

The Role of Detoxification in the Prevention of Chronic Degenerative Diseases

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ABSTRACT: *The impact of environmental toxicity on health is startling; environmental exposure to toxic substances is suggested to cost billions in annual health dollars. Diseases that are linked directly to environmental exposure include many types of cancers and those syndromes characterized by fatigue, muscle weakness, and cognitive dysfunction. Environmental toxicity, however, can lead to a myriad of other conditions. Toxicants in the environment include a wide range of compounds, such as heavy metals, organic pesticides, drugs, and industrial compounds, and our bodies must be able to manage and excrete this wide range of potentially*

damaging substances. One of the most important biochemical processes attending to toxicant removal in our bodies is the biotransformation process—also called the detoxification system—which involves the Phase I cytochrome P450 and Phase II conjugation enzymes. This detoxification system is highly dependent on nutrient support for optimal functioning. It may come as no surprise, then, that nutrients shown to support the biotransformation process have also been shown to ameliorate symptoms or slow the progression of many of the diseases and conditions associated with toxicant exposure.

HOW DO TOXICANTS AFFECT CHRONIC DEGENERATIVE DISEASES?

A recent report on the costs to society suggests that between \$568 billion to \$793 billion is spent per year in Canada and the United States on environmentally-caused disease.¹ One reason for this major impact of environment on health is the magnitude of exposure we all have to toxic substances. We are exposed to environmental toxicants through the air we breathe, the food we eat, and the water we drink, as well as through our skin.

A growing body of literature suggests an association between toxicant exposure and the etiology of a number of chronic conditions, such as chronic fatigue syndrome (CFS), multiple chemical sensitivities (MCS), fibromyalgia (FM), and atherosclerosis.²⁻⁵ Symptoms such as unremitting and debilitating fatigue, myalgias, arthralgias, and cognitive dysfunction are common amongst these syndromes. Moreover, a recent *New York Academy of Sciences* report indicates that individual response to toxicants is varied and is a primary factor in susceptibility to these conditions.⁶

The association between environmental toxicant exposure with syndromes such as MCS, CFS, and FM is gaining acceptance, but even more striking are the connections between environment and the development of many other chronic degenerative diseases (Table 1). For instance, interest in the role of environment on etiology of late onset Parkinson's disease has recently been renewed after an extensive study of twins showed no major evidence of genetic influence on Parkinson's disease in those who contracted the disease after 50 years of age.⁷

It has been known for some time that exposure to low-molecular-weight organic compounds can induce symptoms of Parkinson's disease.⁸ Epidemiological studies show that exposure to pesticides; farming; drinking well water; proximity in resi-

dence to industrial plants, printing plants, or quarries; and chronic occupational exposure to manganese, copper, or a combination of lead and iron are also associated with Parkinson's disease. While the mechanisms of these toxic exposures are not known, an individual's ability to excrete toxins has been shown to be a major factor in disease susceptibility.^{9,10}

Table 1. Common clinical symptoms and conditions associated with environmental toxicity

- Abnormal pregnancy outcomes
- Atherosclerosis
- Broad mood swings
- Cancer
- Chronic fatigue syndrome
- Chronic immune system depression
- Contact dermatitis
- Fatigue
- Fertility problems
- Fibromyalgia
- Headaches
- History of increasing sensitivity to exogenous exposures, odors, or medications
- Joint pain
- Kidney dysfunction
- Learning disorders
- Memory loss
- Mineral imbalances (particularly zinc and calcium)
- Multiple chemical sensitivities
- Muscle pain and weakness
- Nonresponsive or recurrent yeast infections
- Panic attacks
- Parkinson's disease
- Tinnitus
- Unusual responses to medications or supplements
- Worsening of symptoms after anesthesia or pregnancy

Possibly the largest amount of research has focused on the implications of long-term toxin exposure and the risk of initiation and progression of a variety of cancers. Cancer is the third leading cause of death in children—succeeded only by injuries and violence—and the death rate is on the rise. For example, cancer death in children rose by 13% between 1973 and 1997 and, most notably, the incidence of non-Hodgkin's lymphoma and brain cancer in children rose by 30% and 21%, respectively, in the same time period.¹¹ Strong associations exist between these cancers and the exposure to various toxins, including organochlorinated pesticides, which have been shown to damage chromosomal DNA.¹²⁻¹⁴

WHAT ARE TOXINS, TOXICANTS, AND TOXIC SUBSTANCES?

