The Quantum Physics of Flavonoids

By Nita Bishop, ND

By studying the new model of the flavonoids, their mechanisms of action and new metabolic information, we become world-class practitioners, moving to a quantum-physics level of practicing medicine. This requires us to shift our thinking regarding the current tools we use to evaluate the patient, and impacts our subsequent determinations from a therapeutic standpoint. By going deeper into the cellular matrix, we open doors that have never been opened. These doors are the genomic entry points into the cell and might have profound effects for our patients.

For years, we have debated the topic of whether flavonoids are physiologically relevant. We hypothesized that the biological effect of flavonoids was related solely to their antioxidant/anti-inflammatory activity. The overall limited absorption and rapid elimination of flavonoids leads us to perceive that flavonoids are probably relatively biounavailable. We give emphasis to the chalcone form of quercetin, stating this is probably more absorbable. However, huge gaps still exist in solving the flavonoid puzzle. As we become immersed in our day-to-day practice medicine, it's sometimes difficult to see the forest through the trees. We must not forget our ethnobotanical naturopathic roots, which allow us to think multidimensionally; if we listen and observe, the plants will teach us how they use flavonoids.

Flavonoids are involved in cell signaling (via ATP/ADP) through kinases at very low levels. One of the best studies presented at the International Berry Symposium in the summer of 2005 involved tracking radio-labeled flavonoids in mice with probes in their jugular veins,[1] which demonstrated the concept of signal transduction. Scientists from all over the world gathered to present groundbreaking research at the Oregon State Food Sciences Symposium. They demonstrated novel methods to identify and quantify the bioactive compounds (flavonoids) in the berries. They demonstrated the Darwinian-concept "nature vs. nurture" rule whereby environment plays a critical role, triggering certain beneficial chemicals in plants (e.g., short growing season, drastic temperatures, etc.) and activating signal transduction; and it's the flavonoids that power the bioactive chemical pathways in berries. It was the general consensus of opinion at the conference that although we cannot measure with current analytical instrumentation what exactly is happening to flavonoids in the tissues, we still are looking for answers as to how and why flavonoids do what they do in the plants and our bodies. We came one step closer to obtaining further insights on the complexity of flavonoids.

Recent evidence emerging from cell culture experiments suggests that many of the biological effects of flavonoids actually are related to their ability to modulate cell signaling pathways.[2] The most important variable in the flavonoid equation that we might have overlooked is that *flavonoids affect the cell receptors and consequently downstream DNA*. It's a complex cascade of events in the cell which eventually leads to changes in the expression of specific genes. These signal transduction pathways/cell signaling pathways regulate numerous cell processes, including growth, proliferation and apoptosis. Furthermore, the intracellular concentrations of flavonoids needed to affect cell signaling pathways to initiate this cascade of events is an amount *considerably less* than that required to impact cell antioxidant capacity. This might be why, in our clinical observations, flavonoids appear to be effective at relatively low concentrations.

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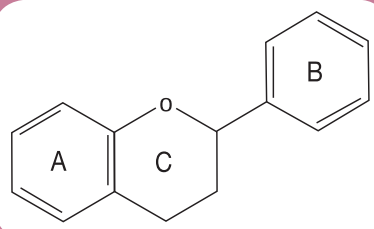
Where do flavonoids accumulate in the tissues? We know that certain flavonoids might have an affinity for certain tissues: milk thistle for the liver, ginkgo for the brain, hawthorne for the heart and bilberry for the eyes. Flavonoids generally have an affinity for the microcirculation/capillary mesh. We also know that when flavonoids are concurrently administered, vitamin C will last several hours longer, specifically in the adrenal tissues.[3]

