Enhances Liver Detoxification *Supports Healthy Estrogen Metabolism*

Increases Antioxidant Protection and Glutathione Production *Promotes Gastrointestinal Health*

*Provides Macronutrients, Phytonutrients, and Cofactors that Support Detoxification of Xenobiotics and Xenoestrogens

DETOX & PROTEIN SUPPORT

Overview of Detoxification†

The human body is exposed to a wide variety of toxins on a daily basis, including chemicals found in foods, environmental toxins and pharmaceuticals. The liver is the body's main detoxification organ which provides enzyme systems that safely process and remove xenobiotics (foreign chemical substances) out of the body, as well as unhealthy hormone metabolites. These detoxification systems are very complex and require a variety of nutrients for optimal function.

There are two main pathways of detoxification in the liver, known as Phase I and Phase II. In Phase I, composed mainly of cytochrome P450 enzymes, non-reactive compounds undergo specific reactions which use oxygen to form a reactive site on the compound. Most pharmaceuticals are metabolized through Phase I biotransformation. This prepares the metabolite for the next step of detoxification knows as Phase II. Phase II is a crucial step—if molecules from Phase I are not fully metabolized by Phase II conjugation, they may cause free radical damage to proteins, RNA and DNA within the cell. Phase II reactions result in the biotransformation of fat-soluble compounds into water-soluble compounds that can then be excreted in the urine, bile or stool.

The ingredients included in **REfuel** were chosen for their ability to support one of the six pathways of Phase II detoxification. N-acetyl cysteine, along with glycine and taurine, is a well-known amino acid that plays a role in supporting the liver. Antioxidants such as lipoic acid, green tea, ellagic acid and the vegetable antioxidant blend provide a synergistic approach to liver support and promote enhanced detoxification.

N-Acetyl Cysteine†

N-acetyl cysteine (NAC) is a sulfhydryl-containing amino acid that is commonly used to support liver health. Though studies have shown the absorption of oral glutathione to be limited, supplementation with NAC has been shown to significantly increase circulating levels of glutathione, a primary antioxidant that protects cellular health.[1-3] Increasing glutathione levels increases the production of specialized antioxidant enzymes, such as glutathione peroxidase, glutathione reductase and detoxification enzymes such as glutathione S-transferase. Through the activity of these enzymes, NAC protects the body from oxidative damage, increases Phase II detoxification, and enhances the normal breakdown of toxins and other metabolic by-products of the body.

Glycine†

One of the six Phase II detoxification pathways is amino acid conjugation (the attachment of amino acids to a toxin). Glycine is one of the amino acids used in this process. Glycine also aids in glutathione conjugation.[4] Glycine preserves intracellular glutathione concentration and protects cells from oxidative damage. This process is mediated by a protein called glycine transporter 1, or GLYT1.[5] Research has shown that glycine treatment of human intestinal cells against an oxidative agent, reduced the intracellular concentration of reactive oxygen species (ROS) when exposed to oxidative challenge.[5]

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

Taurine†

The sulfation pathway is another important Phase II detoxification pathway. During the sulfation pathway, a sulfur-containing molecule is attached to the toxin in order to produce a compound that can be excreted out of the body. Studies show taurine effectively conjugates bile acids [6] and protects the liver against toxic heavy metals such as arsenic by supporting gluthathione levels in the liver.[7]

Lipoic Acid†

Lipoic acid is a potent antioxidant that has been shown to increase glutathione, vitamin E and vitamin C levels in the body.[8] Lipoic acid has been shown to support Phase II detoxification by increasing the activity of enzymes including NAD(P)H, quinine oxidoreductase, and glutathione-S-transferase.[9] Lipoic acid has been used to detoxify mycotoxins (toxic by-products produced by fungi and molds). Lipoic acid has also been shown to reverse age-related loss of glutathione synthesis.[11]

Green Tea Extract†

Green tea is one of the most widely consumed beverages throughout the world for its health- promoting benefits. One of the main polyphenols in green tea includes epigallocatechin-3-gallate (EGCG). Green tea polyphenols have demonstrated significant antioxidant- and inflammatory-balancing effects. Green tea has also been shown to provide Phase II stimulating properties. Studies have shown that green tea extract increases Phase II enzymes such as glutathione transferase, NAD(P)H, quinine reductase, epoxide hydrolase, and UDP-glucuronosyltransferase.[12] EGCG potentiates cellular defense capacity against chemical toxins, ultraviolet radiation, and oxidative stress.[13]