The word "toxin" itself does not describe a specific class of compounds, but rather something that can cause harm to the body. More specifically, a *toxin* or *toxic substance* is a chemical or mixture that may injure or present an unreasonable risk of injury to the health of an exposed organism. Some definitions limit the use of the word "toxin" to poisonous compounds of animal or vegetable origin, and thus to avoid confusion, the Environmental Protection Agency (EPA) and other governmental organizations use the word "toxicant" to denote a toxin.¹⁵ Each toxic substance has a defined *toxic concentration* or *toxic dose* at which it produces its toxic effect. However, most compounds referred to as environmental toxicants are damaging at low doses. A brief list of the most common classes of toxicants is provided below.

Industrial Chemicals and Combustion Pollutants—This is one of the largest categories of toxicants: virtually everyone is exposed to halogenated hydrocarbons, such as polychlorinated biphenyls (PCBs), at some level during an average day.¹⁶ Volatile organic toxicants are a broad category of toxins that can include halogenated hydrocarbons. These toxicants are of particular concern because of their ability to become airborne.

Pesticides—Over 800 different chemicals belong to this class of toxicants. Many of the industrial chemicals are developed for their toxic effects on certain organisms and then commercially sold as pesticides, insecticides, and herbicides. Although manufacturers of these agents try to make them selective for specific types of organisms—hopefully reducing their toxic effects on humans—absolute specificity is nearly impossible to achieve and most pesticides are in some way toxic to humans.¹⁷

Endocrine Disruptors—Common endocrine disruptors in the environment include phthalates found in plastics, PCBs, some pesticides, synthetic steroids in meat, and dichloro-diphenyl-trichloroethane (DDT). Biologists have long noted problems with sterility and malformation of sex organs in many animal species, which have been linked to the presence of these contaminants in the environment. It is important to note that not all estrogenically-active compounds are considered endocrine disruptors. For example, compounds such as isoflavones in soy and lignans from flaxseed are associated with health-promoting and estrogen-

balancing activities, and are considered "selective estrogen receptor modifiers" (SERMs), not endocrine disruptors.¹⁸

Toxic Metals—Toxic metals, including lead, mercury, cadmium, and arsenic, are ubiquitous in the environment and often have delayed effects because they accumulate in the body. For example, lead can be sequestered in the bone, replacing calcium, where it has a half-life of 62 years.¹⁹ Consequences of lead toxicity include DNA damage, depressed immune system function, anemia, hypertension, kidney disease, and increased tooth decay.

Food Additives, Preservatives, and Drugs—The greatest toxin exposure by far is through what we put in our mouths. Foods, drugs, and water all contain toxic substances that move through our gastric system to the intestines where they can be absorbed. Drugs enter our body from more sources than just those that we intend to consume. In fact, certain drugs—including growth hormones and antibacterials—are considered one of the main contaminants of foods.

TOXIC LOAD AND STORAGE OF TOXICANTS

Concern about the effects of low-level, long-term toxin exposure is now being evaluated due to the accumulating epidemiological evidence that low-dose exposure is associated with a myriad of diseases and conditions. It is becoming apparent that toxin exposures cannot be considered individually, because we are not exposed to individual toxins exclusively. Moreover, toxins can act in an additive manner if they exert their toxic effects through the same pathway(s). Even more concerning is the fact that many toxic substances are fat-soluble, so they can sequester in tissues and remain there for many years. In this way, toxins can continue to accumulate so that the body tissues are exposed to much higher doses than environmental concentrations would suggest are present.

HOW DOES THE BODY REMOVE TOXINS?

By far, the majority of toxins are lipid-soluble molecules. While water-soluble molecules are excreted through the urine, lipid-soluble molecules cannot directly enter into the urine and are instead attracted to the lipid in cell membranes. This attraction allows them to be transported inside of cells with ease, where they can sequester and exert their toxic effects.

In order to remove these diverse toxins, the body has a complex, integrated system designed to convert lipid-soluble toxins to water-soluble molecules, after which they can be directly excreted through renal or biliary routes. This system is called the detoxification or biotransformation system, and includes two steps: Phase I Bioactivation and Phase II Conjugation. First pass metabolism uses biotransformation reactions to convert lipid-soluble toxins to water-soluble molecules before they enter circulation. Sometimes the toxins are detoxified before they are even transported to the liver by the same biotransformation reactions in the intestinal tract. About 25% of the biotransformation activity in our bodies occurs in the intestinal mucosa, which makes it the second most active tissue in detoxification. All cells

have some detoxification capacity.

