NUT040 1/97 13M
CLINICAL NUTRITION INSIGHTS

Vol. 5, No. 2

Phytonutrients & Detoxification

BY DR. MARK PERCIVAL

ABSTRACT: *The body's ability to rid itself of toxic substances is largely dependent upon the liver. Overexposure to environmental toxins in the air and in our diet can put excessive strain on the liver's detoxification systems and can rob us of our health. Detoxification in the liver occurs in two general phases: Phase I and Phase II. Depending upon the availability of many critical nutrients, the activity of either phase may be reduced or enhanced. Adequate nutrition helps to insure proper functioning of both phases of detoxification. Scientific research has revealed several compounds present in plant foods that help support the detoxification of toxic substances and are associated with a reduced risk of cancer. Compounds present in cruciferous vegetables, Allium species (garlic, onions), citrus peel, and the spice, turmeric, are among those identified as having health promoting benefits.*

The body is exposed to a large number of foreign chemicals everyday. The majority are manmade chemicals that wind up in our food, air, and water, or are taken in the form of drugs. Overexposure to toxic substances and an inability to properly metabolize them can negatively impact one's health, producing a wide variety of symptoms such as headaches, muscle and joint pain, fatigue, and allergy or flu-like symptoms. This toxic build up can also contribute to inflammatory and neurological disease.[1-5]

LIVER DETOXIFICATION: PROTECTION AGAINST ENVIRONMENTAL TOXINS

The liver is the most important organ in the body involved in detoxification. It is in the liver where toxic substances, such as drugs, alcohol, and environmental toxins, undergo a process called biotransformation which renders them less harmful and helps to facilitate their removal from the body.[6]

Liver detoxification involves a number of enzymatic systems which are divided into two general phases: Phase I and Phase II. Phase I involves the activation of a series of enzymes called the cytochrome P450 mixed-function oxidases. These enzymes begin the process of biotransformation by oxidizing, reducing, or hydrolyzing toxins, creating biotransformed intermediates. Phase II enzymes perform conjugation reactions which help to convert the biotransformed intermediates from Phase I into less toxic, water-soluble substances that are easily excreted or eliminated from the body (Figure 1). Phase II enzymes may also catalyze reactions independent of Phase I activity, acting directly upon a drug or toxin that does not require biotransformation.

In some instances, Phase I enzymes can actually transform a non-toxic foreign substance into a harmful, toxic substance. For example, a relatively harmless component of cigarette smoke is biotransformed during Phase I into a carcinogenic compound. A properly functioning Phase II system should, however, act to detoxify the metabolically activated carcinogen. To effectively eliminate biotransformed intermediates, Phase II enzyme activity must be in balance with Phase I, otherwise toxins may accumulate in the body.

Another potentially damaging effect of Phase I is the production of oxygen free radicals that occurs as a result of cytochrome P450 activity. As a person's toxin load increases, so does cytochrome P450 activity, which can expose the liver to greater oxidative stress. Adequate intake of antioxidants, such as vitamin C and vitamin E, and certain naturally occurring phytochemical compounds help protect the liver against free radical damage.[7]

ADEQUATE NUTRITION SUPPORTS BALANCED DETOXIFICATION ENZYME ACTIVITY

Adequate nutrition helps to insure proper functioning of both Phase I and Phase II detoxification and to reduce the risk of free radical damage produced during the detoxification process.[7,8] Several nutrients such as vitamin C,

vitamin E, and the B vitamins are required for cytochrome P450 activity.[8] Glutathione and the amino acid cysteine help to regulate Phase II conjugation reactions. The activity of each phase may be reduced or enhanced depending on the availability of critical nutrients.[8]

