NUTRITION FOR GLUTATHIONE

You've probably heard about antioxidants, touted for their anti-cancer, anti-aging, and cognition-enhancing benefits. Antioxidants quench free radicals, highly reactive molecules which can damage DNA and interfere with cell function. Toxins, infections, and energy imbalances drive up this "oxidative stress," which is associated with countless diseases and unhealthy aging. However, normal levels of free radicals are beneficial and even necessary for the body to function. Excessive quenching of free radicals may interfere with immune activity, hormone production, and cell signaling.[1,2]

What is glutathione?

Importantly, the most powerful antioxidants are made by the body itself. Supporting our natural antioxidant systems allows the body to regulate oxidative stress on its own terms. Inside our cells, the master antioxidant regulator is glutathione, a simple molecule which may be a central part of disease and health.[3] Furthermore, glutathione is crucial for eliminating some of the most insidious toxins in our environment: pesticides, mold, mercury, and air pollution. Fortunately, glutathione status can be highly influenced by what we eat.

Who should support glutathione?

- Dementia, cancer, liver diseases, diabetes, hypertension, infertility, cystic fibrosis, multiple sclerosis, lupus, HIV, and Parkinson's have been associated with depleted glutathione.[4]
- Antibiotics can impede the mitochondria,[5] and supporting glutathione may reduce the impact.
- High-normal gamma-glutamyl transferase (GGT)[6,7] and low-normal total bilirubin[8] on routine lab work may suggest glutathione depletion due to oxidative stress. Glutathione can also be measured directly in whole blood, though this may inadequately reflect tissue levels (discussed on page 3). Speak with a medical professional to interpret your labs in the context of your overall health.
- Several genetic polymorphisms alter the function of enzymes that create, utilize, and recycle glutathione. Your genes may inform which strategies are best for you, particularly in regards to detox support.[9]
- Those regularly exposed to pesticides, mold, mercury, or air pollution should support glutathione for healthy detoxification.[10–13] Given the pervasiveness of air pollution and pesticides in the modern world, this is just about all of us.

How to use this document

The following chart outlines foods and nutrients that have been demonstrated in research to enhance glutathione in three ways. Different categories should be emphasized depending on your goals:

Synthesis support: Provides precursors for glutathione and stimulates the enzymes that create it.

- *This is the foundational strategy, bolstering glutathione reserves for both antioxidant and detox needs.*

Antioxidant support: Augments the ability of glutathione to quench free radicals and reduce oxidative stress.

- *Add these strategies to reduce the oxidative stress associated with chronic disease, antibiotic use, heavy metal toxicity, or mitochondrial dysfunction.*

Detox support: Activates the enzyme that binds toxins to glutathione, facilitating their elimination.

- *Add these strategies to enhance the removal of toxins and protect the liver.*

The foods and nutrients in the table that follows should be selectively incorporated into a balanced diet with the help of a nutrition professional. The items in each section are listed roughly in order of their strength of evidence. For an overview of glutathione, and the research and rationale behind the table, see the pages that follow.

DIETARY SUPPORTS FOR GLUTATHIONE

ANTIOXIDANT

- **Purple/blue polyphenols**: red grapes, blackberries, chokeberries, black currants, pomegranate, sour cherries, cranberries, raspberries, blueberries, boysenberries
- **Vitamin C**: bell peppers, chili peppers, acerola cherries, rosehips, guava, cantaloupe, parsley, kale, kiwi, broccoli, cauliflower, brussels sprouts, lemons, oranges, strawberry
- **Vitamin E**: sunflower seeds, almonds, hazelnuts, pine nuts, peanuts, Brazil nuts, bell peppers, salmon, olive oil, avocado
- **Rooibos**
- **Green and white tea**
- **Dark roast coffee** (> light roast)
- **Extra virgin olive oil**
- **Salmon** (and other fatty fish)
- **Honeybush**
- **Red palm oil**
- **Cacao** (raw > roasted)
- **Button mushrooms**
- **Selenium***: Brazil nuts (max. 1-2 per day), oats, mushrooms, brown rice, sunflower seeds, fish, poultry, meat
- **Riboflavin**: liver, dairy, mushrooms, almonds, eggs, shellfish, red meat, nutritional yeast, grapes, cacao

