WHITE PAPER

# Whole Food, Nutritional Support for the Body's Natural Detoxification Processes

## ABSTRACT

In modern society, exogenous toxin exposure is essentially unavoidable. The air, water, soil, and food supply are contaminated with common toxicants that include persistent organic pollutants (POPs), pesticides, herbicides, heavy metals, plastic-associated chemicals (PACs), and volatile organic compounds. Exposure to toxicants can cause tissue damage and disturb the physiological function of a range of body systems through the disruption of endocrine signaling, inhibition of enzyme systems, depletion of cellular antioxidants, and modulation of microbial communities in the gut and elsewhere. This can lead to metabolic dysfunction, impaired immune response, and damage to DNA. Many toxins are lipophilic and have a long half-life which can make their elimination more difficult. Detoxification is a natural process in the body, primarily carried out by the liver but also supported by the gallbladder, urinary tract, and skin, that is critical for the elimination of toxins, endogenous metabolic byproducts, and free radicals. Detoxification is a demanding process that requires ATP, key micronutrient cofactors, glutathione, amino acids, and methyl groups. When these compounds are not available in sufficient quantities, detoxification processes can become compromised. The impaired function of organs involved in detoxification, such as in metabolic-associated fatty liver disease (MAFLD), can lead to additional stress on these systems and slowed detoxification processes.

Various vegetables, herbs, and phytonutrients have been found to support detoxification through improved liver function, the induction of gene expression related to detoxification, and the promotion of oxidative balance. The implementation of a comprehensive detoxification program that includes whole extracts of vegetables and herbs, together with lifestyle modification has been shown to result in significant improvements in body composition, blood pressure, markers of cardiovascular health and inflammation, and total antioxidant capacity. These results are consistent with a large body of evidence that nutritional support can significantly enhance detoxification processes.

## TOXIN EXPOSURE IN THE UNITED STATES

Toxins and toxicants can be found nearly everywhere: in the soil, air, water, and even the food supply.[1] The environment contains nearly 80,000 novel chemicals which are registered with the U.S. Environmental Protection Agency (EPA) but not necessarily thoroughly studied for their effects on human health.[1] While the modern age allows for more technology and conveniences, it has also come with the development of synthetic chemicals, pharmaceuticals, and increased agrochemical compounds. These toxicants can eventually contaminate natural resources like water and soil and contribute to health issues in humans.[1]

Common types of toxicants include persistent organic pollutants (POPs), pesticides, herbicides, plastic-associated chemicals (PACs) including bisphenol A and phthalates, and volatile organic compounds found in solvents, fuels, and fragrance ingredients.[1] There are also naturally occurring toxins such as heavy metals, molds, and advanced-glycation end products. These can inhibit enzyme systems, induce oxidative stress, and disturb normal tissue function and eventually damage the brain, lungs, kidney, and liver.[2,3] All of these toxins can be very dangerous to humans when they enter food chains and agricultural systems.[3] Exposure to toxins can cause tissue damage and eventually disturb the function of vital organs in the body, including the nervous, endocrine, immune, reproductive, renal, cardiovascular, and respiratory systems.[4]

Toxins can cause harm to the body through several mechanisms, often occurring simultaneously which creates a complex network of dysregulated metabolism.[5] Toxins are able to cause tissue damage, disrupt endocrine signaling, inhibit enzyme systems, modulate gene expression networks, and exert genotoxic effects.[1] Many toxins also induce oxidative stress through modulation of mitochondrial production of free radicals as well as depletion of cellular antioxidants.[6-8] All of these cellular-level changes result in disturbances to metabolic homeostasis, altered endocannabinoid signaling, impaired immune response, detrimental changes to the gut microbiome composition, and delayed tissue repair.[9-12] Additionally, certain toxins are able to cause structural or functional damage to chromosomes, DNA, and histone proteins, altering gene expression profiles and impairing organelle function in cells.[4] Specific pathways have also been elucidated related to the effects of toxins in specific body systems. For example, toxins can impair neurotransmission and the function of ion channels — a key line of communication for the nervous system — which contributes to the development of neurocognitive conditions due to toxin exposure.[13] Similarly, metabolic effects of toxins may be due to their ability to impair neural circuits that control feeding behavior and alter the differentiation of adipocytes. This can lead to aberrant signaling and insulin dysregulation.[14]

