The Quantum Physics of Flavonoids, Part 2

By Nita Bishop, ND

Editor's Note: Part 1 of this article (**www.naturopathydigest.com/archives/2006/apr/bishop.php**) appeared in the April 2006 issue.

The Vitamin C Connection

Flavonoids usually are found alongside vitamin C in nature. Vitamin C is conveniently found in the pulp of many fruits, while the skins contain the flavonoids. It might be prudent, when giving vitamin C, to supplement with a flavonoid-rich extract, since studies have shown that supplementing vitamin C with flavonoids might prevent the breakdown of vitamin C in the tissues. Flavonoid molecules are hydroxyl radical scavengers. The proposed mechanism by which flavonoids sustain the vitamin C in the tissues might be the flavonoids chelating trace copper ions, scavenging free radicals and preventing rancidity of oils, similar to the way EDTA binds trace metals in a chelation protocol. At the April 2006 Northwest Naturopathic Physicians Conference in Tacoma, Wash., Arnold Leonard, PhD, MD, demonstrated the synergy of flavonoids in oils, citing recent original research from the University of Minnesota that utilized genetic engineering to boost the immune system.

Stimulating Phase II Detoxification Enzyme Activity

The basic structure of a flavonoid is shown above right. Flavonoids are a subcategory of the plant phenolics –very widely found constituents characterized by the same basic structural element: an aromatic ring bearing one
or more hydroxyl groups.

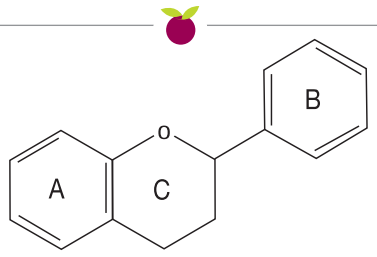
More than 4,000 different types of flavonoids have been described to date. Total average daily intake in the U.S. has been estimated to be approximately 1 gram, although this probably is an overestimation.[16,17] Flavonoids are an extremely complex group of compounds. They are divided into six categories:

- Flavonols are found in onions, kale and broccoli. Quercetin is an example.
- Flavones are found in greens, including thyme and parsley.
- Flavonones are found in citrus fruits.
- Isoflavones are found predominately in legumes. Genistein (found in soy) is an example.
- Catechins are found in tea and apples.

Continued on next page

Anthocyanidin/proanthocyanicins (PCOs)/gallic acid phenolics, which give certain plants their dark purple/blue color, are found in grapes, cherries, blueberries, plums and other colored fruits. Herbs such as hawthorne and bilberry are the most widely occurring.

Flavonoids can be divided further into an anthocyanin aglycone subclass (**see table 1 on page 9**), consisting of cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin. Methylation is the predominant pathway for the peonidin, malvidin, cyanidin and petunidin aglycosides. Glucuronidation is the second most prevalent pathway for the cyanidins. Metabolically, anthocyanins appear to be different from other flavonoids, with much lower quantities excreted in the urine relative to the amount consumed. What happens to the 55 percent to 60 percent of the remaining anthocyanidins that disappear from the GI tract and do not end up in the urine? As per a recent study, it was the anthocyanidins with the most complex glycosylation patterns that remained at higher concentrations for a longer period of time in the GI tract. It was demonstrated that the sugar moieties influenced the absorption/metabolism of anthocyanins *in vivo*.[19] This still leaves questions regarding how the degradation of the anthocyanins occurs. Where do the metabolites end up? We might need more sophisticated GC techniques to discover this.



The basic chemical structure of a flavonoid. Source: Oregon State University Linus Pauling Institute Web site. Micronutrient Information Center.

Newest Cancer Research

Flavonoids have profound effects on the function of immune and inflammatory cells, as determined by a large number and variety of *in vitro* and some *in vivo* observations. Flavonoids exhibit carcinogenesis by several mechanisms. Ample evidence indicates that selected flavonoids can affect and usually inhibit secretory processes, mitogenesis and cell-to-cell interactions, including possible effects on adhesion and the elaboration of effects of cytokines and cytokine receptors. The association between flavonoid intake and cancer protection has up to this point been weak; however, important cancer research is starting to appear.

Recent studies indicate that flavonoids have the ability to inhibit tumor growth *in vitro*. Ellagic acid (specifically, relevant polyphenols in strawberry and raspberry) was extensively discussed at the International Berry Symposium in relationship to esophageal cancers. Dietary administration of strawberries and raspberries inhibited events associated with both the initiation and the promotion/progression of chemically induced esophageal cancer. Previously, it was difficult to track the metabolites of ellagitannins. However, in this study, the involvement of colonic microflora in ellagitannin metabolism was substantiated by urolithin B, a previously described antiangiogenic and hyaluronidase inhibitor compound which emerged as an accurate bioavailable biomarker of ellagitannins.