**May not benefit post-menopausal women or people of African descent. Excess selenium may perpetuate insulin resistance.*

SYNTHESIS

Precursors

- **Amino acids** (cysteine/glycine/glutamine/serine)

  High cysteine:methionine (priority) – eggs, oats, tempeh, tofu, wheat germ, nutritional yeast, seaweed, split peas, lentils, lima beans, edamame, chickpeas, buckwheat, peanuts, hemp seeds, chia, sunflower seeds, flax, pumpkin seeds, cashews, Greek yogurt, fresh cheese

  Low cysteine:methionine – beef, lamb, chicken, turkey, duck, salmon, game meats
- **Whey protein**
- **Sulfur**: broccoli, arugula, garlic, brussels sprouts, savoy cabbage, cauliflower, mustard greens/seeds, kale, turnips

Enzyme support

- **Magnesium**: Seeds (pumpkin, flax, chia, sesame, sunflower); Nuts (Brazil, cashews, almonds); Grains (brown rice, oats, buckwheat, amaranth, wheat germ, quinoa); Legumes (edamame, black beans, peanuts); Greens (seaweed, kale, basil); avocado, cacao
- **Purple/blue polyphenols**: blackberries, red grapes, blueberries, cranberries, black currants, sour cherries, pomegranate, raspberries, chokeberries, boysenberries
- **White and green tea**
- **Cacao**
- **Rosemary**
- **Selenium*** (see left for list)

DETOX

- **Cruciferous vegetables:** (best choices) brussels sprouts, broccoli sprouts, red cabbage; (secondary) broccoli, cauliflower, radish sprouts, white cabbage,
- **Green tea**
- **Purple/blue polyphenols**: red grapes, blackberries, chokeberries, black currants, cranberries, sour cherries, blueberries, raspberries, pomegranate, boysenberries
- **Rooibos**
- **Honeybush**
- **Rosemary**
- **Black cumin seed**

MULTIFUNCTIONAL FOODS

A = antioxidant; P = precursors; E = enzyme support; D = detox

- Purple polyphenols (A/E/D)
- Green tea (A/E/D)
- Rooibos (A/D)
- Brussels sprouts (A/P/D)
- Salmon (A/P)
- Sunflower seeds (A/P/E)
- White tea (A/E)
- Honeybush (A/D)
- Cacao (A/E)
- Rosemary (E/D)
- Oats (P/E)
- Eggs (A/P)

Nutrient sources: cysteine, glycine, serine, glutamine (University of Minnesota Nutrition Coordinating Center via Cronometer.com, mostly combined glutamine/glutamate levels); vitamin E, vitamin C, riboflavin, magnesium, selenium (USDA FoodData Central); sulfur (Doleman et al, 2017, cited[20]); all others from direct human or animal in vivo research, cited following.

SYNTHESIS – PRECURSORS

Glutathione (GSH) is a tripeptide of cysteine, glycine, and glutamate. **Cysteine**, a sulfur-containing amino acid, is considered the rate-limiting precursor, and acts as an extracellular antioxidant itself. In addition to dietary intake, cysteine can be synthesized, mostly from the other more plentiful sulfur amino acid methionine. However, high methionine intake is associated with cardiovascular disease, fatty liver, and insulin resistance, by increasing homocysteine.[14] Rodent studies have found methionine depletion increases GSH and extends lifespan,[15] and that cysteine is superior for GSH repletion.[16] Thus, listed sources are distinguished by cysteine-to-methionine ratio.

Some debate that cysteine is the rate limiter in GSH synthesis. Human studies have found that during low but safe protein intake (<1g/kg) or moderate toxic exposure, **glycine** is instead the rate limiter.[17,18] Glycine amplifies the benefit of supplemental cysteine for GSH.[19] In addition, glycine can synthesize cysteine with inorganic **sulfur**, derived from non-amino acid sources.[20]

While glutamate is abundant in food, supplementing its precursor **glutamine** in the elderly and HIV-positive at 10-20g/day restored depleted GSH levels equally to 1g N-acetylcysteine, though neither increased GSH in healthy controls.[21,22] (None of these supplemental doses are attainable by dietary intake alone, however.) Glutamine is readily converted to glycine, lending dual significance for GSH.