Many toxins are lipophilic, making excretion difficult and also allowing them to cross membranes and reside in adipose tissue and the liver.[15-17] From there, they can wreak havoc on normal tissue metabolism, which is demonstrated by the classification of many toxins as endocrine-disrupting chemicals (EDCs) or metabolism-disrupting chemicals (MDCs).18 Many toxins also have a long half-life, requiring the body's natural detoxification processes to intervene rather than slowly being broken down and leaving the body.[18] In addition to exogenous toxins, lifestyle exposures can also increase stress and contribute to toxin burden, including environmental stress, social isolation, a sedentary lifestyle, and disruptions to mood and sleep.[19]

## DETOXIFICATION IN THE BODY

The body has a natural, three-step process for detoxifying potentially harmful compounds. First, phase I enzymes in the liver activate toxic substances, adding a reactive group such as a hydroxyl, carboxyl, or amino group.[20,21] This can generate free radicals and reactive intermediates that can be more toxic than the parent compound and also induce oxidative damage in cells.[20,22] Phase I reactions are primarily carried out by the cytochrome P450 superfamily of enzymes (CYP450), which act on both endogenous and exogenous substrates such as steroid hormones, pharmaceutical compounds, and xenobiotics.[20,23] These enzymes are located in the liver, kidneys, lungs, and brain, and their expression profile can have a significant impact on a person's ability to detoxify foreign compounds.[20,24]

Next, phase II enzymes conjugate hydrophilic functional groups to the reactive site on toxins, increasing their water solubility and tagging them for transport and elimination.[20,25] Some of the hydrophilic groups involved in phase II include glucuronic acid, sulfate, glutathione, amino acids, acetyl group, or a methyl group.[20,25] Phase II reactions can be carried out by many different enzymes, including sulfotransferases (SULTs), methyltransferases (MTs), UDP-glucuronosyltransferases (UGTs), glutathione S-transferases (GSTs), N-acetyltransferases (NATs), and amino acid transferases.[20,26] Similar to phase I enzymes, genetic variability can affect phase II enzyme activity.[20] Efficient phase II enzymes allow for the excretion of toxins through bile, urine, or sweat during the third and final phase of detoxification, elimination.[27]

## NUTRITIONAL SUPPORT FOR DETOXIFICATION

Detoxification is a demanding process, requiring ATP for essential reactions as well as micronutrient cofactors for enzymatic activity.[20,28] Deficiency of nutrients or compounds involved in the actions of phase I or II enzymes can alter or slow detoxification processes, potentially contributing to a build-up of toxins.[29] Additionally, conjugation compounds used in phase II reactions are excreted with the neutralized toxins. Therefore, the body requires a constant influx of glutathione, amino acids, methyl groups, and other hydrophilic groups to maintain adequate phase II enzymatic reactions. Because of the intense requirements of detoxification, the body's nutritional status, as well as dietary intake, can significantly impact the liver's ability to detoxify potentially harmful compounds.[20,29]

Many vegetables, herbs, and phytonutrients have been found to support detoxification, either directly or indirectly. Some of these dietary compounds support liver health, while others induce expression of genes involved in detoxification. Dietary antioxidants are also important elements of nutritional support for detoxification. Both endogenous and exogenous antioxidants are able to neutralize oxidative species generated as a byproduct of detoxification, promote liver health through maintaining oxidative balance, and also support phase II enzymes.[26]

### *CRUCIFEROUS VEGETABLES*

Several vegetables belonging to the Cruciferae or Brassicaceae family, including broccoli, cauliflower, cabbage, Brussels sprouts, and radishes, have been studied for their ability to modulate detoxification, including inducing expression of CYP450 and phase II enzymes.[20,30-42] Mechanistically, cruciferous vegetables provide vital phytonutrients that protect the liver and induce expression of detoxification enzymes. Much of the research investigating the detoxification-enhancing capabilities of cruciferous vegetables has focused on glucosinolates. Glucosinolates are a group of sulfur-containing phytochemicals in plants that can be hydrolyzed via the enzyme myrosinase to eventually form isothiocyanates, thiocyanates, or nitriles depending on the structure of the original glucosinolate.[43] Myrosinase is activated when plant tissue is chewed or grinded and can be inactivated by cooking.[37,39] Intestinal microbiota are also capable of metabolizing glucosinolates into active isothiocyanates.[44] Metabolites of glucosinolates, including sulforaphane and raphasatin, can induce both phase I and II enzymes, enhancing detoxification and clearance of potentially dangerous compounds.[20,35,37-41,45]

