Physiological Functions of Phytonutrients: A Brief Introduction: Part I

The term *phytochemical* refers to a classification system of botanical chemicals. Broadly stated, phytochemicals are chemicals that plants produce to perform metabolic functions. For example, wood creating cellulose, sugar cane manufacturing sucrose, and opium poppies producing morphine. 1

Phytonutrient, within the context of natural health and nutrition, has come to refer to bio- active plant chemicals that humans eat and have or may well have significant positive effects on human metabolism. *Phytochemicals* that are concentrated or prepared in such a dosage as to have likely therapeutic effects are generally becoming referred to as *nutraceuticals*.

Phytonutrients are not essential for life, but they appear to be essential for optimal health and longevity. They therefore may properly be classified as micro-nutrients, along with vitamins and minerals. The technical classification of the major groups of phytonutrients found in our diets includes: *terpenes, amines, organosulfurs, phenols, polysaccharides, organic acids, and lipids*. One food can contain several classifications of phytonutrients. For example, an orange contains terpenes (*carotenoids and limonoids*) and phenols (*bioflavonoids*).

Phytochemicals can be grouped into families based on their chemical structure and biological activity. In this three part introductory article, we will briefly examine the major groups and some of the sub-groups of *phytonutrients* and how they may contribute towards optimal biological function.

Phytosterols: Inhibition of Cholesterol Absorption, Modulation of Hormone Metabolism, Immune Function, and Inflammatory Physiology

Phytosterols, saponins, phenolics, pectins and soluble fibers are sub-classifications of phytonutrients known particularly for their cholesterol lowering abilities. Examples from each subgroup include flax, pumpkin and sesame seed (*phytosterols*), fenugreek and ginseng (*saponins*), cherries and green tea (*phenolics*), apples and prunes (*pectins*), and oat beta glucan and rice bran (*soluble fibers*). Phytosterols are *lipids*, saponins are *terpenes*, phenolics are *phenols*, and pectins and soluble fibers are *polysaccharides*.

Nuts are the richest source of *phytosterols* in the Western diet. Numerous studies demonstrate that diets rich in nuts and seeds are associated with a decreased occurrence of cardio-vascular disease (CVD). 2

Cold-pressed unrefined vegetable oils such as flaxseed, hazelnut, olive, sesame, wheat germ, and walnut are excellent sources of phytosterols. Refining and hydrogenation drastically reduces phytosterol concentrations by 40-85 %. 3

Phytosterols are poorly absorbed. They lower cholesterol by interfering with its absorption in the small intestine. Three grams of phytosterols daily show significant lipid lowering effects. 4

Algae and fungi also manufacture phytosterols. For example, as presented at the **American Heart Association's** 39th Annual conference in 1999, *ergosterol* from red yeast grown on rice has lipid lowering effects similar to statins. Various mushrooms, seaweeds, and spirulina contain many sterols, including *fuctosterol, sitosterol, ergosterol*.

Phytosterols can also mimic hormone precursors or modulate hormones themselves. For example, Swedish tree pollen, pumpkin seeds, pygeum, and saw palmetto are all used in cases of benign hyper-trophic prostate disease (BHP) and prostatitis. These phytosterols inhibit the conversion of testosterone to dehydroxytestoterone (DHT). 5

Phytosterol steroid mimicry also contributes to the anti-inflammatory effects of cold processed oils, as from flaxseeds and olives. The essential fatty acids (EFA) *lipids* help modulate *eicosanoid* production, the *omega-6 EFA's* being precursors to *prostaglandin E1*, and the *omega 3 EFA's* serving as precursors for *prostaglandin E3*, both anti-inflammatory in action 6

Specially prepared and concentrated phytosterols (*sterols and sterolins*) from sesame seed are used to modulate immune function through thymus hormones (T1 and T2) and interleukins, while modulating DHEA/Cortisol balance as well.7

The Carotenoids: Powerful Antioxidants for Cancer Prevention, Optimizing Cardio-Vascular Dynamics, Protecting Vision