VEGETABLE COMPOUNDS SUPPORT DETOXIFICATION

Population studies from around the world have consistently shown that diets rich in fruits and vegetables are associated with lower risks of cancer.[9] These findings suggest that the antioxidant activity of several vitamins and minerals present in fruits and vegetables plays a protective role against cell damage or mutation caused by free radicals. But what may also be beneficial are the multitude of nonnutrient compounds (phytochemicals) that are present in plant foods.[10-14] Wattenberg has described several mechanisms of action by which phytochemicals appear to inhibit carcinogenesis.[13] Some compounds may act as blocking agents: they prevent, or *block*, carcinogens from reaching or reacting with critical target sites in tissue. Others may act as suppressing agents, compounds which suppress the growth and change of cells that have been exposed to carcinogens and would otherwise cause cancer. Mechanisms by which blocking agents may act: [13]

- Inhibit the biotransformation of noncarcinogenic compounds into carcinogenic compounds.
- Induce detoxification enzyme pathways-including Phase II enzymes which facilitate the removal of carcinogens from the body.
- Scavenge free radicals.

Table 1 lists some of the phytochemicals that have been identified as blocking agents.

Table 1. Various phytochemicals identified as blocking agents.

COMPOUND	SOURCE
isothiocyanates	cruciferous vegetables (broccoli, cabbage, kale)
glucosinolates	cruciferous vegetables
organosulfur compounds	*Allium sp.* (garlic, onions)
curcumin	turmeric
flavonoids	numerous plants
monoterpenes	citrus peel

In several studies, laboratory animals fed a crude, unrefined diet composed of natural constituents containing both nutrients and nonnutrients developed fewer carcinogen-induced tumors than animals fed the same diet, but refined and devoid of the nonnutrient components of food.[13, 15] Higher levels of Phase II enzyme activity were also reported.[15] Phytochemicals may thus offer support for liver detoxification of foreign chemicals and carcinogens.[10, 13]

High on the list of vegetables that support detoxification are the cruciferous vegetables, such as broccoli, cauliflower, Brussels sprouts, watercress and cabbage.[10, 13] Several compounds present in cruciferous vegetables have been shown to be inducers of Phase II detoxification enzymes including glutathione S-transferase and quinone reductase, which catalyze conjugation reactions. The Phase II inducers have been identified as the aromatic isothiocyanates, such as sulforaphane, and indole-3-carbinol. In one study, isothiocyanates appeared to help blunt the carcinogenic effect of cigarette smoke in rats. According to the researchers, the rats given the carcinogen NNK (nicotine-derived nitrosaminoketone) and isothicyanates had a 50% reduction in lung cancer compared with the control rats.[16] The same researchers found that when a group of volunteer smokers chewed 2 ounces of watercress at each meal for 3 days there was a statistically significant increase in the detoxification products of NNK excreted in their urine, compared to baseline measurements.[16]

Another component of cruciferous vegetables, 1-cyano-2-hydroxy-3-butene (CHB), has been shown in laboratory animals to increase glutathione levels in the liver.[17] Glutathione is an important cellular antioxidant and acts as a conjugator during Phase II detoxification. An overload of toxins may deplete glutathione through conjugation activities, decreasing its reducing capacity and contributing to oxidative stress.

The organosulfur compounds present in the *Allium* species (onions, garlic, leeks) are also important inducers of Phase II enzymes.[10, 13,18-20] Epidemiological evidence suggests that regular consumption of garlic is associated with a reduced risk of certain types of cancer. Gastric cancer mortality is approximately 10 times lower in areas of China where garlic consumption is high compared to regions where garlic intake is low.[18] A lower risk of stomach cancer has also been reported in parts of Italy where greater quantities of garlic are consumed.[18]

Garlic and onions also contain flavonoid compounds, such as quercetin, which appear to have anticarcinogenic effects as well. Research suggests that flavonoids may act as either blocking agents or suppressing agents.[11] Quercetin, in particular, has been shown to be a potent antioxidant and blocking agent and has been associated with a reduced risk of skin cancer, leukemia, and experimentally induced cancers in rodents. [11]