Berry fruit extracts and their bioactive compounds, when isolated, significantly inhibited activator protein-1 (AP-1), nuclear factor-KappaB (NFKB) and mitogen-activated protein kisases (MAPKs) signaling induced by UV or 12-tetradocanolyphorbol-13-acetate (TPA). Berry extracts specifically induced apoptosis and differentiation, but had no effect on normal rat blood PMNs or lung alveolar macrophages. Berry extracts inhibited proliferation of A549 tumor xenograft in athymic mice. Berry compounds inhibited migration and invasions of A549 cells. All these data suggest that berry compounds might function as potential chemopreventive and chemotherapeutic agents with little cytotoxicity to normal tissue. The chemopreventative effects of berry fruits might be through their antioxidant properties by blocking reactive oxygen species-mediated AP-l, NF-kappaB and MAPK activation.[22]

Anti-angiogenic effects: modulation of cell signaling pathways by flavonoids could help prevent cancer. Delphinidins inhibit EGFR kinase inhibitors downstream. It's the delphinidin aglycone in the anthocyanidin group of compounds that recently has captured the attention of the French and produced a November 2005 NIH overview on delphinidins in brain cancer research (Quebec study).[23] For neuro-oncologists, multiple genetic abnormalities underlie the development of a glioblastoma multiformae, which makes it extremely resistant to chemotherapeutic treatment. Once diagnosed, the usual survival prognosis is one year or less.

An *in vitro* study from Montreal recently highlighted in *Molecular Epidemiology and Cancer Prevention* (May 2005) demonstrated that EGFR kinase inhibitors (concentrations of delphinidin) inhibited (VEGF) vascular endothelial growth factor-induced tyrosine phosphorylation of VEGFR-2. Inhibition of VEGFR-2 by delphinidin inhibited the VEGF-induced activation of ERK-1/2 signaling and the chemotactic motility of human EC as well as their differentiation into capillary-like tubular structures in Matrigel and within fibrin gels. *In vivo*, delphinidin was able to suppress basic fibroblast growth factor-induced vessel formation in the mouse Matrigel plug. The identification of delphinidin as a naturally occurring inhibitor of VEGF receptors suggests that this molecule possesses important anti-angiogenic properties that might be helpful for the prevention and treatment of cancer.

Following this study, an original article published in *The New England Journal of Medicine* in November 2005 discussed 49 patients with recurrent malignant gliomas who were treated with EGFR kinase inhibitors; nine had tumor shrinkage of at least 25 percent. These findings were validated in 33 patients who received treatment for glioblastomas at a different institution; eight patients had a clinical response.[24]

Berries always have been cherished in culinary traditions; research has verified that berries should be one of those recommended five to nine servings of fruits and vegetables a day. We know that flavonoids are involved in capillary and cerebral blood flow, platelet aggregation, liver function, enzyme activity, collagen, phospholipid, cholesterol and histamine metabolism. Scientists now are unraveling how flavonoids participate in the immune function through gene expression, answering many of the mysteries concerning their bioavailability and metabolism.

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How to Metabolize Toxins With Flavonoids

Phase I and Phase II Liver Detox

	Necessary Nutrients
"Engine De-Grease" P450 Enzymes – Large group of enzymes that change fat-soluble toxins to water-soluble intermediates	**Phytochemicals** •Sulphurophane •Indoles •Glutathione •Flavonoids
Intermediate Compounds May be more toxic that original toxin. Antioxidant protection required.	**Phytonutrients** •Flavonoids •Trace Minerals •Glutathione
Conjugation Methylation, Sulfation Amino Acid Conjugation Glutathione Conjugation Methyl/sulfur chemical groups are added to the intermediate compounds to render them harmless and ready for removal.	**Phytonutrients** •Methyl donor compounds •Sulphurophane •Indoles •Glutathione •Amino Acids

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About the Author

Nita Bishop, ND, co-developed the first Bachelor of Science degree in herbal medicine at Bastyr University and continues her research on flavonoids as adjunct research professor at Southwest College of Naturopathic Medicine. During the past 10 years, she has studied medicinal plants on a global level for formulating new medicines, including the highest testing flavonoids, *Croton lechleri*, at her 220-acre plant nursery in the upper Amazon basin of Peru. She has also traveled to Southern India and worked with the head doctor at a hospital in Coimbatore to study the most potent and highest flavonoid Sanskrit/Ayurvedic plants. Dr. Bishop will be a featured speaker at the 2006 Northwest Naturopathic Physicians Conference in Tacoma, Wash.