Phase I and Phase II biotransformation reactions occur in concert, working together to remove toxins. In brief, the detoxification system converts the lipid-soluble toxin to a water-soluble molecule by connecting (binding) the toxin to another molecule that is water-soluble (i.e., conjugation). This sounds like an easy, one-step process, but it is complicated by the fact that most toxins do not have a reactive site that will easily attach to the water-soluble moiety. Therefore, a reactive site must be made on the toxin before the water-soluble piece can be attached. This is accomplished by the Phase I enzymes.²⁰

Phase I Bioactivation

Phase I reactions are catalyzed by a number of different enzymes; the most significant family of which is the cytochrome P450 family, CYP450. The CYP450s have broad specificity and use the reduced form of nicotinamide adenosine dinucleotide (NADH) as a cofactor in converting oxygen to a hydroxyl group on the lipid-soluble toxicant. The result of this reaction is the generation of a reactive site on the transformed toxicant. This reactive hydroxyl site is very much like that of a reactive oxygen species (ROS), and can readily bind to other molecules, such as DNA and proteins. On occasion, the product from this part of the detoxification process becomes soluble in water after the addition of the hydroxyl group and can be directly excreted. This is the case with caffeine, which undergoes only Phase I activation before excretion. This direct, one-step excretion is not common, however, and most activated toxicants, or reactive intermediates, require conjugation with a larger, more water-soluble moiety to effectively alter their lipid characteristics.

Over 10 families of CYP450 enzymes have been identified in humans, and each of these contains several subfamilies. Many dietary ingredients support CYP450 reactions, including niacin, which is required for generation of NADH. In addition, the activation reaction often also generates ROS directly as a spin-off product. Dietary antioxidants can help protect tissue from damage that may occur by this reaction.

Phase II Conjugation

One of the consequences of Phase I activation is that the product, called the reactive intermediate, is quite often more reactive—and potentially more toxic—than the parent molecule. Therefore, it is important that this molecule be converted to a non-toxic, water-soluble molecule as soon as possible. Conjugation of the reactive intermediate to a water-soluble molecule is accomplished by the Phase II conjugation reactions, which include glucuronidation, sulfation, glutathione conjugation, amino acid conjugation, methylation, and acetylation.

These reactions not only require the water-soluble moiety that will be attached to the toxicant—such as sulfate in the case of sulfation or glucuronic acid in the case of glucuronidation—but also use a large amount of energy in the form of adenosine triphosphate (ATP). In addition to energy repletion, Phase II

reactions require an adequate, continually replenished amount of cofactors since these cofactors are attached to the toxin and then excreted. Several nutrients and phytonutrients support Phase II reactions.

The Role of Energy Production and Oxidative Stress in Toxicity

As can be seen by the above discussion, generation of ATP is vital for adequate biotransformation. Generation of adequate ATP requires healthy, nutrient-supported mitochondria. Unfortunately, many toxicants can inhibit mitochondrial function, which can lead to a decreased capacity to biotransform other toxins.²¹ For example, the toxin MPTP inhibits complex I of the respiratory chain and replication of mitochondrial DNA.²¹ Production of ROS is also a consequence of energy production, and excess presence of these damaging molecules, called oxidative stress, is associated with toxicity.²² Nutrients that support mitochondrial function include the essential cofactors for energy production: thiamin, riboflavin, niacin, pantothenic acid, and magnesium. In addition, nutrients that help protect the body from oxidative stress, such as vitamins C and E, zinc, selenium, and copper, are also beneficial.^{23,24}

Digestion and Excretion in Toxicity

Healthy digestion can have a profound effect on detoxification. Food intake is known to influence drug absorption by altering gastric emptying and intestinal transit, pH, and bile secretion.²⁵ Since drugs are models for how toxins enter the body, it is reasonable that toxins will be affected in similar ways. In particular, toxins that are conjugated in the intestinal tract and during first pass metabolism in the liver are primarily excreted via bile, which requires healthy fecal production. Dietary fiber supports healthy excretion—which is important for removing biotransformed toxins—and has been shown to bind some toxins directly, thereby providing a route for their removal before they can enter the body.²⁶ In addition, adequate intake of water is essential to maintaining healthy kidney function and promoting urinary excretion of toxins already in circulation.