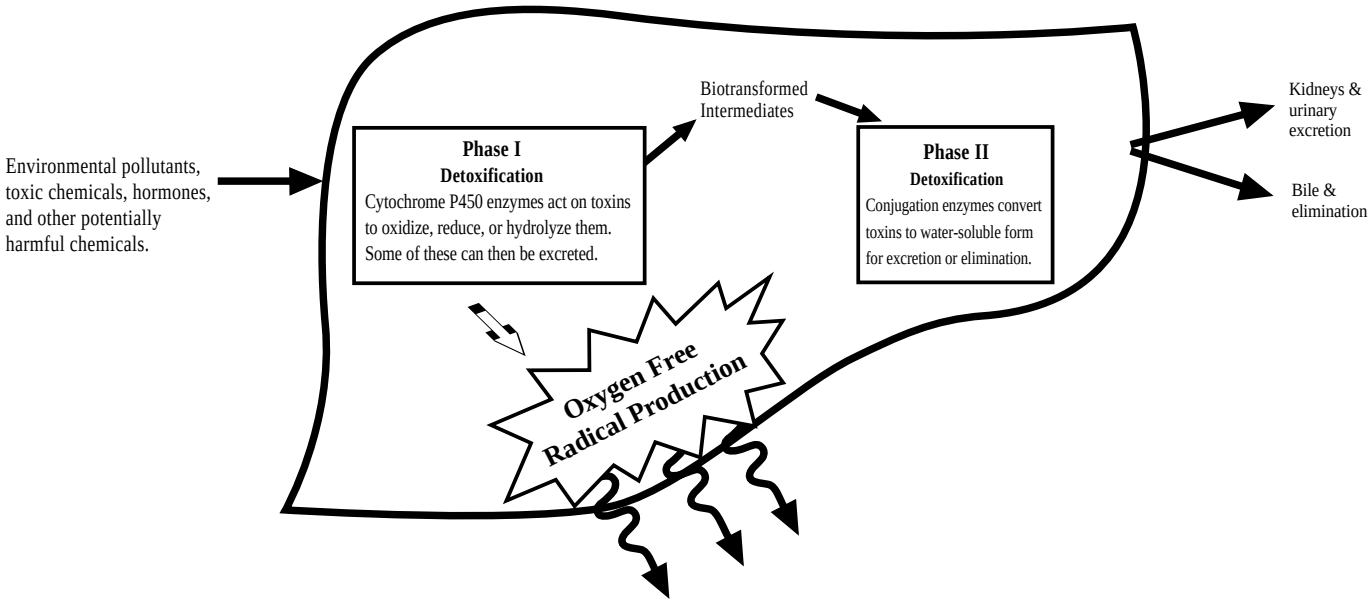
Other compounds that may act as blocking agents and may support xenobiotic detoxification are the monoterpenses from the oil of citrus peel, and curcumin, a natural constituent of the spice turmeric.[10, 13, 21-24] D-limonene is a citrus monoterpene that has been associated with a reduced risk of chemically induced cancer in laboratory animal models.[22, 23] In several animal studies where cancer incidence was reduced with the addition of curcumin to the diet, the activity of phase II enzymes, in particular glutathione S-transferase, was increased.[24-26] One study reported a 32% increase in glutathione-S-transferase activity as well as a 12% increase in glutathione levels in mice fed a 5% turmeric diet compared with control animals. Tumor incidence was decreased by 90% in the mice fed the turmeric-containing diet.[24]

Curcumin also functions as an antioxidant and helps to protect against free radical damage to cells and DNA.[24] Its antioxidant activity may have also contributed to the apparent cancer protective actions reported in the studies.[24]

Conclusion

Good nutrition, rich in essential nutrients, helps to ensure a healthy, properly functioning detoxification system. In addition, recent research suggests that many of the phytochemicals found in plant foods, in particular those found in garlic and cruciferous vegetables such as broccoli, support liver detoxification and are associated with a reduced risk of cancer. Several of these plant compounds appear to induce Phase II enzymes which may inhibit carcinogenesis by detoxification. Induction of Phase II enzymes, such as quinone reductase and glutathione S-transferase, appear to have a protective effect against carcinogenesis in a number of experimental animal studies. Population studies further support the health promoting effects of plant foods.