Carotenoids, a fat soluble group of naturally occurring plant pigments, are a sub-classification of the *terpenes*. Perhaps the most familiar of phytonutrients, *carotenoids* function as powerful antioxidants and immuno-potentiaters. Diets rich in carotenoids are linked with a decreased risk of heart disease, cancer, and degenerative eye diseases such as macular degeneration and cataracts. 8

There are approximately 600 known carotenoids, 50 of which are present in our diets, mostly from fruits and vegetables. Twenty have been identified in the human body. 9

Chemically, carotenoids are classified in two main groups: *carotenes and xanophylls. Carotenes* refer to the carotenoids that contain only carbon and hydrogen (*beta-carotene and lycopene*). *Xanthophylls* refer to compounds that contain in addition a hydroxyl group (*lutein, zeaxanthin, and beta-cryptoxanthin*), a keto group (*canthaxanthin*) or both (*astaxanthin*).

Alpha- carotene, beta-carotene, and cryptoxanthin are the main vitamin A precursors.

Carotenoids are considered potent membrane antioxidants due to their reactivity with singlet oxygen. Ranked by antioxidant power we can list *astaxanthin, canthaxanthin, beta-carotene, zeaxanthin, and lutein* as all stronger than vitamin E!

Leafy green vegetables contain mostly *lutein and zeaxanthin*. Carrots, oranges, sweet potatoes and squash contain mainly *carotenes*. Interestingly, the yellow yolk of eggs is rich in *lutein*, and the *astaxanthin* group from red algae is what makes salmon pink.

Lutein and zeaxanthin are the only carotenoids identified in the macula. There they filter blue light from the retina and inhibit oxidative damage. Such damage leads to macular degeneration, the leading cause of blindness in those over 65.

Researchers at the **University of Utah Medical School** found that *lutein* intake is inversely associated with colon cancer. 10 A study on serum carotenoid levels in women in India with breast cancer showed *lutein and zeaxanthin* to be significantly lower than in healthy controls, at least in postmenopausal women.11

Lycopene is most abundant in tomatoes with smaller amounts in pink grapefruit, watermelon, guava, and rose hips. Lycopene makes up approximately 50% of the total carotenoids in blood plasma of those persons consuming typical Western diets. It protects against prostate, cervical, breast, digestive tract and lung cancers, and perhaps atherosclerosis. 12

Zeta carotene, phytoene and phytofluene are also found in tomatoes and are sometimes referred to as "the three amigos"! The latter two, according to a patent by **Lycored Natural Products**, are more effective in inhibiting LDL oxidation than other carotenoids. They have also filed a patent for a blood pressure lowering combination of *lycopene, phytofluene, phytoene, astaxanthin and canthaxanthin*. The patent claims that administration of these carotenoids in therapeutic dosages can rapidly lower blood pressure by lowering blood viscosity and increasing vessel flexibility.

Astaxanthin, found mostly in red yeasts and red algae, is now fed to salmon, trout, crabs, krill and shrimp in "fish farms" to provide the red and pink color of their natural red algae eating wild brethren. This most powerful of the carotenoid antioxidants has been shown to enhance secondary immune response in humans, and help reduce symptoms of H. pylori, CTS and RA. 13

Beta- carotene intake is associated with reduced risk of breast, stomach, esophageal, and pancreatic cancers. 14 Researchers at **John Hopkins** reported in 1994 that smokers with the lowest blood levels of beta-carotene had approximately a 350% greater risk of heart attack as compared to non-smokers with high beta carotene levels.

Beta-cryptoxanthin, found mostly in fruits like oranges, tangerine and papayas, is second only to beta carotene as a source of vitamin A. Cryptoxanthin, again demonstrating the uniqueness of each phytonutrient, is the only carotenoid that appears to be related inversely to bladder cancer risk. 15

Of note, some carotenoids rich foods like carrots and tomatoes yield more *beta-carotene and lycopene*, respectively, when cooked. *Lutein and lycopene* require fat for optimal uptake of carotenoids whereas dietary fiber inhibits absorption of lutein*, lycopene, and beta-carotene* by 40% to 75 % 16, 17