In addition to support for excretion, overall nutrition provides support for biotransformation in many other ways. Adequate blood glucose levels are important for maintenance of glucuronidation cofactor generation. Interestingly, diabetes is one of the diseases associated with altered Phase I activities.

Support for energy production, as well as generation of new enzymes (protein production), is also vital during detoxification. Therefore, adequate intake of carbohydrates, energy-supportive fats, and high quality protein are essential for providing protective mechanisms against toxic damage.²⁷ Fats can be problematic, since many people consume too much of the wrong kind. Moreover, individuals undergoing toxic exposure may not efficiently absorb nutrients through the intestinal tract if they are also experiencing altered intestinal permeability. Therefore, provision of a highly bioavailable source of fats that can be used directly to support energy production is beneficial. The medium-

chain triglycerides (MCTs) are fats that fit this profile.²⁸ Interestingly, olive oil, in contrast to sunflower, corn, or fish oil, was found to be protective against chemically-induced fibrosis in rats,²⁹ suggesting that it may also be a good source of fat for a detoxification program.

BALANCE AND HEALTHY DETOXIFICATION

The depletion or insufficiency of any cofactor needed in the detoxification process is a significant factor in susceptibility to toxicity. Phase I prepares a toxin for conjugation by the Phase II system, where a water-soluble group is conjugated to the toxin, rendering it non-toxic and promoting its excretion. These two activities work in concert and thus must be balanced. In particular, Phase II activities must be able to keep up with the Phase I generation of reactive intermediates, or an imbalance in the production of reactive substances occurs. When Phase I generates a reactive intermediate that is not immediately conjugated and removed, it can act as a ROS and bind DNA, proteins, and RNA, causing irreversible damage to a cell.

There are many Phase II activities, and support for all of these activities is essential to achieving healthy, balanced, and complete detoxification. Many phytonutrients that are associated with protection from toxin damage (e.g., chemoprevention) can induce the genes for Phase II enzymes, which promotes production of the conjugating enzymes and results in increased Phase II activities. Phytonutrients that are particularly beneficial at inducing Phase II activities include ellagic acid (found in pomegranate and many berries), catechins from green tea and grapes, and the glucosinolates found in crucifers, such as watercress and broccoli.

As mentioned above, Phase I bioactivation is necessary to provide an active site for attachment of the water-soluble group; however, Phase I bioactivation, by its name, "activates" the toxin to a more reactive compound. This double-edged sword means that some activity is essential, but that too much activity can result in the generation of these reactive intermediates too quickly for Phase II to neutralize the reactive intermediates into non-toxic, excretable molecules.

Some phytonutrients support Phase I activity, such as indole-3-carbinol from broccoli, which provides modest support for the CYP1A enzymes. Over-activation of Phase I is a concern, however, and is associated with high, continuous levels of toxins that are known to be particularly effective at inducing Phase I activities. For example, smoking, heterocyclic amines formed on charbroiled beef, and dioxin have all been shown to over-induce CYP1A enzymes, and even low doses of these compounds induce CYP1A much more effectively than the modest support provided by indole-3-carbinol.³⁰⁻³²

BIFUNCTIONAL SUPPORT FOR DETOXIFICATION: ACHIEVING BALANCE

As can be concluded from its name, a compound that provides bifunctional support for detoxification is one that supports optimal activity of both Phase I and Phase II enzyme systems. In the

case of the Phase II enzymes, healthy activity is associated with the induction of these enzymes, thereby providing for higher activity, as well as promoting the generation of their respective cofactors. Since there are many Phase II enzymes, an effective bifunctional modulator will promote several of these activities at the same time. Bifunctional modulators include ellagic acid, catechins, and glucosinolates, some of which are subsequently described in more detail.

Support for healthy Phase I activity requires managing a balanced level of Phase I enzymes. Bifunctional modulators are often capable of inhibiting the Phase I enzymes when they are present at high levels, without inhibiting their entire production. For example, while ellagic acid can inhibit the induction of CYP1A by the mutagen benzo[a]pyrene, possibly by binding directly to the mutagen itself, it does not directly inhibit the constitutive, necessary activity of CYP1A.³³

Many of the bifunctional modulators also promote optimal balance via their ability to act as antioxidants and bind reactive intermediates and the off-shoot ROS from Phase I reactions. Therefore, bifunctional modulators support optimal detoxification balance by modulating Phase I activities, inducing several Phase II activities, and minimizing damage caused by reactive intermediates. These activities of bifunctional modulators are one reason for the association between diets high in fruits and vegetables and reduced susceptibilities to diseases such as cancer, since fruits and vegetables are sources for many bifunctional modulators.

