Botanicals and Nutrients for Cellular Redox Homeostasis, Detoxification & Cellular Integrity

Co-authored by Donald R. Yance, RH (AHG), CN
and Suzanne E. Sky, L.Ac., MTOM

Discussion

HEPATIC DETOXIFICATION AND CELLULAR HEALTH

People of all ages are affected by the presence of xenobiotics and other endocrine disruptors in our environment and food supply. These compounds interfere with hormone balance, disrupt cellular dynamics and disturb overall health.[1]

Metabolism of hormones, xenobiotics, endogenous and exogenous compounds are carried out in the liver by enzymatic activity. Natural compounds can enhance hepatic detoxification integrity naturally by supporting both phase I and phase II liver detoxification pathways through enhancing the enzyme activity that drives the detoxification process.

Phase I enzymes belong to the large family of the cytochrome p450 enzymes. Phase I biochemical transformations can increase the toxicity and activity of compounds. Metabolites catalyzed by the cytochrome p450 enzymes are converted into intermediates that are often highly reactive and can bind to vital macromolecules such as DNA, RNA and proteins.[2]

Phase II detoxification involves the conjugation pathways. This process inactivates potentially harmful compounds, increases their solubility and enhances their excretion through the body's channels of elimination. Phase II detoxification enzymes help neutralize harmful compounds and free radicals before they can damage cellular DNA.[3]

Glutathione (gamma-glutamyl-cysteinyl-glycine or GSH), the most abundant low-molecular weight thiol, along with glutathione S-transferase are the primary redox agents that influence the main enzyme pathway of phase II. Glutathione deficiency is found to contribute to oxidative stress.[4]

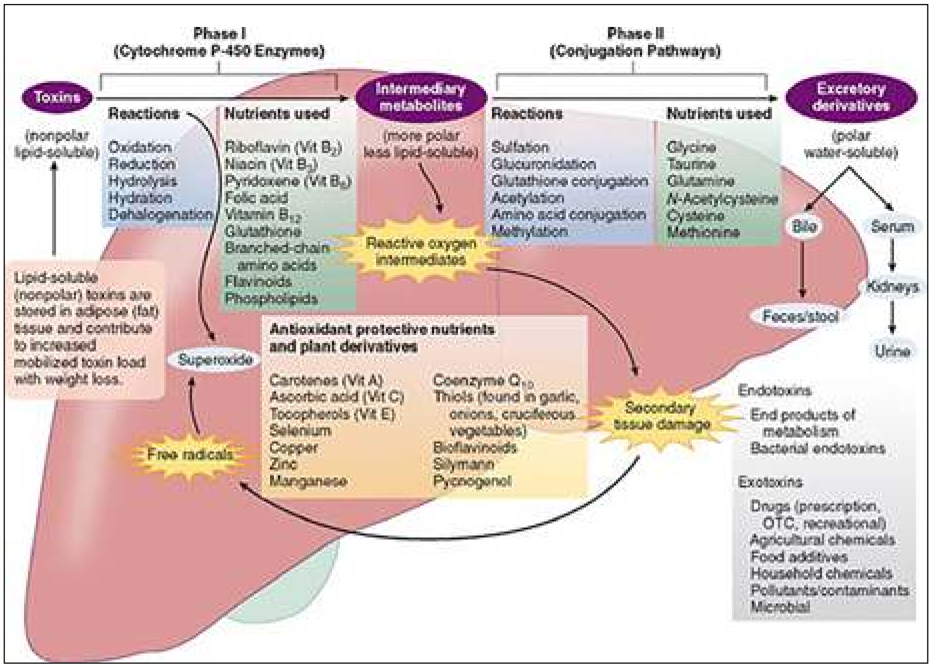
For optimal detoxification and transformation, phase I and phase II activities need to work together in a balanced manner. This is effectively achieved with the botanicals and nutrients featured in this paper.