The Other Terpenes: Limonoids, Saponins and Chromonals

Limonoids, like carotenoids a subclass of the terpenes, are found in citrus fruit peels. Limonoids may be specifically directed toward protection of the lungs. The effects of D-limonene and citrus fruit oils, i.e. orange oil and lemon oil, on induced neoplasia of the lungs and forestomach of female mice inhibited pulmonary adenoma formation and the occurrence of forestomach tumors, thus demonstrating that non-nutrient constituents of the diet may inhibit carcinogen-induced neoplasia.18

Additionally, limonoids may be specific chemo-preventive agents. In animal studies results suggest that the chemotherapeutic activity of limonoids can be attributed to induction of both Phase I and II detoxification enzymes in the liver. 19 Indeed, limonoids in large concentrated therapeutic doses in humans have been reported to support detoxication of hormones and related substances that can have a negative effect on cellular DNA and cell proliferation. 20 But the largest growth segment has been the use of d-limonene in cleaning products!

Eight ounces of OJ would usually contain approximately 19 mg of d-limonene.

The last terpine subclass we will present are the **saponins** and the **chromanols**. As mentioned earlier, saponins have been shown to lower cholesterol by binding to it in the digestive track. According to the molecular biology web site from **Princeton University**, saponins also inhibit the multiplication of cancer cells by interfering with their DNA.21 Alfalfa and other legumes, especially soy, are the most common sources.

The most familiar chromanols are the *tocotrienols* and the *tocopherols*. These two naturally occur in palm oils and whole grain germ and/or bran, yet research has shown that the biologic functions of tocopherols and tocotrienols are unrelated. Tocotrienols appear to inhibit breast cancer cell growth, whereas tocopherols have been most studied for their cardiovascular health effects. 22

Physiological Functions of Phytonutrients: A Brief Introduction, Part 11

The Phenol Group: Antinflammatory, Anticlotting, Antioxidant, Immune Enhancers and Hormone Modulators

Phenols include *antho-and beta-cyanins, flavonoids, isoflavones, lignans* , and *lignins*. Blue, blue-red and violet colorations seen in berries, grapes and purple eggplant are due to their phenolic content. Bilberries, for example, are high in *phenolic anthocyanidins* giving them their reddish hue.

Phenols have been the subject of extensive research as disease preventives. Phenols protect plants and humans from oxidative damage. Perhaps of greatest interest to chiropractic doctors is phenol's ability to block specific enzymes that cause inflammation. They also modify the prostaglandin pathways and thereby protect platelets from clumping. 1

Flavonoids are perhaps best known for their ability to enhance the effects of ascorbic acid. Along with Vitamin C, flavonoids are well known for their ability to protect the vascular system by strengthening, maintaining and repairing capillaries. 2

Once lumped together as vitamin P, science has now discovered well over 1,500 flavonoids! Here is a partial listing: *anthocyanins, proanthocyanins, flavones, flavonols, flavonones, bioflavonoids, flavin-3-4-diols, isoflavones and catechins.*

Flavonoids are found in *apigenin* in chamomile (flavone); *quercetin* in onion and green apples, *rutin* in-buckwheat, *ginkgoflavonglycosides* in ginkgo (flavonols); *hesperidin* in citrus fruits and *silybin* in milk thistle (flavanones); *catechins* in green tea; *isoflavones* in soy; *anthocyanins* in blueberries; and *proanthocyanins* in grape seeds and pine bark.

The biologic functions of flavonoids include action against allergies, inflammation, free radicals, platelet aggregation, microbes, ulcers, hepatotoxins, viruses and tumors. 3 Flavonoids inhibit specific enzymes such as the angiotensin-converting enzyme (ACE) that raises blood pressure, and cyclooxygenase that breaks down prostaglandins, thereby inhibiting platelet aggregation.

Flavonoids reduce the risk of estrogen-induced cancers via interfering with the enzymes that produce estrogen. For example, according to Harper's Biochemistry, flavonoids inhibit estrogen synthesase, an enzyme that binds estrogen to receptors in several organs.