Table 2. Clinical considerations for programs to support biotransformation

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| <ul style="list-style-type: none">• <i>Decrease total load and exposure to toxicants</i>• <i>Provide complete, balanced support for biotransformation and conjugation reactions</i>• <i>Support healthy digestion and excretion</i>• <i>Provide support for energy production during detoxification programs</i>• <i>Support endogenous antioxidant mechanisms for biotransformation and heavy metal detoxification</i>• <i>Provide methyl donors to promote methylation pathways</i> |
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WATER FASTING AND DETOXIFICATION

Water fasting can be detrimental to the body's ability to support detoxification. Fasting and alcohol both over-induce the CYP450E family of enzymes, leading to unbalanced detoxification.²⁷ In addition, fasting results in catabolism of muscle over fat, which is not beneficial to health. Fasting also results in a decreased intake of necessary cofactors, which leads to a decrease in sulfation, glutathione, and glucuronidation conjugation cofactors. In animal models, fasting causes decreased glutathione levels and enhanced susceptibility to toxicity after toxin exposure.³⁴ Thus, the Phase II reactions are decreased and reactive intermediates remain in the body.

NUTRITIONAL SUPPORT FOR BIOTRANSFORMATION

Provision of macronutrients is extremely important in a detoxification program. Fasting has many adverse health effects, including decreased energy production, catabolism of lean tissue, over-induction of some Phase I activities with a concomitant increase in oxidative stress, and decreased levels of Phase II cofactors. Detoxification is an energy-requiring process that puts a metabolic burden on the body. Instead of decreasing nutrient support, a focused, high-impact source of nutrients is essential. However, this source of nutrients should have a low allergy potential in order to decrease the body's burden of inflammation and potential allergen toxins. An overall protein, carbohydrate, fiber, and fat nutrient base is important to maintaining healthy metabolism during a detoxification program.

Benefits of Fiber

Fiber can benefit a detoxification program in many ways. Fiber supports intestinal mucosal cell barriers and colonic health, which decrease toxic burden on the body and provide a first line of defense to the system. Fiber promotes removal of the conjugated toxins that are excreted via bile and may decrease the absorption of some toxins. Most notably, some fibers have been shown to directly bind toxins, thereby removing toxins before they can interact with the body and cause damage at any level. Fibers in rice bran have been shown to preferentially bind mutagens over wheat, corn, barley, or oat fibers.²⁶

High Quality Protein

In addition to nutrition and fiber, a high quality protein, which provides methionine and cysteine in a highly absorbable form, is also of benefit to Phase II conjugation since these amino acids can be used to generate the sulfation and glutathione cofactors. A high quality protein may also benefit those with toxic mercury burdens, since mercury exposure is associated with the depletion of specific amino acids that are precursors to neurotransmitters.³⁵ Methionine is also a component of S-adenosylmethione (SAM), and is required for methylation.

Sulfation Support with N-Acetylcysteine (NAC) and Sodium Sulfate

Sulfate donors such as NAC and sodium sulfate are extremely important in a detoxification program. Oral NAC has been shown to increase the level of glutathione produced in the body. Glutathione is not only the cofactor for glutathione conjugation, but is also a major route for detoxification of heavy metals because of the ability of metals to bind to the sulfur in glutathione.¹⁹ Due to its support of glutathione production, cysteine—a principle factor in combating metal toxicity—becomes depleted in the presence of a toxic load of metals.³⁵ Provision of sulfate cofactors with cysteine (provided as NAC) at 200 to 500 mg per day is suggested to support sulfation cofactor status and glutathione production.