CELLULAR REDOX HOMEOSTASIS

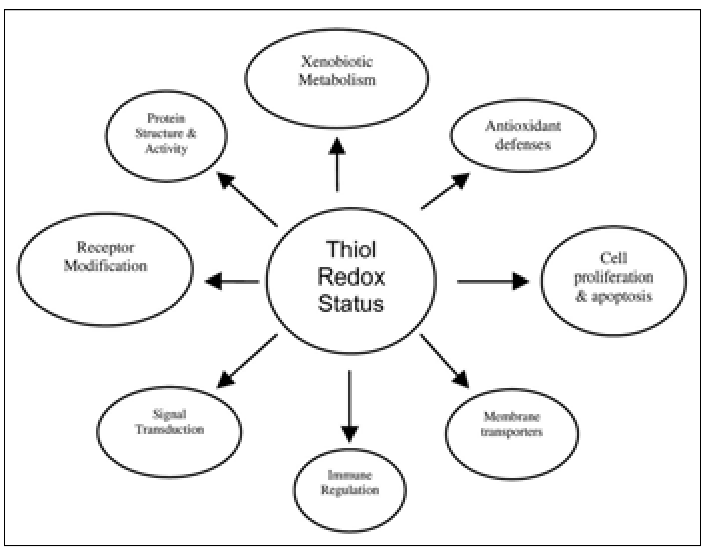
Oxidative stress is widely recognized as a significant factor in the etiology of many diseases including degenerative and chronic conditions.[5] Regulation of the balance between oxidation and reduction influences cellular function, DNA integrity and signal transduction of gene expression. Many pathologies are correlated with dysfunction of the redox state at the cellular level.[5,6]

Cellular health and function depends on redox homeostasis. Homeostatic balance is maintained at the cellular level in favor of a reductive environment. Biological endogenous compounds continuously sense and respond to changes in redox balance working to restore healthy conditions of homeostasis at the cellular level. These endogenous compounds include superoxide dismutase, catalase and other antioxidant (AO) enzymes.[5] When the balance shifts from a reductive to an oxidative environment, changes in cell-signaling cascades occur. Cellular signaling pathways contain redox-sensitive thiol sites that are sensitive to changes in cellular-redox homeostasis.

Increased oxidative stress initiates signaling of specific AO enzymes that enhance recycling of the direct antioxidants. This paper demonstrates how specific nutrients and botanicals can play a vital role in enhancing these processes of detoxification and redox homeostasis.



Nutrient and herbal supplements to support detoxification. Textbook of Functional Medicine. The Institute for Functional Medicine, 2005, p 278, posted on www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/preventive-medicine/integrative-medicine/



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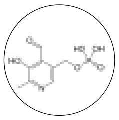


B Vitamins: B6, Folate and B12

B-complex vitamins are co-factors in enzyme reactions that facilitate numerous biochemical responses. Vitamins B6, folate and B12 play a key role in metabolic (energy production) pathways at the cellular level and in the hepatic methylation system. Folate, B12, and particularly B6 function as critical cofactors for enzymes involved with estrogen conjugation and methylation.

B6 is found to help reduce the over-expression of estrogen.[7] Deficiency of vitamin B6 impairs the metabolism of polyunsaturated fatty acids from ALA (alpha-linolenic acid) to EPA and DHA, and especially reduces production of DHA.[8] Many human enzyme systems that involve protein metabolism (catabolism/anabolism) or enzyme production require B6 for proper function.[9]

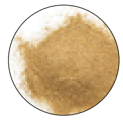
B6 is involved with over 100 physiological processes including conversion of homocysteine to cysteine and the regeneration of a form of folic acid that is involved in DNA synthesis.[10] Pyridoxal 5'-phosphate (P5P) is the biologically active coenzyme form of B6 and plays an important role in DNA synthesis and repair.[11] The P5P form of B6 is essential for DNA synthesis and for methylation processes. P5P can be depleted by toxic compounds. Since B6 is essential for detoxification processes in the liver and cells a deficiency of B6 hampers healthy function of liver detoxification pathways.