Serine is another amino acid precursor to cysteine, requiring inorganic sulfur. Serine has also been shown to increase GSH by both supporting methionine recycling,[23] and regulating gene expression in mice.[24] Increasing total dietary protein however does not raise GSH.[25] Targeting these amino acids may be a preferable strategy.

Whey is a concentrated source of cysteine from dairy, which has been well-researched for effects on GSH. Doses of 12-45g/day for several weeks or more have been shown to increase plasma GSH in HIV,[26–28] overweight,[29] type II diabetes,[30] nonalcoholic steatohepatitis,[31] hepatitis B and C,[32] Parkinson's,[33] stroke,[34] and healthy individuals,[35,36] though specific formulas may vary in efficacy.[27] One research group found whey improved lung function in cystic fibrosis and raised lymphocyte but not blood GSH,[37,38] mirroring findings in cancer patients.[39,40] This suggests plasma GSH may underestimate tissue stores, especially when research shows clinical benefit.[41]

SYNTHESIS – ENZYME SUPPORT

Glutathione is synthesized in two enzymatic steps, and magnesium is an essential cofactor in both. **Magnesium** deficiency inhibits GSH synthesis in rats,[42] and supplementation increases GSH in atopic children.[43] Other dietary compounds may increase the activity or expression of the rate-limiting enzyme glutamate-cysteine ligase (GCL).

- **Purple/blue polyphenols**: Dark purple, red, or blue fruits and vegetables contain shared types of polyphenols, a broad category of health-promoting plant compounds. They owe their hue to anthocyanins, which may be their primary active constituents. Clinical trials have found these foods (listed in the table) raise GSH levels in healthy people,[44–48] and those on hemodialysis.[49] In vitro,[50–52] and rodent[53] studies demonstrate GCL-stimulating activity. The benefits likely extend to other blue/purple whole foods.
- **White and green tea**: Four cups of green tea daily increased blood GSH in adults with metabolic syndrome.[54] Cell culture studies confirm green tea stimulates GCL.[55,56] In mice, white tea raises GSH more effectively than green tea.[57] Considering their shared constituents, and the paucity of research on white tea, similar GCL stimulation can be presumed.
- **Cacao**: In rats, cacao restored GSH levels depleted by a high-fat diet.[58] In a similar study, raw cacao had greater benefit than roasted.[59] In vitro research suggests one mechanism is an upregulation of GCL.[60]
- **Rosemary**: At a human equivalent dose of 10g per day,[61] rosemary protected rats against creosote-induced hepatotoxicity and oxidative stress, increasing glutathione stores.[62] Cell culture studies suggest upregulating GCL is a primary mechanism.[63]
- **Selenium**: Preclinical research has found that selenium (Se) enhances GCL activity, and observational studies show a correlation between Se status and GCL.[64] A US study found that while Blacks had lower blood Se than white subjects, 247mcg Se per day resulted in greater increases of both blood Se and GSH in white than Black individuals.[64] Furthermore, Se supplementation failed to improve GSH status in postmenopausal women.[65] Genetics, hormonal factors, and baseline selenium status may contribute.

ANTIOXIDANT

As an antioxidant, glutathione is a martyr, sacrificing itself to become oxidized and sparing our cells the damage. The enzyme glutathione peroxidase (GPx) facilitates this activity. Glutathione reductase (GSR) recycles GSH back into a reduced state so it can exert its antioxidant effect repeatedly. Some plant compounds can also recycle glutathione directly or reduce its antioxidant burden.