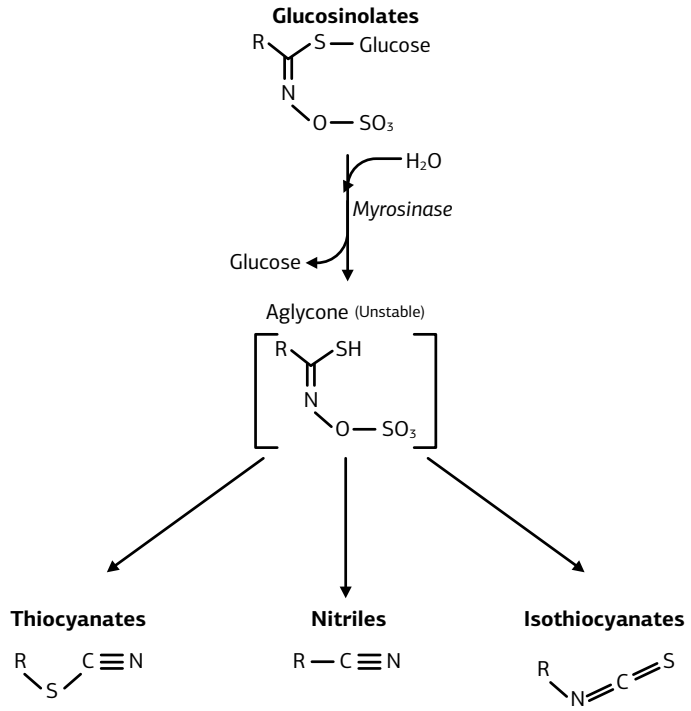


**Figure 1.** Glucosinolates, including those from cruciferous vegetables, are broken down through hydrolysis via the enzyme myrosinase to form thiocyanates, nitriles, and isothiocyanates.

Cruciferous vegetables can also aid in detoxification processes through other mechanisms. For example, organosulfur phytonutrients such as sulforaphane found in cruciferous vegetables activate Nrf2, a transcription factor that regulates both detoxification and antioxidant systems in the body.[20,46,47] Finally, cruciferous vegetables, along with many other whole foods, supply fiber which may help increase the removal of certain toxins by reducing their reabsorption into circulation and supporting elimination.[48,49]

Broccoli remains one of the top-consumed cruciferous vegetables and provides the precursors to detoxification-inducing metabolites, including indole-3-carbinol as well as glucoraphanin, which can be metabolized into sulforaphane.[40,50] Both animal and human studies have demonstrated the ability of broccoli in its whole food form and supplement form to induce detoxification enzymes.[30,31,51,52] However, other lesser-known cruciferous vegetables have been validated as strong modulators of detoxification enzymes, including Spanish black radish (SBR). SBR contains 400% more glucosinolates than other crucifers.[37] One of these glucosinolates, glucoraphasatin, has a similar potency to sulforaphane and is capable of inducing both phase I and II enzymes.[40-42] Multiple models have demonstrated the ability of SBR to induce detoxification

enzymes.[37,40,41] In mice fed a 20% SBR diet, detoxification genes were upregulated and there was enhanced clearance of a toxin as well as protection against negative consequences of the toxin.[37] Similarly, in a human clinical trial, consumption of a Spanish black radish supplement for four weeks resulted in up-regulation of phase I and II liver enzymes with an overall positive effect on the detoxification of acetaminophen.[42]

## *AMINO ACIDS*

Several amino acids play a key role in detoxification pathways, including arginine, glutamine, taurine, and glycine. Endogenous and exogenous sources of these amino acids are used in conjugation reactions involving amino acid transferases and they can also enhance detoxification through stimulating urea production via the urea cycle, which helps rid the body of excess nitrogen.[20,53-57] In pre-clinical models, arginine and taurine enhanced detoxification during mercury- and alcohol-induced toxicity, respectively.[58,59]