Folic acid and B12 are essential for many biological functions including nucleic acid synthesis and methylation reactions. B12 is especially important to help prevent blood deficiency anemia, neurological diseases, neuropathies, depression, and fatigue. It should be combined with folic acid and other methyl donors for those with methylation mutations and/or elevated homocysteine. Plasma homocysteine is considered a useful marker to evaluate patients with suspected vitamin B12 or folate deficiency.[12]

Deficiency of folate increases SAMe (S-adenosylmehtionine), which can lead to DNA hypomethylation. Deficiency can also cause an error in DNA synthesis resulting in chromosome breaks.[13] B6, folic acid, and B12 are all beneficial for homocysteine levels, which is important for nutritional and cardiovascular health.[14-16]

Research suggests that folic acid and B12 should be supplemented together so as not to create a deficiency of one in relation to the other.[17] Folic acid occurs only rarely in foods; it is the metabolically-active form, folate, that is found in the human body and in foods. Folate cofactors are involved in nucleic acid synthesis and in the methylation process.[18]

The preferred form of folate is a stable, water-soluble version of the "L" form of 5-MTHF (5-methyltetrahydrofolate). This is the natural isomer that is the active circulating form of folate in the body and also one of the forms that occurs naturally in food.



Selenium Yeast

Selenium, an essential trace mineral, is usually found in grains, fish, and liver. Selenium comprises a key component of selenoproteins such as glutathione peroxidase. As such, it is exerts antioxidant properties and helps prevent formation of free radicals. Since it reduces reactive oxygen metabolites, glutathione peroxidase helps maintain cell membrane integrity by preventing oxidative damage to lipids, lipoproteins and DNA.[19-25]

Selenium inhibits lipid peroxidation and is found to decrease the binding of various chemical compounds to DNA. This process occurs in liver and kidney membranes where enzymes function as metabolizers of drugs. Over 25 selenoproteins are known to exist in human biochemistry throughout the body. Selenium is also a cofactor in various metabolic pathways and can act to modulate cell signal transduction.[19-25]

Brassica Family Compounds: *Broccoli Seed Extract, Cabbage Sprouts, Diindolylmethane and Wasabi Rhizome*

Vast quantities of research demonstrate the significant health benefits of plants used as food and medicine.[26] Research establishes that cruciferous vegetables possess many powerful, protective, and modulatory attributes. The Brassica genus of plants is known as the mustard family or as cruciferous vegetables. Members of the Brassica family include broccoli, brussel sprouts, cauliflower, cabbage, bok choy, mustard greens, watercress, turnips, horseradish, and wasabi.

Cruciferous vegetables are a source of important phytonutrients, essential nutrients and vitamins. A huge body of research shows that consumption of cruciferous vegetables is associated with a significantly lower risk of many degenerative and chronic diseases.[5] Brassica vegetables are found to decrease oxidative stress, independent of supplementation with vitamins, minerals or fiber.[5]

Brassica family vegetables are very rich in compounds known as glucosinolates that are responsible for their pungent and strong taste.[2] Glucosinolates are metabolized by the plant

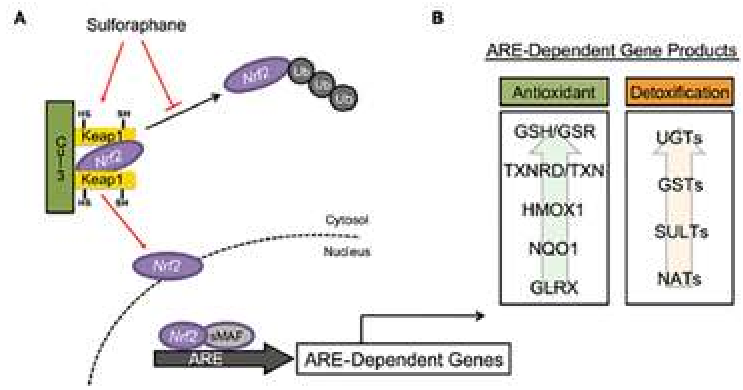


FIGURE 2 | Mechanism of ARE-mediated detoxifying and antioxidant enzyme induction by sulforaphane. (A) Under basal conditions, the transcription factor NRF2 is sequestered within the cytosol by the repressor proteins Keap1 and cullin 3 (CUL3), presenting it for proteosomal degradation via ubiquitination. Sulforaphane, through modification of the highly redox-sensitive cysteine residues of KEAP1, facilitates the dissociation of the KEAP1/CUL3/NRF2 complex, releasing NRF2, which translocates into the nucleus. Once within the nucleus, NRF2 heterodimerically pairs with small Maf transcription factors binding to antioxidant response elements (ARE) contained within the promoter regions of many enzymes, initiating their transcription. **(B)** ARE-mediated gene products are typically classified as either detoxification or antioxidant enzymes. (Adapted and modified from Dinkova-Kostova and Talalay, 2008).