- **Purple/blue polyphenols**: Human studies show that these foods raise the reduced to oxidized glutathione ratio (GSH:GSSH), a marker of GSH antioxidant capacity, and improve markers of oxidative damage.[44–49] As antioxidants, anthocyanins may participate in the direct recycling of glutathione.
- **Vitamin C**: Ascorbic acid may mutually support GSH recycling at modest doses. Daily intake of 500mg vitamin C in healthy humans is sufficient for maximal increases in plasma GSH above imposed dietary ascorbate depletion,[66] or observed deficiency.[67] Lower doses were not studied, though a large seven-year study found that 250mg vitamin C (attainable by food alone) with 100mg vitamin E and 37.5mcg selenium increased plasma GSH in healthy individuals.[68] Doses up to 1g ascorbate daily may be necessary for maximal benefit in type II diabetes,[69–71] though as little as 750mg per week decreased GSH in hemodialysis patients.[72] Lymphocyte GSH and ascorbate correlates in one study,[73] however erythrocyte GSH and plasma ascorbate do not in other research.[66]
- **Vitamin E**: Vitamin E is another antioxidant with a mutualistic relationship to GSH. Short-term high-dose vitamin E supplementation (400-600mg/day) improved glutathione levels and plasma antioxidant capacity in type II,[74] and type I diabetics,[75] as did 100mg within a multi-nutrient trial.[68] However, as with vitamin C, lower dietary doses may be effective in healthy individuals, and trials are lacking.
- **Rooibos**: Six cups of rooibos infusion per day increased the GSH:GSSG ratio, as well as increasing total GSH in serum of healthy humans.[76] A supportive rodent study found rooibos increased hepatic (but not erythrocyte) GPx activity in control conditions, and blunted chemical-induced oxidative liver damage.[77]
- **Green and white tea**: Green tea increased antioxidant capacity in adults with metabolic syndrome without altering GPx activity.[54] Both green and white tea reduce oxidative damage in rodent studies.[57,78]
- **Dark roast coffee**: In healthy subjects, 500ml dark roast coffee naturally rich in N-methylpyridinium and poor in chlorogenic acid increased erythrocyte GSH above both baseline and a light roast coffee with the opposite constituent proportions.[79] The dark roast modestly decreased GPx activity while maintaining lipid peroxidation levels, suggesting coffee may spare GSH, bolstering antioxidant reserve.
- **Extra virgin olive oil**: Regular olive oil consumption reduced cholesterol oxidation and raised GPx activity in individuals with stable coronary heart disease.[80] Refined olive oil, however, showed no benefit.
- **Salmon**: Twice weekly salmon increased GPx and GSR activity, and GSH status in pregnant women.[81]
- **Honeybush**: While honeybush not been studied in humans, a rodent study found it elevated GSH and GSH:GSSG equally to rooibos,[82] which is effective in humans (discussed above).
- **Red palm oil**: A rodent study found red palm oil had equal antioxidant effects to rooibos for blunting chemical-induced hepatotoxicity.[77] This may be at least partly due to vitamin E content (see below).
- **Cacao**: In addition to increasing GSH production, cacao protects against oxidative stress in rodents by increasing GSH antioxidant activity.[58,59]
- **Button mushrooms**: Agaricus bisporus, or its extracts, bolster GPx and GSR activity and total GSH in hepatotoxin- and neurotoxin-exposed rodents,[83–85] and in healthy chickens.[86] The latter also demonstrated increased GSH detoxification activity, an effect likely secondary to improved antioxidant function. The benefits likely extend to other dietary mushrooms.
- **Selenium**: Selenium is a component of the GPx enzyme. One Brazil nut per day (containing on average 290mcg Se) non-significantly increased GPx activity in people with coronary artery disease,[87] while the same significantly increased GPx activity and decreased DNA damage in obese, Se-deficient women.[88] Baseline selenium status, which can be measured in whole blood, may partially determine benefit.
- **Riboflavin**: Vitamin B2 is the cofactor for glutathione reductase, and erythrocyte GSR activity is a verified marker of riboflavin status.[89] Riboflavin is also involved in methionine recycling, necessary to ensure cysteine availability for GSH synthesis.[90] Direct research is lacking, but B2 sufficiency is likely necessary for GSH antioxidant function.