Rosemary†

Rosemary includes polyphenols that are potent antioxidants, which provide a significant boost to immune response and up-regulate detoxification mechanisms of the liver.[14] Carnosol, an antioxidant in rosemary, induces glutathione-s- transferase, as well as other important Phase II enzymes.[15] Rosemary essential oil and carnosol have also been shown to increase intracellular glutathione levels.[16]

Vegetable Antioxidant Blend†

REfuel contains VitaVeggie®, a blend of high-concentration superfood vegetables with significant antioxidant potential. VitaVeggie® is high in ORAC value (oxygen radical absorbance capacity- a method of measuring antioxidant activity) and includes health promoting compounds like sulphoraphane and glucosinolates. Cruciferous vegetables including broccoli, kale, and Brussels sprouts increase the enzyme activity of both Phase I and Phase II detoxification pathways.[17] Sulforaphane induces Phase II detoxification enzymes and supports the body's response to oxidative stress to promote balanced inflammation.[18] Glucosinolates serve as precursors for biologically active metabolites, which induce Phase II enzymes via the activation of Nrf2, the master cellular switch responsible for antioxidant production.[19]

Schizandra Berry Extract†

Schizandra is an adaptogenic botanical used medicinally to help fight off the physical and mental effects of stress. Schizandra is also used to support liver health and neutralize the effects of toxin exposure. Schizandra enhances liver detoxification pathways by increasing the levels of reduced glutathione in the liver as well as glutathione reductase and glutathione-S-transferase activity. In animal studies, schizandra has been shown to support Phase I metabolism and protect the liver from free radical damage induced by toxic chemical exposure following ingestion of carbon tetrachloride.[20]

Psyllium Husks†

Psyllium husk is from the plant *Plantago ovata* and has a large amount of soluble fiber per volume. Psyllium is used to improve gastrointestinal transit time and promotes cardiovascular health by maintaining normal cholesterol levels through the elimination of cholesterol-rich bile. Studies show psyllium husk powder up-regulates genes involved in bile acid synthesis and binds to bile acids in the intestines to gently remove them from the body.[21, 22]

Directions

Mix 2 scoops (37.0 grams) of **REfuel** with 8 oz. of water or the beverage of your choice two times daily, or as recommended by your health care professional.

Does Not Contain

Gluten, yeast, artificial colors and flavors.

Cautions

Do not consume this product if you are pregnant or nursing. Consult your physician for further information.

Without drinking enough liquid, this product may swell in throat, causing blockage or choking. DO NOT use if you have ever had esophageal narrowing or swallowing difficulties. Seek immediate medical help if symptoms of esophageal blockage (chest pain/pressure, regurgitation or difficulty swallowing) occur. May cause allergic reaction in persons sensitive to inhaled or ingested Psyllium.

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Supplement Facts

V3

Serving Size 2 Scoops (37 Grams)
Servings Per Container About 14

2 scoops contain	Amount Per Serving	% Daily Value
Calories	150	
Total Fat	2.5 g	3%*
Saturated Fat	1 g	5%*
Total Carbohydrate	13 g	5%*
Dietary Fiber	6 g	21%*
Total Sugars	5 g	**
Includes 5 g Added Sugars		10%*
Protein	15 g	30%*
Calcium	50 mg	4%
Iron	4 mg	22%
Magnesium (as Magnesium Citrate USP)	100 mg	24%
Sodium	15 mg	<1%
Potassium (as Potassium Citrate USP)	500 mg	11%
Rice Protein (ORYZAPRO)	17.34 g	**
Psyllium Husk Powder (Organic)	4.16 g	**
Glycine USP	500 mg	**
Vegetable Antioxidant Blend (2,500 ORAC):	500 mg	
Broccoli Sprout Concentrate		**
Onion Extract		**
Tomato		**
Broccoli		**
Carrot		**
Spinach		**
Kale		**
Brussels Sprout		**
Taurine	250 mg	**
L-Glutamine USP	150 mg	**
Acetyl L-Carnitine Hydrochloride	125 mg	**
N-Acetyl-L-Cysteine USP	125 mg	**
Alpha Lipoic Acid	50 mg	**
Green Tea Leaf Extract (Standardized to contain 45% EGCg (Epigallocatechin gallate))	50 mg	**
Rosemary Leaf Extract	50 mg	**
Schisandra Berry Extract	50 mg	**
Ellagic Acid	25 mg	**
Glucosinolates	1 mg	**