How are flavonoids metabolized? New advances in research have helped to give us a greater understanding about the bioavailability of flavonoids. A whole new body of research is coming from the French and Chinese on the actual mechanism of metabolism of flavonoids. Flavonoids occur in plants and most foods as glycosides, and when you cook down most flavonoid glycosides (with the exception of flavanols catechins and proanthocyanidins), they reach the small intestine intact. However, when we eat them, there is a complex series of steps involved to absorb them efficiently. When flavonoids reach the colon, they will need sufficient bacteria and enzyme populations present in order to be metabolized and absorbed. To further complicate things, the flavonoid aglycones and flavonoid glucosides (bound to glucose), which also are absorbed in the small intestine, might not last long either, since they are rapidly metabolized to form the methylated, glucuronic or sulfated metabolites involved in Phase I and II. In addition, as previously stated, we lack the sophisticated instrumentation to track the flavonoid *metabolites* and so dismiss them completely as having even lower antioxidant activity than the parent flavonoid. There is quantitative data demonstrating that peak plasma concentrations measured after the consumption of anthocyanins (flavonols and flavanols), including those from tea, were generally less than 1 micromole/liter.[2, 4] Even with very high flavonoid intakes, plasma and intracellular concentrations in humans are likely to be 100 to 1,000 times lower than concentrations of other antioxidants such as ascorbate or glutathione.[5]



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

There is a big difference in the bioavailability of anthocyanins compared to other flavonoid groups (flavonols and flavanols) studied. **Anthocyanins have been used as indices for authenticity in many studies because it's the anthocyanins that are absorbed intact.** Bilberry, elderberry, black currant, blueberry, and red grape are the anthocyanins largely responsible for the antioxidant effects in berries. A unique feature is the pH-dependent molecular structure of the anthocyanin; the pH equilibrium present is likely to have a major effect on anthocyanin bioavailability and bioactivity. Absorption of anthocyanins appears to be greater in the jejunum compared with other regions of the GI tract, suggesting the presence of a complementary active transport mechanism in the jejunum.[6]

How much is retained and how much is excreted? The neuroprotective aspects of flavonoids (blueberries cross the BBB and can be identified in the cortex[7]) and cardioprotective

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aspects (flavonoid supplementation, specifically blueberry, raspberry, cranberry and black currant) might provide beneficial effects to plasma lipid profiles; anti-inflammatory effects also have been elucidated.[8] It was the consensus of the group that flavonoid supplementation does not affect blood platelet activity.

Ethnobotanically, we have learned if a plant is producing protective compounds to kill an invading cell or predator, it might have good potential in cancer applications. When a plant evokes certain protective mechanisms against pathogens, it's a perfect example of signal transduction. The new anti-cancer data suggests the bioactive compounds in the berries have chemotherapeutic effects by blocking reactive oxygen species-mediated AP-l, Nfkappa B and MapK activation.[9] One fascinating study might change the way we view the actual mechanism of cranberry activity in UTIs. The study showed that the crux of cranberry's effectiveness was the proanthocyanidins, which have unusual A-type double linkages in their structures (compared to the B-type linkages in other foods such as chocolate and grapes). This enables cranberry to elicit an *in vivo* bacterial anti-adhesion effect, preventing the coagulation of bacteria into a "biofilm," which is how they generally encapsulate themselves to create greater resistance to the antibiotics.[10]

Certainly the antioxidant properties were elucidated at this conference. Ethnobotanically, they function as stress protectants in plant cells during photosynthesis by scavenging the ROS produced in the photosynthetic electron transport system. They protect plants from the UV radiation of the sun and scavenge UV-generated ROS.[11] This might be why we see that some of the highest testing flavonoids are from plants in equatorial regions. In humans, they become regulators of iron channels involved in phosphorylation, binding to metal ions, which prevent these metals from acting as catalysts to enhance free radical production in the body.[12] Even though all the emphasis on antioxidant activity goes to vitamins C, E, beta carotene, selenium and zinc, the antioxidant activity of flavonoids generally is more potent and effective against a broader range of oxidants than these traditional antioxidant nutrients.[13, 14] But even above and beyond the antioxidant mechanism, there is a lot more going on with flavonoids in the body. Flavonoids act synergistically with other vitamins such as C and E, making them more bioavailable. Based on extensive data, it appears that a combination of antioxidants will provide greater antioxidant protection than any single nutritional antioxidant. Mixtures of antioxidant nutrients appear to work together harmoniously to produce the phenomena of synergy.[15]

Only recently have we discovered that flavonoids act synergistically with other vitamins, such as vitamins C and E, making them more bioavailable.[3,16]

Editor's note: Complete references accompany part two of this article, which will appear in the May issue of *Naturopathy Digest*.

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.

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	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

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.