Support for Methylation with Vitamin B₁₂, Folate, Methionine, and Choline

The methyl donors choline, methionine, and folate are called “labile methyls” because they are used during metabolism and therefore require replenishment. Interestingly, dietary deficiency of labile methyls is the only nutrient deficiency known to be carcinogenic in itself.³⁶ CYP1A enzymes have also been shown to be adversely induced in animals deficient of dietary labile methyls.³⁷ The role of these dietary labile methyls in health promotion is due, in part, to their important role in supporting balanced biotransformation by providing cofactors for Phase II conjugation reactions. Vitamin B₁₂ and folate provide support for the homocysteine cycle, which allows for remethylation of SAM. The biologically-active, natural form of folate is 5-methyl-tetrahydrofolate.³⁸

Provision of choline is particularly important. Because choline can be synthesized endogenously from methionine, it has been assumed that dietary sources are not required; however, much experimental data has challenged this assumption and shown that dietary sources of choline are essential. For example, choline deficiency has been shown to result in fatty liver and other liver diseases.^{39,40} Recently, the Food and Nutrition Board of the National Academy of Sciences has designated choline as an essential nutrient.⁴¹

Ellagic Acid from Pomegranate

In animal studies, ellagic acid has been shown to significantly reduce tumor incidence in chemically-induced lung and liver tumorigenesis, protect from carbon tetrachloride liver damage, enhance glutathione production, and decrease lipid peroxidation.⁴²⁻⁴⁴ Ellagic acid may also act directly against some metal toxicity (e.g., nickel) by chelating the metal and promoting its excretion, thereby providing protection from liver damage and oxidative stress.⁴⁵

Ellagic acid is a bifunctional modulator that promotes balanced detoxification via several mechanisms: 1) it induces production of glutathione-S-transferases and other Phase II activities at the gene level, 2) it modulates CYP1A activities so that these enzymes are not over-induced, and 3) it binds directly to some toxic substances, such as benzo[a]pyrene-related compounds from pollution, rendering them non-toxic and promoting their excretion.^{33,46} Ellagic acid can also bind directly to DNA, protecting the DNA from carcinogenic mutations.³³

Catechins from Green Tea

A large body of literature studying the health benefits of catechins is available. These data suggest that catechins—a class of flavonoids found in high concentrations in green tea extracts—are bifunctional modulators that provide many beneficial activities, including induction of Phase II glucuronidation and glutathione conjugation enzymes. Prospective animal experiments have shown that green tea catechins possess anticarcinogenic and antimutagenic potential.^{47,48} These compounds are

strong antioxidants, and have also been shown to directly bind many toxic substances.

Epidemiological data suggest that catechins may be protective against many types of cancer in humans, while other data suggest that consumption of catechin-containing beverages, such as tea, is inversely associated with Parkinson's disease.^{48,49} These activities have prompted the National Cancer Institute to investigate the potential of green tea extract containing catechins as a chemotherapeutic agent.⁵⁰

Interestingly, catechins have been shown to induce some Phase I activities; however, more recent data suggests that catechins selectively inhibit some Phase I activities as well.⁵¹⁻⁵³ A recent cell culture study showed that catechins inhibited the over-induction of Phase I activities by a toxic substance, but were able to moderately induce Phase I activity themselves when the toxin was not present.⁵⁴ This ability to modify levels of Phase I, promoting a moderate induction and inhibiting an over-induction, may account for some of the beneficial activities of catechins. In addition, this study showed that a full spectrum of catechins was necessary for this effect, and that different catechin molecules provide differential CYP450 antagonist and agonist functions.

The strong antioxidant activity of catechins also enables these compounds to bind to the reactive intermediates produced by Phase I that are not immediately conjugated by a Phase II reaction—another reason this class of flavonoids may promote balanced detoxification. One cup of tea contains between 100 to 200 mg of catechins,⁴⁷ which is suggested to account for at least 90% of the observed beneficial effects of green tea.⁵⁴ Green tea catechins have also been shown to promote optimal intestinal microflora and pH and support healthy bowel function—three qualities that further support optimal detoxification.⁵⁵

Glucosinolates from Watercress

Watercress (*Nasturtium officinale*), like other crucifers such as broccoli sprouts, contains high levels of glucosinolates. Glucosinolates are precursors to several bioactive isothiocyanates, including phenylethyl isothiocyanate (PEITC). In humans, research has shown that glucosinolates can be effectively converted to PEITC by gut flora after consumption of watercress.^{56,57}

