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

\[
\text{NH}_2 \quad \text{O} \quad \text{SH} \quad \text{H} \quad \text{N} \quad \text{COOH}
\]

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

[Diagram showing the process of glutathione action]

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 substan-
tially 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, neuro-
degenerative 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, inflam-
mation, 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 chemother-
apy, 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.

“What 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 oxida-
tive chemotherapeutics. As the body of literature
on glutathione in the context of active malign-
nancy 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 corre-
late 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 mol-
ecules 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**

\[
\begin{align*}
\text{L-Cysteine} + \text{L-Glutamate} & \rightarrow \text{Y-glutamyl-L-cysteine} + \text{L-Glycine} \\
\text{ATP} & \rightarrow \text{ADP + Pi} \\
\text{ATP} & \rightarrow \text{ACP + Pi} \\
\text{Reduced Glutathione (GSH)} &
\end{align*}
\]

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.
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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.
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.

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.
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Selected References