Several amino acids also support detoxification indirectly. For example, glutamine and glycine are involved in glutathione synthesis which helps support antioxidant defense systems while glycine and ornithine exhibit cytoprotective and hepatoprotective effects.[54-56,60] Importantly, many of these amino acids require vitamin and mineral cofactors during synthesis, including vitamin $B_6$ in taurine synthesis and magnesium for ornithine synthesis.[20]

## *ANTIOXIDANTS*

Because phase I generates oxidative species, the balance between phase I and phase II enzymes is critical to ensuring healthy detoxification without causing oxidative stress.[42] Endogenous antioxidants, dietary antioxidants, and antioxidant enzymes help scavenge free radicals and ROS that occur as a result of normal metabolism and detoxification.[61] Additionally, antioxidants are very important for general liver support as the liver is the primary site of metabolism and detoxification of foreign compounds.[21] Antioxidants from whole foods, such as carrots, alfalfa, or barley, provide support by neutralizing free radicals and providing additional support to phase II enzymes.[62-64] Many whole food sources of antioxidants also deliver essential micronutrients and dietary compounds, such as chlorophylls, carotenoids, flavonoids, and phenolic acids, and minerals which have many beneficial effects on the body.[64,65]

Glutathione (GSH) is an important antioxidant for detoxification because it can directly scavenge free radicals and is required for phase II conjugation via GSTs.[20] When glutathione is deficient, toxins can bind to sulfhydryl proteins in the liver, causing lipid peroxidation, and damaging hepatocytes.[42] While it is difficult for the body to absorb glutathione from food and supplements, it can be synthesized from the amino acid precursors glycine, glutamic acid, and cysteine.[20,61] N-acetyl cysteine has also been shown to restore deplete GSH levels in humans, functioning as a source of cysteine which is commonly the rate-limiting amino acid in glutathione synthesis.[61,66] As such, consuming these amino acids can support detoxification indirectly. Glutathione balance can be supported by a healthy diet and specific nutrients and compounds including vitamin B6, magnesium, selenium, milk thistle, turmeric, and folic acid.[67-71]

## *HERBS*

Significant evidence from pre-clinical models has demonstrated that many herbs like garlic, rosemary, and dandelion are able to induce detoxification enzymes.[72-75] Herbs like burdock, dandelion, and milk thistle also support liver health and promote healthy inflammation which further contributes to healthy liver function and overall well-being.[76-78] Milk thistle has been studied extensively because of its hepatoprotective effects, mostly attributed to silymarin, that can oppose the actions of biological and chemical toxins.[79] Milk thistle scavenges free radicals, regulates inflammation, and possesses chelating properties.[79] Similarly, dandelion leaf may protect the liver through its antioxidant and anti-inflammatory actions, as well as potentially increase the levels of glutathione.[80] In a pre-clinical study, dandelion extract protected both the liver and kidneys from damage due to the food additive sodium benzoate, as well as helped ameliorate consequences associated with exposure.[81]

## *PHYTONUTRIENTS*

Many vegetables and fruits provide phytonutrients that support detoxification through the induction of detoxification enzymes as well as through their antioxidant effects on cells. For example, resveratrol and astaxanthin can modulate the

expression of CYP450 enzymes while anthocyanins, lycopene and curcumin regulate the activity of Nrf2.[82-86] Phytonutrients also likely exert synergistic effects, providing even more benefits.[43]

### *ADDITIONAL WHOLE FOOD SUPPORT FOR DETOXIFICATION*

Many whole food plants beyond cruciferous vegetables support detoxification. For example, beets can activate phase II enzymes, including GST, and possess strong antioxidant properties as well as anti-inflammatory actions which can help support the liver.[87,88] In pre-clinical models of toxin-induced liver injury, beetroot juice helped reduce DNA damage and protect the liver from oxidative damage.[89-91] Other whole food sources that support detoxification include:

- **Alfalfa,** which contains sulfur-rich bioactive compounds that aid in detoxification, enzymatic activity, and maintaining oxidative balance.[92]
- **Sweet potato leaves,** which increased phase I and II enzymes, induced Nrf2 to help reduce oxidative stress in the liver, and reduced toxin concentration in the plasma, liver, and intestinal mucosa due to increased enzymatic activity in a pre-clinical mode.[84,93]
- **Juniper berries,** which possess high antioxidant activity and can activate phase II enzymes, including SOD.[94]
- **Pectins,** a type of structural polysaccharide found in plant cell walls, that are involved in the detoxification of heavy metals by acting as chelating agents.[95-97]