* Percent Daily Values are based on a 2,000 calorie diet.
** Daily Value not established

References

1. Witschi A, et al. The systemic availability of oral glutathione. *Eur J Clin Pharmacol* 1992;43:667-9.
2. De Rosa SC, et al. N-acetylcysteine replenishes glutathione in HIV infection. *Eur J Clin Invest* 2000 Oct;30(10):841-2.
3. Atkuri KR, Mantovani JJ, Herzenberg LA, et al. N-Acetylcysteine—a safe antidote for cysteine/glutathione deficiency. *Curr Opin Pharmacol* 2007 Aug;7(4):355-9. Review.
4. Liska DJ. The detoxification enzyme systems. *Altern Med Rev* 1998; 3(3):187-198.
5. Howard A, Tahir I, et al. Glycine transporter GLYT1 is essential for glycine-mediated protection of human intestinal epithelial cells against oxidative damage. *J Physiol* 2010; 588(Pt 6):995-1009.
6. Birdsall T C. Therapeutic applications of taurine. *Altern Med Rev* 1998; 3(2):128-136.
7. Das J, Ghosh J, et al. Protective role of taurine against arsenic-induced mitochondria-dependent hepatic apoptosis via the inhibition of PKCdelta-JNK pathway. *PLoS One* 2010; 5(9):e12602.
8. Smith A R, Shenvi S V, et al. Lipoic acid as a potential therapy for chronic diseases associated with oxidative stress. *Curr Med Chem* 2004; 11(9):1135-1146.
9. Flier J, Van Muiswinkel F L, et al. The neuroprotective antioxidant alpha-lipoic acid induces detoxication enzymes in cultured astro glial cells. *Free Radic Res* 2002; 36(6):695-699.
10. Rogers, SA. Lipoic acid as a potential first agent for protection from mycotoxins and treatment of mycotoxicosis. *Arch Environ Health* 2003; 58(8):528-532.
11. Shay KP, Moreau RF, et al. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. *Biochem Biophys Acta* 2009; 1790(10):1149-1160.
12. Yu R, Jiao JJ, et al. Activation of mitogen-activated protein kinases by green tea polyphenols: potential signaling pathways in the regulation of antioxidant-responsive element-mediated phase II enzyme gene expression. *Carcinogenesis* 1997; 18(2):451-456.
13. Na HK, Surh YJ. Modulation of Nrf2-mediated antioxidant and detoxifying enzyme induction by the green tea polyphenol EGCG. *Food Chem Toxicol* 2008; 46(4):1271-1278.
14. Offord EA, Mace K, et al. Mechanisms involved in the chemoprotective effects of rosemary extract studied in human liver and bronchial cells. *Cancer Lett* 1997; 114(1-2):275-281.
15. Singletary KW. Rosemary extract and carnosol stimulate rat liver glutathione-S-transferase and quinone reductase activities. *Cancer Lett* 1996; 100(1-2):139-144.
16. Chen CC, Chen HL, et al. Upregulation of NF-E2-related factor-2-dependent glutathione by carnosol provokes a cytoprotective response and enhances cell survival. *Acta Pharmacol Sin* 2011; 32(1):62-69.
17. Nestle M. Broccoli sprouts as inducers of carcinogen-detoxifying enzyme systems: clinical, dietary, and policy implications. *Proc Natl Acad Sci U S A* 1997; 94(21):11149-11151.
18. Kim HJ, Barajas B, et al. Nrf2 activation by sulforaphane restores the age-related decrease of T(H)1 immunity: role of dendritic cells. *J Allergy Clin Immunol* 2008; 121(5):1255-1261.

19. Haack M, Lowinger M, et al. Breakdown products of neoglucobrassicin inhibit activation of Nrf2 target genes mediated by myrosinase-derived glucoraphanin hydrolysis products. *Biol Chem* 2010; 391(11):1281-1293.

20. Zhu M, Yeung RY, Lin KF, Li RC. Improvement of phase I drug metabolism with Schisandra chinensis against CCl4 hepatotoxicity in a rat model. *Planta Med* 2000 Aug;66(6):521-5.

21. Chan, MY, Heng C K. Sequential effects of a high-fiber diet with psyllium husks on the expression levels of hepatic genes and plasma lipids. *Nutrition* 2008; 24(1):57-66.

22. Burton R, Manninen V. Influence of a psyllium-based fibre preparation on faecal and serum parameters. *Acta Med Scand Suppl* 1982; 668:91-94.