplement sales, and academics. In addition to writing, she is currently on the faculty at the Nutrition Therapy Institute in Denver, CO. www.SarahCookND.com

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