Artichokes and cordyceps mushrooms are also whole food sources of nutritional support for detoxification. Artichokes enhance the body's detoxification processes, exert antioxidant effects, and support liver metabolism by protecting hepatocytes from oxidative stress and possibly helping liver cells regenerate.[98-101] In a pre-clinical model of acetaminophen-induced liver damage artichoke leaf extract protected the liver and this effect was further enhanced when artichoke leaf was co-administered with silymarin from milk thistle, demonstrating the synergistic effect of plant compounds.[102] Finally, cordyceps mushrooms provide antioxidant support and help protect the liver through the presence of micronutrients and bioactive compounds, including cordycepin.[103]

### *NUTRITIONAL SUPPORT THROUGH THE WHOLE FOOD MATRIX*

Consuming food in the whole food matrix, as opposed to a highly processed form, is an important nutritional recommendation for those looking to reduce their toxin exposure and enhance the body's natural detoxification processes. The whole food matrix is the naturally occurring form of a food, including the unique structure of constituents as well chemical dynamics and interaction among compounds.[104] The whole food matrix can affect nutrient bioavailability and absorption in the GI tract, including for essential amino acids and vitamins that are required by phase I and II enzymes.[104,105] Consumption of a whole food-style diet has been associated with many benefits and reduced risk of developing certain diseases.[67,106]

Because detoxification is a complex physiological process, isolated compounds and phytonutrients may not yield the same effects as consuming whole food sources of bioactive compounds. To help gain understanding of the effect of the whole food matrix, Standard Process conducted three clinical trials on SP Detox Balance™, a blend of vegetables, herbs, and several essential amino acids, to assess how a whole food nutritional support program modulates detoxification.

## CLINICAL RESEARCH SUPPORTING SP DETOX BALANCE™

The first clinical investigation into SP Detox Balance™ assessed body composition, measures of detoxification, and metabolic and inflammatory panels in participants who were considered either obese (BMI >30) or overweight (BMI > 27) with co-morbidities.[18] Participants consumed SP Detox Balance™ for 28 days as part of a 12-week program with weekly group and individualized dietary, exercise, and behavioral support. Consumption of SP Detox Balance™ as part of the therapeutic lifestyle support resulted in significant improvements in body composition, including BMI, weight, body fat, fat mass, waist and hip circumference as well as waist-to-hip ratio.[18] Resting blood pressure was reduced, as well as several measures of physical fitness. Consumption of SP Detox Balance™ as part of the therapeutic lifestyle intervention also resulted in improvements in the cardiovascular and inflammatory markers homocysteine and endothelin, respectively. While still in a normal range, zonulin and lipopolysaccharides immunoglobulin M were significantly reduced. Participants who

consumed SP Detox Balance™ also reported significant improvements in brief pain and intermittent pain interference based on the validated Brief Pain Inventory questionnaire. While there is not currently a gold standard for assessing detoxification capabilities, several measures demonstrated increased detoxification processes including the phase II marker D-glucaric acid and the phase II marker mercapturic acid.[18]

Next, in a randomized, controlled trial, healthy adults consumed SP Detox Balance™ for 28 days while participating in a healthy diet education session.[26] Healthy adults in the control group received only the healthy diet education session.[26] There was no change in body composition measures in the group consuming SP Detox Balance™ while measures of physical and emotional health also remained stable.[26] However, consumption of SP Detox Balance™ resulted in a 40% increase in total antioxidant capacity, a measure which combined antioxidant activities of all serum constituents including vitamins, proteins, lipids, glutathione, and uric acid. There was also a 13% decrease in ROS-associated oxidative stress in peripheral blood mononuclear cells isolated from subjects who consumed SP Detox Balance™. Upon further investigation, it was found that reduced glutathione and the ratio of reduced to oxidative glutathione stayed stable, a sign of balanced redox homeostasis due to the body's ability to recycle glutathione. However, the activity of the phase II antioxidant enzymes superoxide dismutase (SOD) and glutathione S-transferase (GST) were increased 23% and 13% respectively, suggesting increased glutathione turnover. Theoretically, increased glutathione turnover with overall stable glutathione balance could indicate increased detoxification and replenishment of glutathione pools via SP Detox Balance™. However, these data are not conclusive of this outcome and more clinical trials are needed to further affirm this hypothesis.