Watercress itself also contains particularly high levels of PEITC. PEITC from watercress has been shown to inhibit chemically-induced lung and colon carcinogenesis in rats and promote excretion of carcinogens in humans.⁵⁸⁻⁶⁰ The proposed mechanisms of these activities include inhibition of select Phase I activities with concomitant induction of Phase II glucuronosyl transferases and glutathione S-transferases.^{56,61,62} This bifunctional activity of watercress has been proposed as one of the reasons why crucifers have been shown to be chemoprotective in epidemiological data.⁶³

Silymarin from Milk Thistle

Several recent reviews have discussed the traditional use of silymarin as a hepatoprotectant, while recent studies show more specific liver-protectant functions of silymarin.⁶⁴⁻⁶⁶ For example, silymarin, at around 400 mg per day, has been shown to improve indices of liver function in patients with various etiologies of liver disease—including those exposed to toxic levels of industrial phenolics, such as toluene.⁶⁵ Silymarin has also been shown to increase serum glutathione and glutathione peroxidase in patients with liver disease and induce glutathione transferase activity in animals.^{65,67} Silymarin glycosides possess strong antioxidant activity, and therefore silymarin may act as a bifunctional modulator.^{66,68}

Artichoke

Traditional medicine has long used artichoke extract (*Cynara scolymus*) as a hepatoprotectant, and several bioactives have been identified, including chlorogenic acid, cynarin, caffeic acid, and luteolin.^{69,70} Consumption of encapsulated artichoke extract has been shown to increase the absorption of these bioactives in humans, resulting in the production of beneficial metabolites such as ferulic acid.⁷¹ Ferulic acid, chlorogenic acid, and cynarin provide strong antioxidant protection, which may account for some of their health-promoting activities.^{69,70} Moreover, in cultured liver cells, artichoke extract not only provided antioxidant protection against a toxic chemically-induced insult, but also decreased the loss of cellular glutathione reserves.⁷²

SUMMARY

Optimizing the body's ability to manage and excrete toxins is essential for optimal health. Several recent reviews have discussed targeted, nutrient-based detoxification intervention therapies for patients with CFS, FM, MCS, and Parkinson's disease, as well as in apparently healthy individuals.⁷³⁻⁷⁷

Decreasing exposure to toxins is extremely important in all programs. Airborne toxins are of particular concern since, by entering through nasal passages, they can bypass the blood-brain barrier and travel through the olfactory nerve directly to the brain. However, minimizing toxin exposure is only one part of a successful strategy to decrease susceptibility to toxicity-related conditions. Low-allergy-potential, targeted nutrition that provides the full spectrum of cofactor precursors, support for excretion, and bifunctional inducers for balanced Phase I and Phase II biotransformation may promote balanced detoxification and optimal health throughout life.

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The Role of Detoxification in the Prevention of Chronic Degenerative Diseases: A Summary

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Low-level, long-term exposure to toxins such as heavy metals (e.g., lead, mercury, arsenic, cadmium), pesticides, industrial compounds, and pollutants is associated with chronic fatigue syndrome (CFS), multiple chemical sensitivities (MCS), fibromyalgia (FM), neurodegenerative diseases such as Parkinson's, atherosclerosis, and many types of cancers.^{8,12-14} Common signs and symptoms of environmental toxicity include acne, rashes, headaches, aches and pains, fatigue, muscle weakness, tinnitus, fertility problems, memory loss, and chronic immune system depression.

Toxins can remain in the body for many years; therefore, we are exposed to much higher toxin doses than present environmental concentrations suggest. Research suggests we all maintain toxin contamination within our bodies on a regular basis due to this lifetime of exposure.

HOW DOES THE BODY REMOVE TOXIC SUBSTANCES?

An individual's ability to remove—or detoxify—toxins is a primary factor in susceptibility to toxin-related conditions.²⁻⁶ In order to remove (excrete) the multitude of diverse toxins, the body has a complex system that converts them into non-toxic molecules for removal. This complex system occurs in two phases—Phase I and Phase II—that together convert (biotransform) a toxic molecule into a non-toxic molecule that can be easily excreted. The majority of detoxification occurs in the liver; however, all tissues have some ability to detoxify, including the intestines, skin, and lungs.