DETOX

Glutathione is an important substrate for phase II detoxification. GSH is conjugated with metabolized toxins – including pesticides, mycotoxins, mercury, and air pollution – to neutralize their potentially damaging reactivity and facilitate their elimination. The glutathione sulfotransferase (GST) enzyme family catalyzes this conjugation, and various dietary components stimulate GST activity:

- **Cruciferous vegetables**: The benefits of cruciferous vegetables (CV) for phase II GSH conjugation are well-established, but not all are equal. A crossover clinical trial found brussels sprouts and red cabbage markedly induced GST activity in plasma, while broccoli and white cabbage had no effect.[91] In another study, 300g of brussels sprouts daily enhanced rectal (but not duodenal or lymphocyte) GST.[92] Riso et al confirmed that 10 days of 200g steamed broccoli does not increase plasma GST activity in healthy individuals,[93] though a single portion acutely raised GST activity in smokers.[94] By inference, individuals with higher toxic exposures may benefit more from CV. Broccoli sprouts on the other hand enhanced GST-mediated benzene detoxification in healthy volunteers in two trials.[12,95] Broccoli sprouts also improved liver enzymes in adults with hepatic steatosis, an effect attributed to GST induction in a parallel rodent study.[96] Sprouts contain more sulforaphane, the primary GST-stimulating constituent, than mature broccoli. Regardless, high general CV intake has benefits. A daily 1-2lb mix of cabbage, broccoli, cauliflower, and radish sprouts modestly increased GST activity in healthy volunteers, though GSTM1/ GSTT1-null genotypes benefitted most.[9] Lampe et al suggest apiaceous vegetables may blunt the GST-enhancing benefits of CV,[9,97] however rodent studies find apiaceous vegetables significantly induce GST activity.[98,99] The possible mechanisms and interactions warrant further research.
- **Green tea**: Green tea polyphenols induce GST enzymes during in vivo toxic stress in rodents[100,101] and in vitro toxic stress in piglets,[102] though not in control conditions.[82] While human studies on green tea have not measured GST activity, four cups a day of decaffeinated tea reduced DNA damage in smokers, though only those who are GSTM1/GSTT1-positive.[103] This suggests GST as well as antioxidant involvement.
- **Purple/blue polyphenols**: A small, three-week clinical trial found 250g pomegranate juice daily did not increase erythrocyte GST expression.[46] A larger study found GST activity decreased during two weeks on mixed purple fruit juices, before rebounding significantly above baseline after a washout and second juice intervention.[47] This supports the notion that anthocyanins may act as hormetic stressors.[1,104]
- **Rooibos and honeybush**: Both rooibos and honeybush infusions as the sole source of drinking water increased GST activity in rats under control conditions, in contrast to green tea.[82] Human studies with rooibos have not measured GST activity.
- **Rosemary**: Water soluble rosemary extract, but not isolated its polyphenols rosmarinic acid or caffeic acid, significantly induced hepatic GST expression in healthy rats,[105] and normalized blunted GST activity in creosote-induced hepatotoxicity.[62]
- **Black cumin seed**: One study in chickens found that black cumin, or its extract thymoquinone, markedly increased hepatic GSH and GST-alpha content under control conditions, and blunted aflatoxin-induced DNA damage by stimulating GST-mediated detoxification.[11]

EXCLUSIONS: Medicinal herbs and nutraceuticals without common dietary use have been excluded from this resource, as such should be prescribed with broader, patient-centered indications by a professional. Several other plant constituents have been excluded due to inappropriate or conflicting research findings:

- **Turmeric**: Rodent studies have found GSH-enhancing benefits of turmeric extracts, principally curcuminoids, though the human equivalent doses (HED) are unrealistically high.[106,107] In vitro research confirms curcuminoids stimulate GCL.[108] One human study has shown turmeric and black pepper extract improves GSH status, at a high dose of 1.5g curcumin.[109] Despite its popular use for detoxification, curcumin may decrease GST enzyme activity.[110]
- **Quercetin**: Research on GSH and the flavonol quercetin is conflicting. Rodent studies have found ~10g/day HED decreases,[111] and increases GSH.[112] Typical human intake is 6-20mg; ~140mg HED decreased GSH and GSR activity in rats,[113] while up to 2.5g HED had no antioxidant effect in piglets.[114] One week taking a black currant/apple beverage (9.6mg quercetin) raised GPx activity, but also protein oxidation in humans,[115] while 1g/day quercetin capsules decreased lipid peroxidation but did not affect GSH status after exercise.[116] While quercetin may stimulate GST,[114] it may counterproductively inhibit GCL.[111]

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