Boddupalli S, Mein JR, et al. *Induction of phase 2 antioxidant enzymes by broccoli sulforaphane: perspectives in maintaining the antioxidant activity of vitamins A, C, and E.* Frontiers in Genetics. January 2012. Volume 3. Article 7:1-15. doi: 10.3389/fgene.2012.00007

enzyme myrosinase and by the gastrointestinal microflora to the biologically active isothiocyanate (ITC) form, to indole-3-carbinol (I3C) and other protective, beneficial compounds.[27] Cabbage is rich in the ITC known as phenylethyl and broccoli seeds are especially rich in the ITC sulforaphane.[28]

Isothiocyanates (ITCs)

ITCs are highly studied for their widespread activity and ability to modulate health through a wide variety of mechanisms. The many ITC compounds influence cellular, redox, and hepatic processes. These powerful phytochemicals demonstrate cyto-protective qualities. ITCs and a diet high in cruciferous vegetables are found to protect against oxidative stress, cellular and DNA damage, regulate gene transcription, and modulate redox homeostasis. They influence the TCA (Krebs) cycle and modulate cellular metabolic processes. Brassica compounds influence enzyme response in phase I and phase II detoxification pathways and help modulate healthy estrogen ratios. ITCs are found to benefit health and prevent multiple degenerative conditions.[2,5,27-36]

ITCs, such as sulforaphane (SFN), act as indirect antioxidants, which means they exert an antioxidative influence indirectly through inducing expression of antioxidant (AO) enzymes and hepatic phase II detoxification enzymes.[5,30] These enzymes regulate glutathione metabolism and directly quench reactive oxygen species. AO enzymes include glutathione reductase, glutathione peroxidase, and others, which researchers state act as primary defense mechanisms against many degenerative and chronic disease conditions.[5]

Many AO enzymes are redox cycling enzymes that maintain redox homeostasis through mediating the activity of free radical scavengers such as vitamins A, C, E, and glutathione. SFN and other ITCs benefit cellular redox balance through their ability to modulate the recycling and maintenance of many free radical scavengers.

SFN induces AO enzymes through specific metabolic pathways involving transcription factors. This elicits response of cyto-protective genes and facilitates cellular response to stress.[5,27]

ITCs enhance hepatic detoxification pathways and are found to be powerful modulators of xenobiotic-metabolizing enzymes.[28,31,32] ITCs can inhibit metabolic activation of problematic compounds in the phase I cytochrome p450 enzymes' pathway. SFN is found to significantly downregulate cytochrome p450 expression.[36]

Phase II detoxification enzymes act as a defense mechanism possessing broad antioxidant activity.[32] Compounds found in the Brassica family, particularly the ITCs, including SFN, are potent inducers of phase II compounds.[28,31,32] ITCs induce many phase II conjugating enzyme systems including glutathione S-transferases, reportedly through influencing nuclear transcription.[27] Cruciferous vegetable intake is found to significantly reduce oxidative stress and to suppress mutagenic activity.[27] ITCs influence estrogen metabolism, enhancing metabolites with lower estrogenic activity.[27,33]

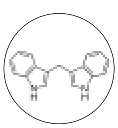
Phase II enzymes play a vital role in protecting cells from DNA damage by reactive oxygen species and other harmful

Mechanisms through which ITCs modulate homeostasis:

- enhance enzyme activity
- modulate gene health
- facilitate beneficial estrogen ratios
- modulate redox homeostasis
- act as indirect antioxidants
- are cyto-protective
- induce antioxidant responses in hepatic detoxification and antioxidant gene expression
- regulate gene transcription
- influence the TCA (Krebs) cycle
- balance metabolic processes at the cellular level
- are epigenetic modulators

compounds.[31] A specific sequence of DNA known as antioxidant response element (ARE) is contained in the genes for many of the phase II enzymes. One way that ITCs increase phase II enzyme activity is through increasing transcription of ARE-containing genes.[31]

ITCs and I3C are found to be cyto-protective through induction of the phase I and II detoxification pathways. They are considered to be epigenetic modulators because of their ability to modulate cell signaling.[34] ITCs are found to induce apoptosis.[27] ITCs, including SFN, are found to induce p53-independent apoptosis and to modulate protein expression.[35] ITCs are found to modulate cell-signaling pathways and cell cycle perturbations and to promote apoptosis. They also modulate signaling mediators including NFkB.[2,27]