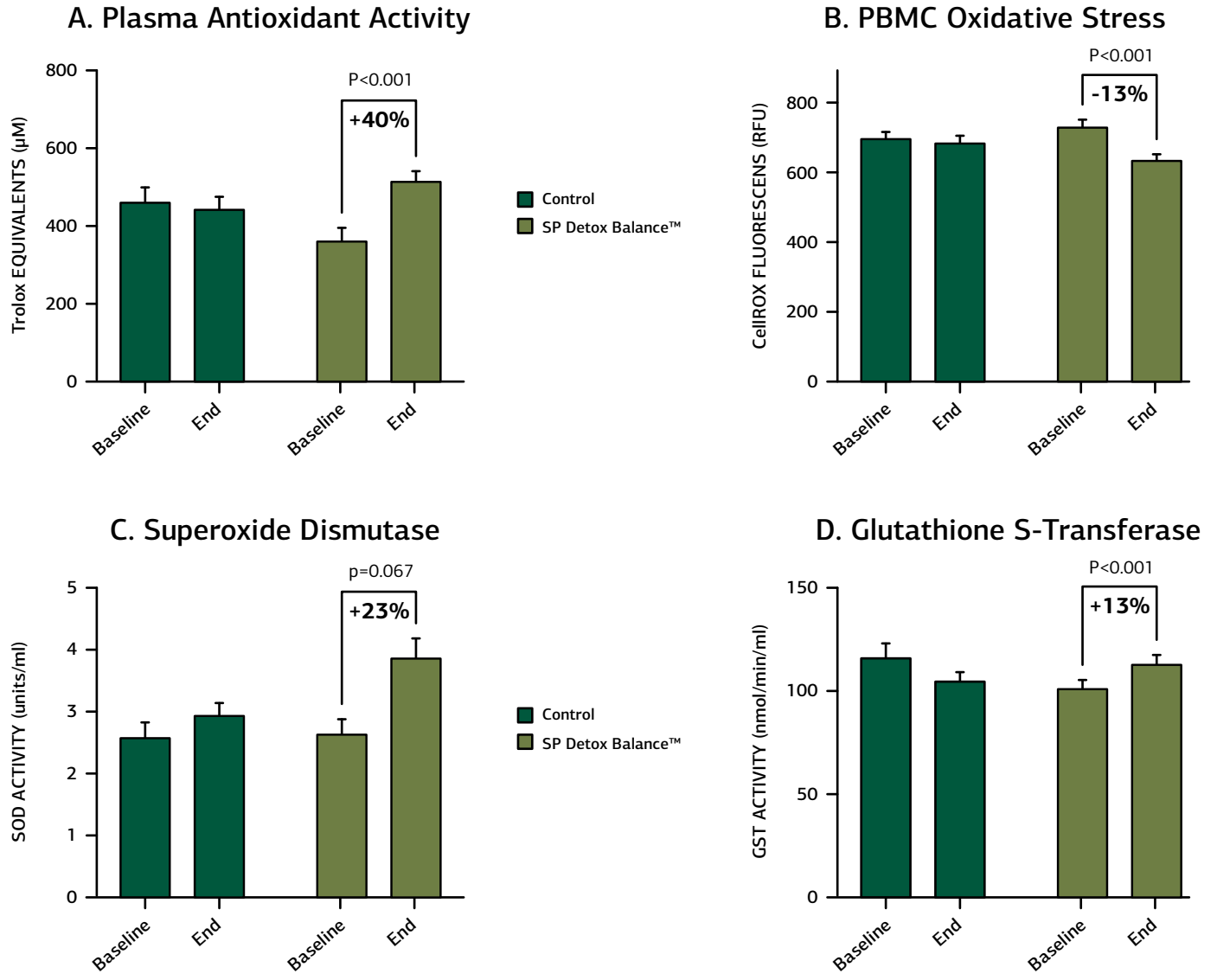


**Figure 2.** Consumption of SP Detox Balance™ for 4 weeks resulted in increased plasma antioxidant activity (A), decreased oxidative stress in peripheral blood mononuclear cells (B), and increased activity of the phase II antioxidant enzymes SOD (C) and GST (D).