Cataracts are a common development in diabetics who, unable to metabolize sugar normally, build up damaging levels of "alcohol sugars" that cause the clouding of the lens. Flavonoids appear to retard their development by interfering with aldose-reductase, which converts galactose into the potentially harmful galacticol. 4

Anthocyanidins are flavonols that provide cross-links that connect and strengthen intertwined strands of collagen protein. Collagen protein is the most abundant protein in the body as it makes up a large proportion of muscle sheaths, skin, tendon, ligament, and bone matrix.

Anthocyanidins are powerful water-soluble antioxidants that inhibit free radicals, which are one of the main causes of aging. Larger doses are often useful in conditions wherein there is a profuse free radical cascade, such as trauma, inflammation, allergic reactions, and heavy exercise.

Catechins, the polyphenolic compounds that provide the antioxidant activity of green tea, are members of the flavan-3 class of flavonoids. The most common catechins are gallic esters, named epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin gallate (EGCG), the later viewed as the most significant. All are found in green tea and are thought to be responsible for many of the protective benefits of this beverage. Such benefits include promotion of apoptosis of cancer cells in prostate, stomach, skin, lung, breast and colorectal tissues. Initial studies suggest that this may be related to an anti-angioneogenesis effect. 5 According to Dr James F.Balch, co-author of the best seller Prescription for Nutritional Healing, green tea both lowers cholesterol and acts as a powerful antioxidant that helps inhibit the oxidation of cholesterol. According to a recent study presented in the Annual Meeting of the **American Academy of Neurology**, green tea polyphenols may also have a protective effect on Parkinson's disease.

Isoflavones, of which *genistein* and daidzein are the most known and studied, are most abundant from kudzu, soy beans and other legumes. In spite of their name, isoflavones are rather distant cousins of flavonoids. Isoflavones, which are phytoestrogens, effectively modulate estrogen levels in humans and are therefore often of clinical value in low estrogen states like menopause, or imbalanced and toxic estrogen sensitive conditions

like breast, uterine and prostate tumor growth. It is now well recognized that peoples who consume traditional diets rich in fermented soy foods experience less breast, uterine and prostate cancers.

Lignans are found in seeds and grains, especially flaxseed. The lignan found in flaxseed is called *secoisolariciresinol glucoside (SDG).* The **National Cancer Institute** reports that vegetarians have higher concentrations than omnivores, as do tumor free patients when compared with breast and colon cancer patients.

According to Dr. Dan Junke and Charles A. Weisman, authors of, Flaxseed Lignan - The Power of SDG in Promoting Health, lignans are weak phytoestrogens that also have anti-viral, anti-bacteria, anti-fungal, antioxidant, and immune enhancing properties.

Lignans are not to be confused with *lignins* which are a non-carbohydrate dietary fiber that, along with polysaccharides, occur in the cell walls of plants.

The Physiological Functions of Phytonutrients, A Brief Introduction, Part III

The Organosulfur Group: Detoxifiers, Cardiovascular Risk Reducers, and Non-Specific Immunity Supporters

The strength of evidence for the health benefits of fruits and vegetables is convincing for many cancers. 1 Clearly underlying the importance of the *organosulfur group*, cruciferous vegetables were the first to be promoted by the **American Cancer Society** as cancer preventive!

Generally, the organosulfur group provides sources of sulfur vital for phase II enzymes activities (such as for glutathione S-transferase AKA GST) involved in detoxication of carcinogens. More specifically, organosulfurs provide *glucosinolates* which are converted into several bio-transformation products in the human body, particularly *indole-3-carbinol, isothiocyanates, and thiosulfonates*. The sulfur compounds in these three groups are slightly different and, consequently, each has specific health benefits.

The **indoles** and **isothiocyanates** are most especially found in the *cruciferae family* of brassica and mustard plants. These includes horse radish, cabbage, broccoli, Brussels sprouts, kale, arugula, bok choy, cauliflower, mustard seeds and greens, watercress, turnip greens, daikon, wasabi, and kohlrabi.

