Quercitin Queries

Phytonutrition refers to the consumption of certain bio-active plant chemicals (phytochemicals) that have significant positive health effects. Most phytonutrients are not essential for life, but more and more appear to be essential for optimal health and longevity. They therefore may now 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, and organic acids. Our presentation herein concerns the *polyphenol-flavonoid-flavonol* called *quercitin,* a major dietary flavonoid.

The Phenol Flavonoids

Phenols are a class of chemical compounds consisting of a hydroxyl group (-OH) attached to an aromatic hydrocarbon group. The simplest of the class is phenol (C6H5OH). Multiple chains of phenols are called *polyphenols*. Phenols protect plants and humans from oxidative damage. They block specific enzymes that cause inflammation and allergies, and modify the prostaglandin pathways and thereby protect platelets from clumping. [1] They help the liver detoxify and inhibit specific enzymes such as the angiotensin-converting enzyme (ACE) that raises blood pressure. [2]

Once lumped together as "vitamin P", science has now discovered well over 1,500 phenol flavonoids! They 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. [3]

Quercetin Qualities

Quercetin is a member of the class of flavonoids called *flavonols*. It is widely distributed in the plant kingdom in rinds and barks. Especially rich sources of quercitin include green apple skins, onions, red wine, green tea, St. John's Wort, and seed pods of the Brazilian shrub “fava d´anta” (Dimorphandra mollis).

Quercetin has anti-allergy, anti-inflammatory, immune modulating, anti-viral, anti-cancer, lipid antioxidant and gastro-protective properties. It may also have activity in preventing secondary complications of diabetes and in treating category III chronic prostatitis (non-bacterial chronic inflammatory prostatodynia). [4] Let’s make a closer examination of the physiology behind two of these properties.

The better known anti-allergy effects of quercetin likely relate to its inhibition of:
1) degranulation of mast cells, basophils and neutrophils.
2) tyrosine kinase and nitric oxide synthase while modulating NF-kappaB, the inflammatory mediator.
3) the release of histamine and other mediators of allergic reactions, possibly by stabilizing cell membranes so that they are less reactive to allergens.
4) inhibiting formation of inflammatory prostaglandins and leukotrienes. [5, 6]

In relation to its putative activity in preventing the secondary complications of diabetes (micro-vascular damage to the insulin independent retina, kidney and nerves) quercitin inhibits *aldose reductase*, the first enzyme of the "sorbitol-aldose reductase pathway" (AKA polyol pathway). Hyperglycemia enhances the flow rate of this pathway which has been linked to diabetic complications such as cataracts, retinopathy, neuropathy and nephropathy. [7]

To explain briefly, cells use glucose for energy. Glucose not used for energy enters the *sorbitol-aldose reductase pathway*. Aldose reductase reduces glucose to the sugar alcohol sorbitol, which is oxidized into fructose, which is returned to the normal glycolysis pathway for energy production. In uncontrolled diabetics, who have more blood sugar than liver *glycolysis* can handle, this patho-physiology ultimately favors the production of too much sorbitol. The resultant over abundance of sorbitol may then glycate the nitrogens on proteins, like collagen, causing a degradation of proteins known as "cross linking". These "cross linked proteins" are known as *advanced glycation endproducts* (AGEs). Excessive activation of the sorbitol-aldose reductase pathway also increases pro-oxidant levels and deplete endogenous antioxidant reserves. [8]

Quercitin Questions: What About Bioavailability?

In nature quercetin is typically as a *carbohydrate conjugate*. Pure quercetin itself is an "aglycone" or "aglucon", meaning that pure quercetin does not possess a sugar moiety in its structure. Regarding the bioavailability of these quercetin conjugates, the main determinant of absorption of quercitin is the nature of the sugar moiety. For example, quercitin from apples and tea contains predominantly poorly absorbed galactoside, rhamnoside and arabinoside conjugates, while onion contains mainly the much more bioavailable glucosides. [9, 10, 11, 12]

Supplemental quercetin it is usually derived from the flavonoid *rutin* extracted from the seed pods of the Brazilian shrub “fava d´anta” (Dimorphandra mollis). This is treated with acid to obtain quercetin as a very thin powder of greenish yellow color. This commonly found supplemental form of quercitin, however, is poorly absorbed from the gastrointestinal tract. Bromelain and papain are often added to the formula increase absorption. [13] Fortunately, scientists have developed a proprietary procedure for conversion of the inactive precursors in Dimorphandra mollis to the biologically absorbable and therefore highly bioactive form called "isoquercitrin" AKA *isoquercitn/rutin 50/50.* Isoquercitin/rutin 50/50 is much better absorbed due to this proprietary conversion to the more bioavailable glucoside carbohydrate portion of the molecule. This more effective form, though more expensive, is now available for use in supplements and functional foods.