FIGURE 1
DETOXIFICATION IN THE LIVER



REFERENCES

1. Hilleman B. Multiple chemical sensitivity. C&EN July 22, 1991:26-42.
2. Rooney PF, et al. A short review of the relationship between intestinal permeability and inflammatory joint disease. Clin and Exper Rheumatol 1990;8:75-83.
3. Smith MD, et al. Abnormal bowel permeability in ankylosing spondylitis and rheumatoid arthritis. J Rheumatol 1985;12:299-305.
4. Steventon GB, et al. Xenobiotic metabolism in Alzheimer's disease. Neurology 1990;40:1095-98.
5. Steventon GB, et al. Xenobiotic metabolism in Parkinson's disease. Neurology 1989;39:883-87.
6. Vander AJ, Sherman JH, Luciano DS. Nonimmune metabolism of foreign chemicals. Human Physiology the Mechanisms of Body Function. 1994:738-740.
7. Anderson KE, Kappas A. Dietary regulation of cytochrome P450. Annu Rev Nutr 1991;11:141-167.
8. Bland JS. Detoxification and rejuvenation. The 20-day rejuvenation diet program. 1997:105-120.
9. Block G, et al. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer 1992;18(1):1-29.
10. Wattenberg LW. Chemoprevention of cancer. Cancer Res 1985;45:1-8.
11. Bokkenheuser VD, et al. Natural anticarcinogens. Acta Chir Scand Suppl 1991:562:71-76.
12. Zhang Y, et al. A major inducer of anticarcinogenic protective enzymes from broccoli: Isolation and elucidation of structure. Proc Natl Acad Sci 1992;89:2399-2403.
13. Wattenberg LW. Inhibition of carcinogenesis by minor dietary constituents. Cancer Res (Suppl) 1992;52:2085s-2091s.
14. El-Bayoumy K. Evaluation of chemopreventive agents against breast cancer and proposed strategies for future clinical intervention trials. Carcinogenesis 1994;15:2395-2420.
15. Sparnins VL, et al. Glutathione S-transferase activity: Enhancement by compounds inhibiting chemical carcinogenesis and by dietary constituents. JNCI 1982;68:493-496.
16. Hecht SS, et al. Chemoprevention by isothiocyanates. J Cell Biochem Suppl 1995;22:195-209.
17. Wallig MA, et al. Separation of toxic and glutathione-enhancing effects of the naturally occurring nitrile, cyanohydroxybutene. Fund Appl Toxicol. 1992;19:596-606.
18. Liu J, et al. Inhibition of 7,12-dimethylbenz[a]anthracene-induced mammary tumors and DNA adducts by garlic powder. Carcinogenesis 1992;13:1847-1851.
19. Tadi PP, et al. Organosulfur compounds of garlic modulate mutagenesis, metabolism, and DNA binding of aflatoxin B1. Nutr Cancer 1991;15:87-95.
20. Sumiyoshi H, Wargovich MJ. Chemoprevention of 1,2-dimethylhydrazine-induced colon cancer in mice by naturally occurring organosulfur compounds. Cancer Research 1990;50:5084-5087.
21. Goud VK et al. Effect of turmeric on xenobiotic metabolizing enzymes. Plant Foods Hum Nutr 1993;44(1):87-92.
22. Maltzman TH, et al. Effects of monoterpenoids on in vivo DMBA-DNA adduct formation and on phase I hepatic metabolizing enzymes. Carcinogen 1991;12:2081-2087.
23. Elegbede JA et al. Effects of anticarcinogenic monoterpenes on phase II hepatic metabolizing enzymes. Carcinogenesis 1993;14:1221-1223.
24. Azuine MA, Bhide SV. Chemopreventive effect of turmeric against stomach and skin tumors induced by chemical carcinogens in Swiss mice. Nutr Cancer 1992;17:77-83.
25. Susan M, Rao MNA. Induction of glutathione S-transferase activity by curcumin in mice. Arzneim-Forsch/Drug Res 1992;42:962-964.
26. Goud VK, et al. Effect of turmeric on xenobiotic metabolizing enzymes. Plant Foods Hum Nutr 1993;44:87-92.