In another randomized, controlled study, 35 participants were assigned to consume SP Detox Balance™ according to the 28-day detoxification program or a control supplement that contained plant-based protein sources.[28] Measures were assessed at baseline, 4 weeks, and 6 weeks to understand the immediate results of the 28-day detoxification program as well as two weeks after consumption stopped. Similar to the previous study in healthy individuals, there were no changes in body composition or vital signs in the SP Detox Balance™ group or control group. Participants in the detoxification program, however, reported improvements in their metabolic symptoms via Metabolic Screening Questionnaire, as well improvements in measures of sleep quality and well-being. At baseline, participants who had elevated total urine porphyrins demonstrated higher total red blood cell (RBC) toxic metal concentration and urine D-glucaric acid levels. At the end of the intervention, RBC toxic metals were reduced along with urine porphyrins and urine mutagenicity, a measure of toxin burden, which indicates enhanced efficiency of detoxification processes.[28] The mutagenicity potency in participants consuming SP Detox Balance™ remained low at the week 6 measurement.

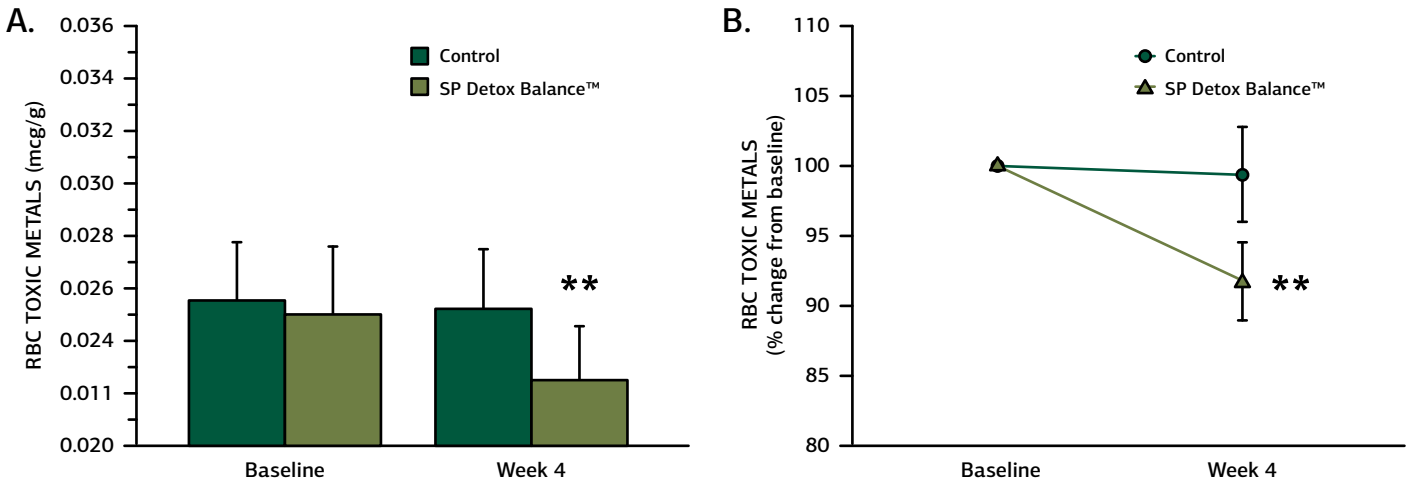


**Figure 3.** Consumption of SP Detox Balance™ for 4 weeks resulted in a significant decrease in red blood cell (RBC) toxin metals concentration, shown as the absolute value (A) and percent change compared to baseline (B).

## CONCLUSION

Under normal circumstances, the body is able to efficiently neutralize and eliminate potentially harmful compounds. However, chronic exposure or an elevated toxin burden can overwhelm the body's natural processes and may result in symptoms and health conditions over time. Three clinical studies demonstrate the ability of SP Detox Balance™ to positively influence several measures of health and markers of detoxification processes*. These results are consistent with a large body of evidence that nutritional support of detoxification enzymes and antioxidant systems can significantly enhance detoxification processes. Consumption of cruciferous vegetables, antioxidants, hepatoprotective herbs, and key phytonutrients can indirectly and directly support the body's natural metabolic detoxification processes.

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

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