In Phase I, a functional group is added to the toxic molecule producing an intermediate that needs to be further transformed. Phase II detoxification involves a process called conjugation, in which various enzymes in the liver attach protective compounds to the intermediate, making it less harmful and more readily excretable. Because the products of Phase I can be highly reactive and more harmful than the original compound, achieving and maintaining a balance between the Phase I and Phase II processes is critical. Furthermore, a significant side effect of all this metabolic activity is the production of reactive oxygen species (ROS) as the toxins are transformed, resulting in oxidative stress. Nutrients that help protect from oxidative stress include vitamins C and E, zinc, selenium, and copper.^{23,24}

ACHIEVING BALANCED DETOXIFICATION

Optimal detoxification requires that both Phase I and Phase II pathways function optimally and in balance with each other. Bifunctional modulators are phytonutrients that support balanced detoxification by modulating Phase I and promoting Phase II. This minimizes damage by ROS. Fruits and vegetables contain many bifunctional modulators, which is one reason these foods are associated with reduced susceptibilities to cancer and degenerative diseases.

NUTRITIONAL SUPPORT FOR DETOXIFICATION

Detoxification is an energy-requiring process that puts a metabolic burden on the body. Therefore, water or juice fasts are not beneficial because they deplete the body of the essential nutrients required for healthy detoxification. These fasts can have many adverse health effects, including decreased energy production, breakdown of lean tissue instead of fat, increased oxidative stress, and unbalanced detoxification.²⁷

Instead of decreasing nutrient support, a focused, high-impact, low-allergy-potential source of macronutrients should be provided.

High quality protein provides methionine and cysteine, which are beneficial to Phase II and may help with toxic metal burdens.³⁵ Medium chain triglycerides (MCTs) support energy production,²⁸ and olive oil may protect against chemically-induced liver damage.²⁹ Fiber supports fecal excretion of toxins and the integrity of the intestinal barrier, which decreases toxic burden. In particular, rice bran can directly bind some toxins, thereby removing them before they can enter the body and cause damage.²⁶

Nutrients that support energy production include vitamin B₁ (thiamin), vitamin B₂ (riboflavin), vitamin B₃ (niacin), vitamin B₅ (pantothenic acid), and magnesium. In addition, the following nutrients and phytonutrients provide targeted support for optimal detoxification:

N-Acetylcysteine and Sodium Sulfate promote generation of glutathione, which is a major route for detoxification of heavy metals, and supports Phase II sulfation.^{19,35}

Vitamin B₁₂, Folate, Methionine, and Choline promote balanced detoxification by supporting Phase II methylation and healthy homocysteine recycling. Choline deficiency is causative for liver disease, and thus choline is a newly-designated essential nutrient.³⁹⁻⁴¹ The biologically-active, natural form of folate is 5-methyltetrahydrofolate.³⁸

Ellagic Acid from pomegranate significantly reduces tumors in animals with chemically-induced cancers, protects from toxin liver damage, enhances glutathione production, decreases lipid peroxidation, and binds and promotes the excretion of some metals.⁴²⁻⁴⁵ Ellagic acid is a bifunctional modulator that can bind some toxins directly, rendering them non-toxic, and can directly bind and protect DNA.^{33,46}

Catechins from green tea are bifunctional modulators that are strong antioxidants, possessing anticarcinogenic and antimutagenic potential.^{47,48} Catechins are associated with lower incidence of Parkinson's disease.^{48,49} The National Cancer Institute is currently investigating the chemotherapeutic potential of green tea catechins.⁵⁰ Catechins also promote healthy gastrointestinal function.⁵⁵

Watercress (Nasturtium officinale) contains high levels of glucosinolates, which are precursors to several bioactives that can inhibit chemically-induced cancers in animals and promote excretion of carcinogens in humans.⁵⁶⁻⁶⁰ The bifunctional activity of watercress is one of the proposed mechanisms for its chemoprotective effect.^{56,61-63}

Silymarin from milk thistle is a well-known liver-protectant that may improve liver function in patients with liver disease and toxicity.⁶⁴⁻⁶⁶ Silymarin increases glutathione and is a strong antioxidant.⁶⁵⁻⁶⁸

Artichoke (Cynara scolymus) is also a liver-protectant with a long history of traditional use that provides strong antioxidant protection and may decrease the loss of glutathione after toxic exposure.⁶⁹⁻⁷²

SUMMARY

Minimizing exposure to toxins is only one part of a beneficial detoxification program. Low-allergy-potential, targeted nutrition providing the full spectrum of Phase II supportive cofactors, bifunctional modulators for balanced detoxification, and support for energy production and excretion may optimize balanced detoxification and promote optimal health throughout life.