The thiosulfonates are predominant in the *allium family* where garlic, onion, leek, asparagus, shallots, chive and scallion are representative. 2

A recent case controlled study reported that cruciferous consumption of 1-2 servings per day (150 –220 gm) reduced breast cancer risk by 40-50% in post-menopausal women. In such women elevating daily intake from the current average 9 gm per day to 193 gm garnered a favorable shift in urinary excretion ratio of 2-hydroxy- versus 16-alpha-hydroxysterone, the so-called "good " and "bad" estrogen metabolites, at least as far as breast cancer is concerned. 3

Inhibition of esophageal, lung and several other cancers has been shown in animal studies at **Ohio State University**. Here, scientists proposed that activation of *cytochrome P450 enzymes* was the likely cancer-protective method. 4

The protective agents of the brassica family are thought to be most especially the phytonutrients isothiocyanate, specifically *sulforaphane*, and indole-3-carbinol (I3C), with its metabolite *diindolymethane* (DIM).

Know that the phytonutrient content of cruciferous vegetables can vary widely. For example, sulforaphane (of import as it helps turn on t4 cells so they recognize cancer cells and destroy them) in three-day old broccoli sprouts was measured and found to be *ten - to - one hundred times higher* than the amount in mature broccoli. 7 One-hundred and twenty-five (125) mg of such broccoli "super sprouts" may be equal to approximately one five-ounce serving of most mature broccoli! 5

Two reductionist approaches to ingesting physiologically significant amounts of organosulfurs are broccoli extracts of indole-3-carbinol (I3C) and di-indolyl-methane (DIM). According to Dan Lukaczer, N.D., director of clinical research, **Functional Medicine Research Center**, Gig Harbor, WA, I3C is a *secondary metabolite* in cruciferous vegetables. A secondary metabolite is one formed after an enzyme in the vegetable (*myrosinase*) is exposed to a phytochemical in the vegetable (*glucobrassicin*). This can occur only when vegetable cells are crushed or eaten, and is referred to as *enzymatic hydrolysis*. Once formed I3C is then broken down in the presence of stomach acid into several by-products such as the aforementioned diindolylmethane (DIM), which are then absorbed. Both appear to be of value in inhibiting cancer cells in animal cancer models, but it is not clear that DIM is the only breakdown product of importance.

As most of the research to date has focused on I3C, it may be prudent to utilize supplements containing I3C instead of DIM. I3C must be taken with meals and persons so supplementing must have sufficient acidifying capacity in their stomachs. Nonetheless, the Bob Livingston Newsletter councils that DIM should be taken with a light meal containing some fat. 400 mg of DIM represents the amount one might normally ingest in 2 to 3 pounds of brassica.

However, The Journal of the National Cancer Institute relates that it only took three and one-half servings a week of broccoli, Brussels sprouts and cauliflower, which contain high levels of indoles, to decrease the risk of prostate cancer by 41 percent. 8 Interestingly, the bio-availability of indoles is increased by light cooking.

Though the **thiosulfonates** are also able to assist Phase II detoxication, and thereby enhance protection against carcinogenesis, they are perhaps better known for their ability to promote a more favorable HDL- LDL ratio, lower blood pressure and stimulate non-specific immunity

Like their cruciferous cousins, when thiosulfonates are cut or smashed the sulfur compounds release bio-transformation products including: *allicin, ajoene, allylic sulfides, vinyl dithin and D-allyl mercaptocysteine.* Some of these are considered anti-atherosclerotic, some antioxidant, some anti-cancer agents, while others are antibacterial, antiviral and antifungal. 9,10,11,12 The Commission E monograph in Europe declares garlic antibacterial, anti-mycotic, lipid-lowering, an inhibitor of platelet aggregation (thus prolonging bleeding and clotting time) with concomitant enhancement of fibrinolytic activity.

Organic Acids: Antioxidant Cancer Preventives, Liver Protectors, and Inflammatory Mediators.