These facts underline the importance of compiling food and supplement composition tables with individual glycosides listed. Manufacturers, doctors and consumers of quercitin containing products need to know that they are using the most bioavailable forms of quercitin.

An ingested dose of quercetin is absorbed from the small intestine and is then transported to the liver via the portal circulation, where it undergoes significant first pass metabolism. Quercetin and its metabolites are distributed from the liver to various tissues in the body. Quercetin is strongly bound to albumin in the plasma. Peak levels of plasma quercetin occur from 0.7 to 7 hours following ingestion, and the elimination half-life of quercetin is approximately 25 hours. [14]

Quercitin Qualifiers

Quercitin has no known contraindications and is generally well tolerated. Fears that quercetin might be carcinogenic have not been supported by recent research. Adverse effects reported with oral quercetin include gastrointestinal effects such as nausea, and rare reports of headache and mild tingling of the extremities. There are no reports of over-dosage with oral quercetin. Doses of quercetin used range from 200 to 1,200 milligrams daily. [15]The new higher bioavailable isoquercitin/rutin 50/50 may demonstrate efficacy at even lower dosages.

1.) Hertog, M.G., et al. Lancet, 342: 1007-11, Oct. 23, 1993.
2.) Kinsella, J.E., et al. Food Technology, 47: 85-90, April 1993
3.) Murray, R.K., et al. Harper's Biochemistry, 23 ed.: 196. New York; Appleton & Lange, 1994.
4.) Shoskes DA, Zeitlin SI, Shahed A, Rajfer J. Quercetin in men with category III chronic prostatitis: a preliminary prospective double-blind, placebo-controlled trial. Urology. 1999; 54:960-963. The researchers concluded: "Few therapies have shown durable efficacy with these disorders. Quercetin is efficacious, inexpensive, well tolerated and safe."
5.) Middleton Jr E, Anne S. Quercetin inhibits lipopolysaccharide-induced expression of endothelial cell intracellular adhesion molecule-1. Int Arch Allergy Immunol. 1995; 107:435-436.
6.) Sato M, Miyazaki T, Kambe F, et al. Quercetin, a bioflavonoid, inhibits the induction of interleukin 8 and monocyte chemoattractant protein-1 expression by tumor necrosis factor-alpha in cultured human synovial cells. J Rheumatol. 1997; 24:1680-1684.
7.) Costantino L, Rastelli G, Gamberini MC, et al. 1-Benzopyran-4-one antioxidants as aldose reductase inhibitors. J Med Chem. 1999; 42:1881-1893.
8.) Brownlee M (2001). "Biochemistry and Molecular Cell Biology of Diabetic Complications". Nature 414 (6865): 813-820. PMID: 11742414
9.) Day AJ, Gee JM, DuPont MS, Johnson IT, Williamson G. Absorption of quercetin-3-glucoside and quercetin-40-glucoside in the rat small intestine: the role of lactase phlorizin hydrolase and the sodium-dependent glucose transporter. Biochem Pharmacol 65, 1199–1206. 2003
10.) Crespy V, Morand C, Besson C, Manach C, Demigne C, Remesy C. Comparison of the intestinal absorption of quercetin, phloretin and their glucosides in rats. J Nutr 131, 2109–2114. 2001
11) Day AJ, Bao YP, Morgan M, Williamson G. Conjugation position of quercetin glucuronides and effect on biological activity. Free Radic Biol Med 29, 1234–1243. 2000
12) Quercetin glycone conjugates include rutin and thujin. Rutin is also known as quercetin-3-rutinoside. Thujin is also known as quercitrin, quercetin-3-L-rhamnoside, and 3-rhamnosylquercetin. Onions contain conjugates of quercetin and the carbohydrate isorhamnetin, including quercetin-3,4'-di-O-beta glucoside, isorhamnetin-4'-0-beta-glucoside and quercetin-4'-0-beta-glucoside. Pure quercetin itself is practically insoluble in water. The quercetin carbohydrate conjugates have much greater water solubility then quercetin.
13) Ibid. 4
14) PDR Health http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/que_0219.shtml
15) Ibid, 14