Diindolylmethane (DIM)

DIM is the bioactive form of indole-3-carbinol (I3C), a compound found naturally in cruciferous vegetables. DIM is valued for its ability to support healthy estrogen metabolism through modulating hepatic clearance in the phase I and II pathways. DIM promotes healthy estrogen metabolism by preventing the stronger, more stimulating estrogens from binding to receptors. This shifts metabolism to favor the beneficial forms of estrogen.[37-39]

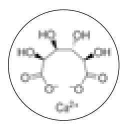
I3C is shown to induce apoptosis and to inhibit activation of various transcription factors including NFkB. It suppresses free radical production, and is found to be hepato-protective.[40,41] I3C and DIM upregulate expression of phase 1 and phase II enzymes. These compounds also regulate many genes that control cellular processes including cell cycle and signal transduction.[41]

Hormonal homeostasis, including a beneficial ratio of estrogens and their metabolites, influences the health of both men and women. The cruciferous compounds I3C and DIM are found to shift the metabolism of the primary estrogen, estradiol (one of the most bioactive forms of estrogen) to a more beneficial pathway. These compounds are found to decrease the production of unhealthy metabolites of estrogen and to modulate healthy estrogen metabolism.[31,42]

Wasabi Rhizome (*Wasabia japonica*)

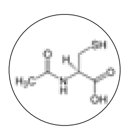
The Wasabi plant, native to Japan, is traditionally found growing in or near cold mountain streams. Cultivated in Japan since around the 10th century, Wasabi is a member of the Brassica family. Wasabi is a highly-prized culinary ingredient in Japan. Unfortunately, most of the Wasabi paste served in North American restaurants is an imitation product combining horseradish, Chinese mustard and food coloring. True Wasabi rhizome has a fiery, hot flavor that quickly dissipates, leaving a lingering, sweet taste and no burning sensation.[43]

Wasabi contains a dozen or more ITCs including a number of unique ones. The ITC from Wasabi known as 6-Methylthiohexyl isothiocyanate (6-MTITC) is found to suppress COX-2 expression and to exert cyto-protective effects.[44,45]



Calcium-D-Glucarate

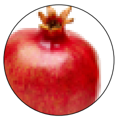
Calcium-D-glucarate (CDG) is the calcium salt of D-glucaric acid, which is produced naturally in small amounts in all mammals. Glucaric acid is found in many fruits and vegetables especially oranges, apples, grapefruit, and cruciferous vegetables. CDG is found to inhibit the enzyme beta-glucuronidase, produced by colonic microflora, which is involved in phase II liver detoxification. Elevated beta-glucuronidase activity is associated with risk factors for various health conditions.[46] CDG influences regulation of estrogen metabolism through its role in the phase II liver pathways. CDG enhances glucuronidation and the excretion of potentially harmful compounds during this process.[46,47]



N-Acetyl-L-Cysteine

N-acetyl-L-cysteine (NAC) is a sulfur-containing amino acid. It exerts antioxidant activity and also replenishes levels of the body's natural antioxidant glutathione. Glutathione decreases lipid peroxidation of cellular membranes and calms oxidative stress.

NAC is a cofactor of glutathione conjugation and supports detoxification of heavy metals. The amino acid cysteine becomes depleted in the presence of a toxic load of metals.[48] NAC, a thiol-containing compound, plays a role in modulating redox signaling.[49] Optimal cellular levels of glutathione enhances cellular function and contributes to healthy redox homeostasis. NAC supports glutathione status.[6]



Ellagic Acid from Pomegranate (*Punica granatum*)

Pomegranate is one of the oldest cultivated fruits, long used for food and medicinal purposes. The word pomegranate comes from the Latin meaning "fruit of many seeds".[50] In Ayurvedic medicine, pomegranate is considered a complete pharmacy in itself.

Pomegranate rind is high in polyphenol compounds and is particularly known for its ellagic acid content.[51,52] Ellagic acid isolate is known to exert antioxidant properties and decrease lipid peroxidation.[52,53] In animal studies, ellagic acid is found to increase activity and expression of antioxidant enzymes and to downregulate activation of NFkB.[54]

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu.com.

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