Phytochemicals in this group are small to large complex carbon compounds found in grains, herbs, teas, a few vegetables and some fruits. These compounds, which include *esters and lactones*, act primarily as antioxidants, cancer preventives, liver protectors, and inflammatory mediators. 13 They include *oxalic acid* found in spinach, rhubarb, tea and coffee; *tartaric acid* in apricots and apples; *cinnamic acid* in aloe and cinnamon; *caffeic acid* in burdock and hawthorn; *ferulic acid* in oats and rice; *gallic acid* in tea, *coumaric acid* in turmeric; *salicylic acid* in spearmint; and *tannic acid* in nettles, tea, and berries.

Perhaps of most current interest is **ellagic acid**, which is found in guava, currants, apples, grapes, strawberries, and most particularly in red raspberries and wild chart cherries. According to the **Hollings Cancer Institute at the University of South Carolina**, ellagic acid is a proven anti-carcinogen, anti-mutagen, and anti-cancer initiator!

Nine years of study have shown that for breast, pancreas, esophageal, skin, colon and prostate cancer cells ellagic acid strongly inhibits cancer cell division within 48 hours, and promotes apoptosis (normal cell death) within 72 hours. Clinical tests also show that ellagic acid prevents the destruction of the *p53 gene* by cancer cells. Additional studies suggest that one of the mechanisms by which ellagic acid inhibits mutagenesis and carcinogenesis is by forming adducts with DNA, thus masking binding sites that might otherwise be occupied by the mutagen or carcinogen. 14

Organic acids can form complexes with other phytochemicals to yield a new compound with even more powerful effects. For example, gallic acid complexes combine with polyphenolic catechins to form *catechin gallates*. Catechin-gallate complexes (esters) are antioxidants with enhanced anti-cancer and anti-tumor effects. 15 This surprising finding again argues for the oft repeated conservative guideline in supplementing phytonutrients for general health benefits: consider first a wide spectrum from fruits, vegetables, legumes, grains and spices, of all colors, over mega doses of single or several phytonutrients.

The Amines: Carcinogen Deactivators and Enzymatic Therapy

The amines include both **chlorophyll** (as in *chlorella, spirulina, hydrilla, and the leafy greens and grasses*) and **plant enzymes** (as in *papain and bromelain*). Chlorophyll is well known to detoxify carcinogens found in cooked muscle meats (*heterocyclic amines*), smoked or barbecued foods (polycyclic hydrocarbons), and peanut mold (*aflatoxin*). 16 Chlorophyll has also been recognized for its anti-inflammatory, anti-mutagenic, and antioxidant properties. 17,18 Nakamura found that the naturally occurring chlorophyll derivative, *pheophorbide*, showed antioxidant activity against lipid auto-oxidation comparable to alpha-tocopherol, AKA Vit. E. 17,19,20

Chlorophyll has been cited as strengthening the immune response, therapeutic for inflammation of the ear and the mucous membrane of the nose and sinuses, supportive of normal kidney function, accelerating wound and ulcer healing, and reducing fecal, urinary, and body odor in geriatric patients. 21,22

Plant enzymes are well accepted as useful in assisting digestion, having the advantage of being active in a wide PH range. Taken in between meals, they assist in injury resolution by increasing the blood enzymes available to digest proteins related to fibrolytic and inflammatory process and immune responses.

In Conclusion

Phytochemicals can be grouped into families based on their chemical structure and biological activity.1 We have made a very cursory review of the major phytonutrient compounds, namely the *terpenes, polysaccharides, lipids, phenols, organosulfurs, organic acids, and amines*.

Research shows individual phytonutrients can:

- facilitate cell-to-cell communication,[2]
- modify cellular receptor uptake of hormones,[3]
- convert to vitamin A,[4]
- repair DNA damage from toxic exposure,[5]
- detoxify carcinogens through the activation of the cytochrome P450 and Phase II liver enzyme systems,[6]
- serve as antioxidants to help prevent various forms of cancer,[7]
- cause apoptosis (cell death) in cancer cells,[8]
- enhance immune response,[9]
- help prevent cardiovascular disease,[10]
- help prevent osteoporosis,[11]
- help prevent macular degeneration and cataracts.[12]

The take home message is that our dietary and supplementation habits would do well to include a wide variety of whole plant foods and whole food supplements nutrient dense in a broad spectrum of phytonutrients.

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Footnotes, Conclusion

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